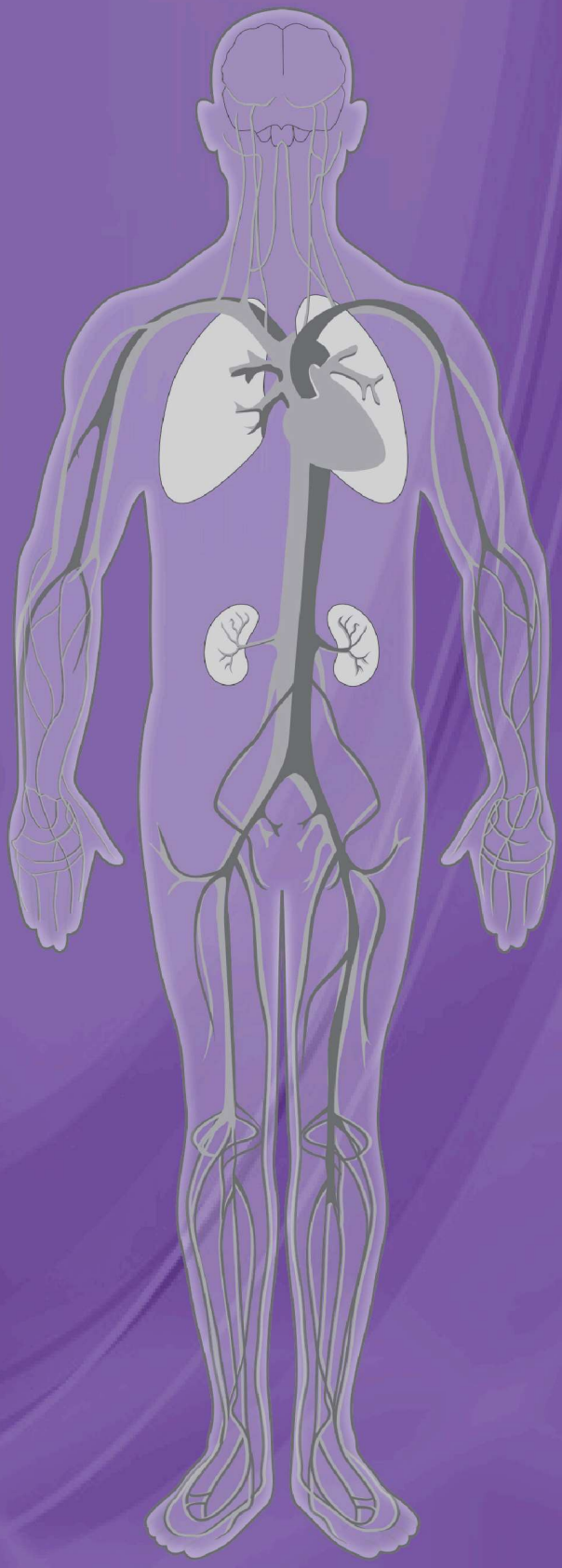
ISCCM™

Critical Care Update 2022



Editors
Deepak Govil
Rajesh Chandra Mishra
Dhruva Chaudhry
Subhash Todi

Foreword
Deepak Govil

4th Edition

JAYPEE

Critical Care Update 2022

ISCCM™

Critical Care Update 2022

Fourth Edition

Editors

Deepak Govil
MD EDIC FICCM FCCM
Director, Critical Care
Institute of Critical Care and Anaesthesia
Medanta—The Medicity
Gurugram, Haryana, India

Rajesh Chandra Mishra
MD (Medicine) FNCCCM EDICM FCCM FCCP FICCM FICP
Honorary Consultant, Intensivist, Internist (Sleep Apnea)
Khyati Multispeciality Hospital
Ahmedabad, Gujarat, India

Dhruva Chaudhry
MD (Medicine) DNB DM (Pulmonary and Critical Care Medicine)
Professor and Head
Department of Pulmonary and Critical Care Medicine
Postgraduate Institute of Medical Sciences
Rohtak, Haryana, India

Subhash Todi
MD MRCP
Director
Department of Critical Care
Advanced Medicare and Research Institute
Kolkata, West Bengal, India

Foreword
Deepak Govil

JAYPEE

JAYPEE BROTHERS MEDICAL PUBLISHERS
The Health Sciences Publisher
New Delhi | London

Jaypee Brothers Medical Publishers (P) Ltd

Headquarters

Jaypee Brothers Medical Publishers (P) Ltd
EMCA House, 23/23-B
Ansari Road, Daryaganj
New Delhi 110 002, India
Landline: +91-11-23272143, +91-11-23272703
+91-11-23282021, +91-11-23245672
Email: jaypee@jaypeebrothers.com

Corporate Office

Jaypee Brothers Medical Publishers (P) Ltd
4838/24, Ansari Road, Daryaganj
New Delhi 110 002, India
Phone: +91-11-43574357
Fax: +91-11-43574314
Email: jaypee@jaypeebrothers.com

Overseas Office

JP Medical Ltd
83 Victoria Street, London
SW1H 0HW (UK)
Phone: +44 20 3170 8910
Fax: +44 (0)20 3008 6180
Email: info@jpmedpub.com

Website: www.jaypeebrothers.com
Website: www.jaypeedigital.com

Critical Care Update 2022

First Edition: 2019
Second Edition: 2020
Third Edition: 2022
Fourth Edition: March **2022**

ISBN: 978-93-5465-652-1

Contributors

Aakanksha Chawla Jain
MD IDCCM IFCCM
Consultant
Department of Respiratory Medicine and Critical Care
Indraprastha Apollo Hospital
New Delhi, India

Abhinav Gupta MD DNB FNB EDIC
Consultant
Department of Intensive Care
Homerton University Hospital
Homerton Row, London, UK

Abhishek Prajapati
MBBS DTCD IDCCM EDIC EDARM FCCU FIECMO PhD (Medicine)
Consultant
Department of Critical Care, Pulmonology and Medicine
Shree Krishna Hospital, Pramukhswami Medical College
Bhaikaka University
Anand, Gujarat, India

Abhishek Shrivastava
MBBS MD PDCC FIECMO
Head
Department of Anesthesiology, Critical Care and Emergency Medicine
Regency Superspeciality Hospital
Lucknow, Uttar Pradesh, India

Aditya Nagori BE PhD
Post-Doctoral Fellow
Department of Computational Biology
Indraprastha Institute of Information Technology
New Delhi, India

Aditya Shukla MD (Anesthesia)
Head
Department of Critical Care and Emergency Medicine
Regency Hospital Ltd
Kanpur, Uttar Pradesh, India

Ahsan Ahmed MBBS DA DNB EDIC IFCCM
ICU In-charge and
Assistant Professor
Department of Anesthesiology
KPC Medical College and Hospital
Kolkata, West Bengal, India

Ahsina Jahan Lopa MBBS FICM
ICU In-charge
Department of ICU and Emergency
Ashiyan Medical College Hospital
Dhaka, Bangladesh

Ajay Prajapati MBBS MS MCh
Consultant
Department of Neurosurgery
Maulana Azad Medical College
New Delhi, India

Ajit Kumar DA MD
Additional Professor
Department of Anesthesia
All India Institute of Medical Sciences
Rishikesh, Uttarakhand, India

Ajith Kumar AK MD DNB EDIC FICCM
Senior Consultant
Department of Critical Care Medicine
Manipal Hospitals
Bengaluru, Karnataka, India

Ajmer Singh MD
Director
Department of Cardiac Anesthesia
Institute of Critical Care and Anaesthesiology, Medanta—The Medicity
Gurugram, Haryana, India

AK Singh
MD (Chest) DNB (Respiratory Medicine) MNAMS FICCM
European Diploma (Respiratory Medicine)
Consultant
Department of Pulmonary and Critical Care
Regency Hospital
Kanpur, Uttar Pradesh, India

Akhil Taneja
MD IDCCM IFCCM EDIC Fellow-IDSA/SHEA Fellow-ECMO (TSS)
Principal Consultant
Department of Critical Care Medicine
Max Super Specialty Hospital
New Delhi, India

Akshay Kumar Chhallani
DNB (General Medicine) FNB (Critical Care Medicine) MNAMS FICP FICP
Consultant Physician and Intensivist
Department of Critical Care Medicine
Apollo Hospital
Navi Mumbai, Maharashtra, India

Alok Sahoo MD IDCC
Associate Professor
Department of Anesthesia and Critical Care
All India Institute of Medical Sciences
Bhubaneswar, Odisha, India

Amina Mobashir
DNB (Respiratory Medicine) IDCCM EDRM
Consultant, Institute of Respiratory and Critical Care Medicine and Sleep Disorders
Max Hospital
New Delhi, India

Amit Gupta
MBBS MD DNB Fellow (Critical Care)
Senior Consultant and Medical Director
Department of Pulmonology and Critical Care
Medlink Healthcare
Patiala, Punjab, India

Amit Kumar Mandal
MBBS DTCD DNB (Respiratory Diseases)
Director
Department of Pulmonology, Sleep and Critical Care
Fortis Hospital
Mohali, Punjab, India

Amit Singhal
BLK-Max Superspeciality Hospital
New Delhi, India

Amitkumar Prajapati
MBBS (Anesthesia) IDCCM EDIC FIECMO
Consultant Intensivist
Department of Critical Care
Shalby Hospital
Ahmedabad, Gujarat, India

Amol Kulkarni MBBS DNB (Medicine) IDCCM
Consultant
Department of Medicine and Critical Care
Seth Nandlal Dhoot Hospital
Aurangabad, Maharashtra, India

Amrish Patel
MBBS DTCD Fellow in Critical Care (Indo-Australia) FCCS
Consultant Pulmonologist and Critical Care Specialist
Department of Pulmonology and Critical Care
Sterling Hospital
Ahmedabad, Gujarat, India

Amrita Prayag MBBS MSc (Pharmacology)
Research Consultant
Department of In-House Research
Deenanath Mangeshkar Hospital
Pune, Maharashtra, India

Anand Sanghi
MBBS DA DNB FNB EDIC (London)
Head
Department of Critical Care Medicine
Choithram Hospital and Research Centre
Indore, Madhya Pradesh, India

Anand Tiwari
MBBS DA DNB IDCCM FNB (Critical Care Medicine) FICCM
Senior Consultant
Department of Neurotrauma Intensive Care Unit
Ruby Hall Clinic
Pune, Maharashtra, India

Anant Pachisia MBBS MD FNB
Associate Consultant
Department of Critical Care Medicine
Institute of Critical Care and Anaesthesiology
Medanta—The Medicity
Gurugram, Haryana, India

Andrew Conway Morris
MB ChB (Hons) BSc (Hons) PhD MRCP FRCA FFICM
Division of Anesthesia
Department of Medicine
University of Cambridge
Cambridge, UK

Anil Jain MD
Director, Cardiac Surgery
Epic Hospital
Ahmedabad, Gujarat, India

Anirban Bose MBBS DNB FNB
Associate Consultant
Medica Institute of Critical Care
Medica Superspeciality Hospital
Kolkata, West Bengal, India

Anirban Hom Choudhuri
MD FICCM PGDMLE FIAMLE
Director Professor
Department of Anesthesia and Intensive Care
GB Pant Hospital
New Delhi, India

Anjan Trikha DA MD FICA MAMS FAMS
Professor, Department of Anesthesiology and Intensive Care
All India Institute of Medical Sciences
New Delhi, India

Ankur Bhavsar MBBS DA IFCCM EDIC
Head, Critical Care Unit
Spandan Multispeciality Hospital
Vadodara, Gujarat, India

Ankur Sharma
MD (Anesthesia) PDCC (Transplant Anesthesia)
Associate Professor
Department of Trauma and Emergency
All India Institute of Medical Sciences
Jodhpur, Rajasthan, India

Anuj Clerk
MBBS MD FNB (Critical Care) IDCCM EDIC FIECMO CCIDC
Director, Critical Care Services
Department of Critical Care Medicine
Sunshine Global Hospital
Surat, Gujarat, India

Anushka Mudalige
MBBS MD (Anesthesiology) FRCA FFICM EDIC
Consultant Intensivist
Department of Medical Intensive Care Unit
Colombo North Teaching Hospital
Ragama, Gampaha, Sri Lanka

Apurba Kumar Borah MBBS DA IDCCM
Head
Department of Critical Care Medicine
Narayana Superspeciality Hospital
Guwahati, Assam, India

Arjun Alva MBBS MD (Anesthesia)
Administrative Head and Consultant
Department of Critical Care Medicine
NH, Mazumdar Shaw Multispeciality Hospital
Bengaluru, Karnataka, India

Arlene Torres APRN
Intensive Care Solutions
Department of Critical Care Services
Baptist Hospital of Miami
Miami, Florida, USA

Arpan Chakraborty
MD FNB (Cardiac Anesthesia)
Senior Consultant
Department of Critical Care, ECMO Services and Cardiac Anesthesia
Medica Superspecialty Hospital
Kolkata, West Bengal, India
Past President
ECMO Society of India

Arti Singh
MS (Obst and Gyne) DNB (Obst and Gyne) MNAMS
Head and Senior Consultant
Department of Obstetrics and Gynecology
Regency Hospital
Kanpur, Uttar Pradesh, India

Arun Dewan MBBS MD
Principal Director (Critical Care) and Director (Internal Medicine)
Department of Internal Medicine and Critical Care
Max Smart Super Speciality Hospital
New Delhi, India

Arun K Baranwal
MD PG Dip (Critical Care) FCCM FRCPCH FICCM FIAP
Department of Pediatrics
Advanced Pediatrics Center
Postgraduate Institute of Medical Education and Research
Chandigarh, India

Arunaloke Chakrabarti
MD DNB FIDSA FECMM FAMS FNASc
Professor and Head
Department of Medical Microbiology
Postgraduate Institute of Medical Education and Research
Chandigarh, India

Arundhati Dileep
AB (Internal Medicine) Fellow (Pulmonary and Critical Care)
Fellow
Department of Pulmonary Medicine
Bronx Health Centre
New York City, New York, USA

Arvind Baronia MD
Principal
Government Medical College, Uttarakhand
Ex-Professor and Head
Department of Critical Care Medicine
Sanjay Gandhi Postgraduate Institute of Medical Sciences
Lucknow, Uttar Pradesh, India

Ashish Bhalla
MD (Medicine) FRCP (Edinburgh; Glasgow) FICCM
Professor
Department of Internal Medicine
Postgraduate Institute of Medical Education and Research
Chandigarh, India

Ashish K Khanna MD FCCP FASA FCCM
Associate Professor, Vice Chair for Research
Department of Anesthesiology
Section on Critical Care Medicine
Wake Forest School of Medicine
Atrium Health Wake Forest Baptist Medical Center
Winston-Salem, North Carolina, USA

Ashit V Hegde MD MRCP
Consultant
Department of Internal Medicine and Intensive Care
PD Hinduja Hospital
Mumbai, Maharashtra India

Ashootosh Mall MD (Medicine)
Intensivist
City Hospital
Gorakhpur, Uttar Pradesh, India

Ashutosh Bhardwaj
MD IDCCM EDICM FIECMO
Head and Senior Consultant
Dharamshila Narayana Superspeciality Hospital, New Delhi, India

Asif Ahmed
MBBS DNB (Anesthesiology) (Gold Medal) IDCCM
Senior Consultant and Head
Department of Critical Care Medicine
Tata Main Hospital
Jamshedpur, Jharkhand, India

Asish Kumar Sahoo MBBS MD DM
Associate Consultant
Department of Critical Care and Emergency Medicine
Sir Gangaram Hospital
New Delhi, India

Atul Prabhakar Kulkarni
MD (Anesthesiology) FISCCM PGDHHM FICCM
Professor and Head
Division of Critical Care Medicine
Department of Anesthesiology, Critical Care and Pain
Tata Memorial Hospital, Homi Bhabha National Institute
Mumbai, Maharashtra, India

Avinash Agrawal MD IDCCM IFCCM FCCP
Professor
Department of Critical Care Medicine
King George's Medical University
Lucknow, Uttar Pradesh, India

Avinash Tank MS MCh (SGPGIMS) FIAGES
Director
Dwarika Super-Speciality Centre for Liver-Gastro, Obesity and Cancer Surgery
Ahmedabad, Gujarat, India

Avneep Agarwal MD
Staff Physician
Department of Intensive Care and Resuscitation
Department of General Anesthesiology
Cleveland Clinic
Cleveland, Ohio, USA

Babu Abraham MD MRCP (UK) FICCM
Consultant
Department of Critical Care Medicine
Apollo Hospitals
Chennai, Tamil Nadu, India

Balasubramanian S
MD (General Medicine) DNB (Nephrology)
Senior Consultant Nephrologist
Department of Nephrology
Apollo Hospitals
Chennai, Tamil Nadu, India

Banambar Ray MD FICCM
Head
Department of Critical Care Medicine
SUM Ultimate Medicare
Bhubaneswar, Odisha, India

Banshi Saboo MD PhD
Diabetologist
Diabetes Care and Hormone Clinic
Ahmedabad, Gujarat, India

Barkha Bindu MBBS MD DNB DM
Consultant
Department of Neuroanesthesiology and Neurocritical Care
Paras Hospital
Gurugram, Haryana, India

Bhagyesh Shah
MBBS DA IDCCM MBA (Healthcare Management)
Consultant
Department of Intensive Care Unit
CIMS Hospital
Ahmedabad, Gujarat, India

Bhalendu Vaishnav MD (General Medicine)
Professor and Head
Department of Medicine
Pramukhswami Medical College and Shree Krishna Hospital
Anand, Gujarat, India

Bharat Jagiasi MD FICCM
Head
Department of Critical Care Medicine
Reliance Hospital
Navi Mumbai, Maharashtra, India

Bharat Parikh MD
Consultant Medical Oncologist
Department of Medical Oncology
Hemato Oncology Clinic
Ahmedabad, Gujarat, India

Bhavini Shah
Director, Microbiology
Director, Academics and Research
Neuberg Supratech Reference Laboratories
Ahmedabad, Gujarat, India

Bhuvna Ahuja
MD (Anesthesiology and Critical Care) FIAPM
Assistant Professor
Department of Neurosurgery and Neurocritical Care
Lok Nayak Hospital
New Delhi, India

Bikram Kumar Gupta
MBBS MD PDCC FACEE EDIC
Head
Department of Critical Care Medicine
Heritage Institute of Medical Sciences
Varanasi, Uttar Pradesh, India

Biren Chauhan
MBBS MHA (Master in Hospital Administration)
Group Chief Operating Officer
Department of Administration
Sunshine Global Hospitals
Surat, Gujarat, India

BK Rao MD (Anesthesia)
Senior Consultant and Chairman
Department of Critical Care and Emergency Medicine
Sir Ganga Ram Hospital
New Delhi, India

Brajendra Lahkar MD (Internal Medicine)
Director
Department of Critical Care Medicine and Internal Medicine
Health City Hospital
Guwahati, Assam, India

Carlos Sanchez MD
Head
Department of Critical Care Services
Hospital General de Quevedo (IESS)
Quevedo, Ecuador

Chandrakanta Singh
Specialist Emergency Medical Officer
Department of Emergency Medicine
Sanjay Gandhi Postgraduate Institute of Medical Sciences
Lucknow, Uttar Pradesh, India

Chandrashish Chakravarty
MD (AIIMS) MRCP (UK) SCE (Respiratory Medicine) (UK) EDIC MNAMS Fellow in CCM (USA)
Consultant
Department of Critical Care Medicine
Apollo Multispecialty Hospital
Kolkata, West Bengal, India

Chirag Matravadia MD (Medicine)
Head
Department of Critical Care Medicine
Wockhardt Hospital
Rajkot, Gujarat, India

Chirag Mehta MD
Senior Consultant Cardiac Anesthetist
EPIC Hospital
Ahmedabad, Gujarat, India

Debasis Pradhan MD IDCCM EDIC EDAIC
Specialty Registrar
Department of Anesthesia
University Hospital of Derby and Burton
Derby, UK

Dedeepiya V Devaprasad
MD DNB EDIC FICCM
Senior Consultant and In-charge
Department of Critical Care Medicine
Apollo Hospitals
Chennai, Tamil Nadu, India

Deeksha Singh Tomar
DA IDCCM IFCCM EDIC
Consultant
Department of Critical Care
Narayana Superspecialty Hospital
Gurugram, Haryana, India

Deepak Govil MD EDIC FICCM FCCM
Director, Critical Care
Institute of Critical Care and Anaesthesia
Medanta—The Medicity
Gurugram, Haryana, India

Deepak Malviya MD (Anesthesiology)
Professor and Head
Department of Anesthesiology and Critical Care Medicine
DR RML Institute of Medical Sciences
Lucknow, Uttar Pradesh, India

Deepak Vijayan MD EDIC MBA
Head and Consultant
KIMS Health
Thiruvananthapuram, Kerala, India

Deepika Jain MD DNB EDAIC IDRA
Assistant Professor
Department of Anesthesia and Intensive Care
GB Pant Hospital
New Delhi, India

Deepu K Peter
MD DNB (Respiratory Medicine)
Assistant Professor
Department of Respiratory Medicine
Command Hospital
(Northern Command)
Udhampur, Jammu and Kashmir, India

Deven Juneja
DNB FNB EDIC FCCP IFCCM FCCM
Director
Department of Institute of Critical Care Medicine
Max Super Speciality Hospital
New Delhi, India

Dhiren Shah MBBS MS MCh
Director CVTS and Heart and Lung Transplantation
CIMS Hospital
Ahmedabad, Gujarat, India

Digvijaysinh Jadeja
MBBS MD (Medicine) EDIC
Senior Consultant Intensivist
Department of Critical Care
Gokul Hospital
Rajkot, Gujarat, India

Dilipbhai Patel

Dipanjan Chatterjee
Senior Consultant
Department of Critical Care, ECMO Services and Cardiac Anesthesia
Medica Superspecialty Hospital
Kolkata, West Bengal, India

Diptimala Agarwal
MBBS DA PGDHA FICCM
Director and Head
Department of Critical Care and Anesthesiology
Shantived Institute of Medical Sciences
Agra, Uttar Pradesh, India

Divya Pal MD IDCCM FNB
Consultant
Department of Critical Care Medicine
Institute of Critical Care and Anaesthesiology
Medanta—The Medicity
Gurugram, Haryana, India

Edward Smith BSc MB ChB FRCA
Department of Critical Care
University Hospital Coventry and Warwickshire
Coventry, UK

Farhad Kapadia MD FRCP DA (UK) EDIC
Consultant
Department of Medicine and Intensive Care
Hinduja Hospital
Mumbai, Maharashtra, India

Fredrik Olsen MD PhD
Department of Anesthesiology and Critical Care
Sahlgrenska University Hospital
Gothenburg, Sweden
Department of Anesthesiology
Section on Critical Care Medicine
Wake Forest School of Medicine
Atrium Health Wake Forest Baptist Medical Center
Winston-Salem, North Carolina, USA

Ganshyam Jagathkar MD FNB FICC
Director
Department of Critical Care
Medicover Hospital
Hyderabad, Telangana, India

Gaurav Pratap Singh DA IDCCM IFCCM
Senior Consultant
Department of Critical Care Medicine
Max Super Specialty Hospital
New Delhi, India

Gauri R Gangakhedkar DA DNB
Assistant Professor
Department of Anesthesiology, Critical Care and Pain
Tata Memorial Centre, Homi Bhabha National Institute
Mumbai, Maharashtra, India

Gautham Raju
MD PDCC (Critical Care Medicine) FNB (Critical Care Medicine) EDICM
Assistant Professor
Department of Critical Care Medicine
St John's Medical College and Hospital
Bengaluru, Karnataka, India

Gavin D Perkins
MD FRCP FFICM FERC F Med Sci
Professor
Department of Critical Care Medicine
Warwick Medical School
University of Warwick
Coventry, England, UK

Geethu Joe MD Microbiology
Consultant Microbiologist
Jupiter Hospital
Pune, Maharashtra, India

Gentle S Shrestha
MD (Anesthesiology) Fellow in Adult Critical Care (University of Toronto) EDIC FCCP FNCS
Associate Professor
Department of Critical Care Medicine
Maharajgunj Medical Campus, Institute of Medicine, Tribhuvan University
Kathmandu, Bagmati, Nepal

Gerald Marín García MD
Attending Physician
Department of Pulmonary and Critical Care Medicine, VA Caribbean Healthcare System
San Juan, Puerto Rico

Girish V Hiregoudar
DNB (Medicine) IDCCM
Consultant Physician and Intensivist
Apple Saraswati Hospital
Kolhapur, Maharashtra, India

Gloria Rodríguez-Vega
MD FACP FCCP FNCS MCCM
Chief
Department of Critical Care Medicine
HIMA San Pablo-Caguas
Caguas, Puerto Rico

Gopal Raval
MB DNB (Respiratory Medicine) DTCD MNAMS EDARM FICCM FCCS (Critical Care)
Consultant Pulmonologist and Critical Care Specialist
Department of Critical Care Medicine
Sterling Hospital and Shilp Chest Disease Centre
Ahmedabad, Gujarat, India

Gunjan Chanchalani
MD IFCCM FNB FICCM EDICM
Chief Intensivist
Department of Critical Care
KJ Somaiya Hospital and Research Centre
Mumbai, Maharashtra, India

Gurpreet S Wander
MBBS MD (Medicine) DM (Cardiology)
Professor and Head
Department of Cardiology
Dayanand Medical College and Hospital
Unit-Hero DMC Heart Institute
Ludhiana, Punjab, India

Gyanendra Agrawal
MD (Internal Medicine) DM (Pulmonary and Critical Care Medicine)
Director
Department of Respiratory and Critical Care Medicine
JAYPEE Hospital
Noida, Uttar Pradesh, India

Haider Abbas MD FRCP
Professor and Head
Department of Emergency Medicine
King George's Medical University
Lucknow, Uttar Pradesh, India

Harendra Thakker
MD DNB FCCP (USA) FCCS (Critical Care)
Senior Consultant
Department of Pulmonary and
Critical Care Medicine
Shalby Multispeciality Hospital
Ahmedabad, Gujarat, India

Harjit Dumra MD (Medicine)
Head
Department of Critical Care Medicine
Sterling Hospital
Ahmedabad, Gujarat, India

Harsh Sapra MBBS DA FRCP
Director
Medanta—The Medicity
Gurugram, Haryana, India

Himanshu Pandya MD (Medicine)
Dean
Professor of Medicine and
Medical Education
Pramukhswami Medical College, Bhaikaka
University
Karamsad, Gujarat, India

Hossam Elshekhali
MBChB (Egypt 2002) Master's degree in Intensive Care Medicine (Egypt 2011) EDIC ESICM 2018
Specialist Critical Care Medicine
Department of ICU
Mediclinic Parkview hospital
Dubai, UAE

HR Rajathadri MD
Senior Resident
(DM Critical Care Medicine)
Department of Anesthesiology, Pain
Medicine and Critical Care
All India Institute of Medical Sciences
New Delhi, India

Jagannath Jare DNB FNB EDIC(I)
Associate Consultant
Department of Critical Care Medicine
PD Hinduja Hospital
Mumbai, Maharashtra, India

Janarthanan S
MD (Anesthesiology), Fell. Onco Crit Care IDCCM IFCCM EDIC
Assistant Professor
Department of Critical Care
Sri Ramachandra Medical Centre and
Sri Ramachandra Institute of Higher
Education and Research
Chennai, Tamil Nadu, India

Jasbir Singh Chhabra
MBBS MD FRCA DICM (UK)
Consultant, Department of Intensive Care
Lancashire Teaching Hospitals NHS Trust
Preston, Lancashire, UK

Javier Perez-Fernandez MD FCCM FCCP
General Manager, Intensive Care Solutions
Department of Critical Care Services
Baptist Hospital of Miami
Miami, Florida, USA

Jay Kothari MD FNB
Consultant and Head
Department of Critical Care
Apollo Hospital International Ltd
Gandhinagar, Gujarat, India

Jay Prakash
Assistant Professor
Department of Critical Care Medicine
Rajendra Institute of Medical Sciences
Ranchi, Jharkhand, India

Jeetendra Sharma
MD IDCCM IFCCM FICCM
Chief, Critical Care Medicine and Chief,
Medical Quality, Artemis Hospital
Gurugram, Haryana, India

Jerry P Nolan FRCA
Professor
School of Clinical Sciences
University of Bristol, Bristol, UK
Consultant
Department of Anesthesia and Intensive
Care Medicine
Royal United Hospital Bath, UK

Jigar Mehta MD
Director
Department of Critical Care Service
KD Hospital
Ahmedabad, Gujarat, India

Jigeeshu V Divatia MD FCCM FICCM
Professor and Head
Department of Anesthesiology, Critical Care
and Pain
Tata Memorial Centre, Homi Bhabha
National Institute
Mumbai, Maharashtra, India

Jignesh Shah MD DNB IFCCM EDIC
Professor
Department of Critical Care Medicine
Bharati Vidyapeeth (Deemed to be
University) Medical College
Pune, Maharashtra, India

Jothydev Kesavade MD
Chairman and Managing Director
Jothydev's Diabetes and Research Centre
Thiruvananthapuram, Kerala, India

Juhi Chandwani
MD DA DNB FFARCSI EDIC EPGDHA
Senior Consultant
Department of Anesthesia and Critical Care
Royal Hospital
Bowsher, Muscat, Oman

Justin A Gopaldas
MBBS DNB (Internal Medicine) MRCP
Consultant Intensivist
Department of Critical Care Medicine
Manipal Hospitals
Bengaluru, Karnataka, India

JV Peter
MD DNB FAMS FRACP FJFICM FCICM FICCM
FRCP (Edin) MPhil
Professor
Medical Intensive Care Unit
Christian Medical College
Vellore, Tamil Nadu, India

K Subba Reddy
MD PDCC IDCCM IFCCM EDIC
Head
Department of Critical Care Medicine
Apollo Health City
Hyderabad, Telangana, India

K Swarna Deepak
MBBS MD (Internal Medicine) MRCP (UK) EDIC (Denmark) IDCCM IFCCM
Consultant
Department of Intensive Care Medicine
Lead Consultant
Infectious Diseases ICU, ApoKOS
Associate Professor, Internal Medicine
Apollo Health City
Apollo Institute of Medical Sciences and
Research
Hyderabad, Telangana, India

Kalpana Jain MD
Senior Consultant Cardiac Anesthesiologist
Epic Hospital
Ahmedabad, Gujarat, India

Kalpana Krishnareddy MBBS FRCA EDIC
Head and Adjunct Clinical Professor
Department of Critical Care
Mediclinic Parkview Hospital
Al Barsha, Dubai, UAE

Kalpesh Shah MBBS MD (Anesthesia)
Director and Founder
Aarogyam Post-ICU Clinic
Ahmedabad, Gujarat, India

Kamal Maheshwari MD MPH
Anesthesiologist
Department of Outcomes Research
Cleveland Clinic
Cleveland, Ohio, USA

Kanwalpreet Sodhi DA DNB IDCCM EDIC
Director and Head
Department of Critical Care
Deep Hospital
Ludhiana, Punjab, India

Kapil Borawake
DNB (Medicine) IDCCM FICCM
Director
Department of Intensive Care and General Medicine
Vishwaraj Hospital and Research Centre
Pune, Maharashtra, India

Kapil Zirpe MD (Chest) FCCM FICCM
Head
Department of Neuro Critical Care
Ruby Hall Clinic, Grant Medical Foundation
Pune, Maharashtra, India

Khalid Khatib MD (Medicine) FICCM FICP
Professor
Department of Medicine
SKN Medical College
Pune, Maharashtra, India

Khusrav Bajan MD EDIC
Consultant Physician and Intensivist
Department of Medicine and Critical Care
PD Hinduja Hospital
Mumbai, Maharashtra, India

KR Balakrishnan MS MCh
Director
Institute of Heart and Lung Transplant and Mechanical Circulatory Support
Chennai, Tamil Nadu, India

Krunalkumar Patel
MBBS MD IDCCM FIECMO
Consultant Intensivist
Department of Critical Care
Sunshine Global Hospital
Surat, Gujarat, India

Kunal Punamiya MBBS MHA
Chief Executive Officer
Department of Administration
SL Raheja Hospital
Mumbai, Maharashtra, India

Kunal Sahai MBBS MD FICP FIMACGP
Awarded Honorary Professor IMA
Associate Professor
Department of Medicine
Narayana Medical College
Kanpur, Uttar Pradesh, India

Kushal Rajeev Kalvit
Senior Registrar
Division of Critical Care Medicine
Department of Anesthesiology, Critical Care and Pain
Tata Memorial Hospital, Homi Bhabha National Institute
Mumbai, Maharashtra, India

Lalit Gupta MBBS DA DNB MNAMS
Associate Professor
Department of Anesthesia
Maulana Azad Medical College
New Delhi, India

Lalit Mishra MBBS MD FCCM
Consultant Chest Physician
Kailash Hospital, Noida, Uttar Pradesh
Former Consultant, Apollo Hospital, New Delhi, India

Lalit Singh MD FICCM
Professor and Head
Department of Respiratory and Critical Care Medicine
Shri Ram Murti Smark Institute of Medical Sciences
Bareilly, Uttar Pradesh, India

Lalit Takia MD DM (Pediatric Critical Care)
Assistant Professor
Department of Pediatrics
Atal Bihari Vajpayee Institute of Medical Sciences and
Ram Manohar Lohia Hospital
New Delhi, India

Lalita Gouri Mitra
DA MD DNB MNAMS (Anesthesia)
Professor and Officer In-charge
Department of Anesthesia, Critical Care and Pain
Homi Bhabha Cancer Hospital and Research Centre
Mullanpur, Chandigarh, India

Lilanthi Subasinghe
MBBS MD MRCP (UK) EDIC
Consultant
Department of Neurotrauma Centre
Intensive Care Unit
National Hospital of Sri Lanka
Colombo, Sri Lanka

Lokendra Gupta
MD FNB (CCM) MRCEM (UK)
Medanta Hospital
Lucknow, Uttar Pradesh, India

Luis A Vázquez Zubillaga MD
Fellow, Critical Care Medicine
Department of Pulmonary and Critical Care Medicine
VA Caribbean Healthcare System
San Juan, Puerto Rico

Maharshi Desai MD FNB
Consultant Critical Care
Department of Critical Care
Apollo Hospital International Ltd
Gandhinagar, Gujarat, India

Mahfouz Sharapi MBBS FCAI
Department of Anesthesia
Beaumont Hospital, RCSI
Dublin, Ireland

Manasi Shahane
DNB (General Medicine) FNB (Critical Care Medicine)
Associate Consultant
Department of Critical Care and Emergency Medicine
Deenanath Mangeshkar Hospital and Research Center
Pune, Maharashtra, India

Manish Bharti
EDIC FNB CCM MD DA MBA (HCA)
Senior Consultant and Intensivist
Department of Critical Care Medicine
Sharda School of Medical Sciences and Research, Sharda University
Greater Noida, Uttar Pradesh, India

Manish Munjal MD FICCM FCCM
Medical Director
Manglam Medicity Hospital
Jaipur, Rajasthan, India

Manoj Edirisooriya
MBBS MD MRCP (UK) EDIC
Consultant Intensivist
Department of Critical Care
Lyell McEwin Hospital
Elizabeth Vale, SA, Australia

Manoj Goel MD
Director
Department of Pulmonology, Critical Care and Sleep
Fortis Memorial Research Institute
Gurugram, Haryana, India

Manoj Kumar Rai MD (Medicine)
Senior Consultant and Head
Apollo Hospitals
Bilaspur, Chhattisgarh, India

Manoj Singh
MD DNB (Chest) FNB EDIC FICCM
Consultant Chest and Critical Care
Department of Respiratory, Critical Care and Sleep Medicine
Apollo Hospital International Ltd
Gandhinagar, Gujarat, India

Mansi Dandnaik MD IDCCM EDICM
Consultant Critical Care Specialist
Department of Critical Care
Sterling Hospital
Ahmedabad, Gujarat, India

Mayank Vats
MD DNB FNB MRCP FRCP FACP FCCP
Pulmonologist, Critical Care Physician
Rashid Hospital
Rajasthan, India

Meghena Mathew
Consultant
Department of Critical Care Medicine
Apollo First Med Hospital
Chennai, Tamil Nadu, India

Minesh Mehta
MD (Medicine) FNB (Critical Care Medicine)
Senior Physician and Intensivist
Department of Intensive Care Unit
Shalby Hospital
Ahmedabad, Gujarat, India

Mohan Maharaj
MD (Anesthesia) PDCC IDCCM MBA
Head
Department of Anesthesia and Critical Care
CARE Multi-Specialty Hospital and Trauma Centre
Visakhapatnam, Andhra Pradesh, India

Monika Gulati
MD (Anesthesia) FCICM (Australia and New Zealand)
Senior Consultant
Department of Intensive Care Medicine
Ng Teng Fong General Hospital
National University Health System (NUHS)
Singapore

Mradul Daga
MD MSc (Infectious Disease)
Professor
Department of Internal Medicine and Infectious Disease
Institute of Liver and Biliary Sciences
New Delhi, India

Mrinal Sircar
MD DNB DTCD EDIC EDARM
Director
Department of Pulmonology and Critical Care
Fortis Hospital
Noida, Uttar Pradesh, India

Mritunjay Kumar
MD DNB MNAMS FIACTA DHM
Assistant Professor
Department of Anesthesiology, Pain Medicine and Critical Care
All India Institute of Medical Sciences
New Delhi, India

Mukesh Patel MD (Chest)
Pulmonologist and Critical Care Specialist
Sterling Hospital
Ahmedabad, Gujarat, India

Mukul Misra MD DM (Cardiology)
Ex-Professor and Head
Department of Cardiology
Dr Ram Manohar Lohia Institute of Medical Sciences, Lucknow
Director
Department of Cardiology
Chandan Hospital Limited
Lucknow, Uttar Pradesh, India

Muralidhar Kanchi
MD FIACTA FICA MBA FASE PhD
Director (Academic), Senior Consultant and Professor
Department of Cardiac Anesthesia and Critical Care
Narayana Institute of Cardiac Sciences, Narayana Health
Bengaluru, Karnataka, India

Nagarajan Ganapathy
MD DA (Anesthesiology)
Director
Department of Critical Care
Dhanvantri Institute of Medical Education and Research
Erode, Tamil Nadu, India

Nagarajan Ramakrishnan
AB (Internal Medicine, Critical Care, Sleep Medicine) MMM FACP FCCM FICCM FISDA
Master's Degree in Medical Management (MMM)
Senior Consultant and Director
Department of Critical Care Services
Apollo Hospitals
Chennai, Tamil Nadu, India

Naman Shastri MD FASE FTEE
Chief Consultant Cardiac Anesthesiologist and Intensivist
EPIC Hospital
Ahmedabad, Gujarat, India

Narendra Rungta MD FCCM FICCM FISCCM
Chairman and Managing Trustee
Critical Care Foundation
Jaipur, Rajasthan, India

Neeraj Yadav MBBS DNB
Consultant
Department of Anesthesiology, Critical Care, and Medicine
Regency Superspeciality Hospital
Lucknow, Uttar Pradesh, India

Neeru Gaur DA DNB IDCCM
Consultant
Department of Critical care
Rajasthan Hospital
Jaipur, Rajasthan, India

Nikhil Kothari MD (Anesthesia) PhD MAMS
Additional Professor
Department of Anesthesiology and Critical Care
All India Institute of Medical Sciences
Jodhpur, Rajasthan, India

Nikhilesh Jain
DNB (Med) MRCPI PDCC (Critical Care) FCCCM FIECMO
Director and Operational Head
Department of Critical Care Services
CHL Hospitals
Indore, Madhya Pradesh, India

Niraj Tyagi MBBS EDIC
Attending Consultant
Department of Critical Care and Emergency Medicine
Sir Ganga Ram Hospital
New Delhi, India

Niren Bhavsar MD
Consultant and Cardiothoracic Transplant Anesthetist
Department of Cardiothoracic Anesthesiology
CIMS Hospital
Ahmedabad, Gujarat, India

Nirmal Jaiswal MD (Med) FCCS
Chief Intensivist and ICU Director
Teacher IDCCM
Suretech Hospital and Research Center
Wockhardt Multispeciality Hospital
Nagpur, Maharashtra, India

Nitin Arora FRCA FRCP (Edin) DICM FFICM
Consultant Intensivist
Heartlands and Good Hope Hospitals
University Hospitals Birmingham
NHS Foundation Trust, UK

Nitin Rai MD DM
Assistant Professor
Department of Critical Care Medicine
King George Medical University
Lucknow, Uttar Pradesh, India

Om P Sanjeev
Assistant Professor
Department of Emergency Medicine
Sanjay Gandhi Post Graduate Institute of Medical Sciences
Lucknow, Uttar Pradesh, India

Pablo Santillan
Anesthesiologist
Francisco Hernandez N35-50 y America

Palepu B Gopal MD FRCA CCST FCCM FICCM
Consultant and Head
Department of Critical Care Medicine
Continental Hospitals
Hyderabad, Telangana, India

Pankaj Anand MD IDCCM FCCP
Senior Consultant
Department of Critical Care
Fortis Escorts Hospital
Jaipur, Rajasthan, India

Paola Perez BAChM MD
Department of Medical School
University of Virginia
Charlottesville, Virginia, USA

Parikshit S Prayag MBBS MD ABIM ABMS
Consultant
Department of Infectious Diseases
Deenanath Mangeshkar Hospital and Research Center
Pune, Maharashtra, India

Patrick M Wieruszewski PharmD
Departments of Anesthesiology and Pharmacy
Mayo Clinic
Rochester, Minnesota, USA

Payel Bose
MD (Anesthesiology) FNB (Critical Care Medicine) EDIC SCE Acute Medicine (UK) IDCCM IFCCM
Senior Consultant
Department of Critical Care Medicine
Medica Superspecialty Hospital
Kolkata, West Bengal, India

Piyush Mathur MD FCCM FASA
Staff Anesthesiologist and Critical Care Physician
Department of General Anesthesiology
Anesthesiology Institute
Cleveland Clinic, Cleveland, Ohio, USA

Poonam Malhotra Kapoor
MD DNB MNAMS FIACTA FTEE
Professor
Department of Cardiac Anesthesia
Cardio-Thoracic Center
All India Institute of Medical Sciences
New Delhi, India

Prachee Makashir
MD (Medicine) DNB (Medicine) IDCCM
Professor
Bharati Vidyapeeth (DTU) Medical College Hospital and Research Centre
Pune, Maharashtra, India

Prachee Sathe MD FRCP FCCCM
Director
Department of Critical Care Medicine
Ruby Hall Clinic, Pune
Hon Professor
Department of Critical Care Medicine
DY Patil Medical College
Pune, Maharashtra, India

Pradeep Bhatia MD FICCM FICA
Professor and Head
Department of Anesthesiology and Critical care
All India Institute of Medical Sciences
Jodhpur, Rajasthan, India

Pradip Bhattacharya MD
Professor and Head
Department of Critical Care Medicine
Rajendra Institute of Medical Sciences
Ranchi, Jharkhand, India

Pradeep M D'Costa
DNB (Gen Med) Certificate in Critical Care (ISCCM)
ICU In-charge
KEM Hospital
Intensivist, Sahyadri Hospital
Pune, Maharashtra, India

Pradeep Rangappa
DNB (Int Med) FJFICM EDIC FCICM PGDipECHO MBA (HCS) FICCM PGDMLE (NLSUI)
Consultant Intensive Care Physician
Manipal Hospital
Yeshwantpur, Bengaluru, Karnataka, India

Pradeep Reddy Pakanati MD IDCC
Consultant
Department of Critical Care
Medicover Hospital
Hyderabad, Telangana, India

Pragyan Routray
MD (Internal Medicine) IDCCM
Consultant and Head
Department of Critical Care
CARE Hospitals
Bhubaneswar, Odisha, India

Prakash Deb
MD DA DNB EDAIC (UK) IDCCM PDF (Critical Care Medicine)
Assistant Professor
Department of Anesthesia, Critical Care and Pain
North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS)
Shillong, Meghalaya, India

Prakash Jiandani MD (Medicine)
Chief Intensivist
Department of Critical Care
Lilavati Hospital and Research Centre
Mumbai, Maharashtra, India

Prakash KC
MD (General Medicine) DNB (Nephrology)
Senior Consultant Nephrologist
Department of Nephrology
Apollo Hospitals
Chennai, Tamil Nadu, India

Prakash Shastri MD FRCA FICCM
Vice Chairman and Senior Consultant
Department of Institute of Critical Care Medicine
Sir Ganga Ram Hospital
New Delhi, India

Pranay Oza BHMS
ECMO Co-Director
Department of Cardiology and Critical Care and ECMO Services
Riddhi Vinayak Critical Care and Cardiac Center (RVCC)
Mumbai, Maharashtra, India

Prasad Rajhans
MD (anesthesia) FICCM FCCM (USA)
Chief Intensivist
Department of Critical Care and Emergency Medicine
Deenanath Mangeshkar Hospital and Research Center
Pune, Maharashtra, India

Prasanna Kumar Mishra MD
Consultant
Department of Anesthesia and Critical Care
Ashwini Hospital
Cuttack, Odisha, India

Prashant Nasa
MD FNB (Critical Care Medicine) EDICM SCE-Acute Medicine
Head
Department of Critical Care Medicine
NMC Specialty Hospital
Dubai, UAE

Pratibha Dileep MD (Medicine)
Head
Department of Critical Care Medicine
Zydus Hospital
Ahmedabad, Gujarat, India

Praveen Kumar MD FNB EDIC
Associate Staff Physician
Department of Critical Care Medicine
Critical Care Institute, Cleveland Clinic
Abu Dhabi, UAE

Prithwis Bhattacharyya MD PDCC
Professor and Head
Department of Critical Care Medicine
Pacific Medical College and Hospital
Udaipur, Rajasthan, India

Priyanka H Chhabra
MD DNB (Anesthesia & Critical Care Medicine)
Associate Professor
VMMC and Safdarjung Hospital and Safdarjung Hospital
New Delhi, India

Priyanka Singhani MD DNB
Associate Professor
Safdarjung Hospital
New Delhi, India

Purushotham Godavarthy
DNB (Anesthesiology) IDCCM
Consultant ICU
Department of Anesthesiology and Critical Care
Command Hospital
Chandigarh, India

Quirino Piacevoli MD PhD
Professor and Head
Department of Anesthesia and Intensive Care
San Filippo Neri Hospital
Rome, Italy

Rachit Patel
MBBS DA IDCCM EDIC FCCU PhD (Medicine)
Consultant
Department of Critical Care, Pulmonology and Medicine
Shree Krishna Hospital, Pramukhswami Medical College
Bhaikaka University
Anand, Gujarat, India

Raghu RV MD
Senior Resident
Department of General Medicine
Maulana Azad medical college
New Delhi, India

Rahul Jaiswal MD DM
Director and Senior Surgeon
ReSTORA Care Clinic
Noida, Uttar Pradesh, India

Rahul Pandit
MD FJFICM FCICM FCCP EDIC IFCCM DA
Director
Department of Critical Care Medicine
Fortis Hospital
Mumbai, Maharashtra, India

Rajeev A Annigeri MBBS MD DNB CFN
Senior Consultant Nephrologist
Department of Nephrology
Apollo Hospitals
Chennai, Tamil Nadu, India

Rajeev Kumar Bansal
MD DNB (Gastroenterology)
Consultant Gastroenterologist and Hepatologist
Salus Hospital
Rajkot, Gujarat, India

Rajeev Soman MD FIDSA
Consultant Infectious Diseases
Jupiter Hospital
Pune, Maharashtra, India

Rajendra P Mathur
MD (Medicine) DM (Nephrology)
Consulatant Nephrologist
Institute of Liver and Biliary Sciences
New Delhi, India

Raj Raval MD IFCCM
ICU and Emergency Services
SAL Hospital
Ahmedabad, Gujarat, India

Rajesh Chawla MD FCCM FCCP
Senior Consultant
Department of Respiratory Medicine and Critical Care
Indraprastha Apollo Hospitals
New Delhi, India

Rajesh Kumar Pande
MD PDCC FICCM FCCM
Senior Director and Head
Department of Critical Care Medicine
BLK-Max Super Specialty Hospital
New Delhi, India

Rajesh Maniar MD DPM
Director
GIPS Hospital
Ahmedabad, Gujarat, India

Raju Shakya MD IDCCM IFCCM
Fellow, Critical Care Medicine
Department of Critical Care
Indraprastha Apollo Hospitals
New Delhi, India

Rakesh Garg
MD DNB FICCM FICA PGCCHM MNAMS CCEPC FIMSA Fellowship in Palliative Medicine
Additional Professor
Department of Onco-Anesthesiology and Palliative Medicine
Dr BR Ambedkar Institute Rotary Cancer Hospital
All India Institute of Medical Sciences
New Delhi, India

Rakhee Baruah MD IDCCM
Senior Consultant
Department of Critical Care Medicine
Health City Hospital
Guwahati, Assam, India

Ram E Rajagopalan
AB (Internal Medicine) AB (Critical Care)
Professor and Head (Clinical Services)
Department of Critical Care Medicine
Sri Ramachandra Medical Centre and
Sri Ramachandra Institute of Higher Education and Research
Chennai, Tamil Nadu, India

Ramanathan Kollengode
MD DNB (Anes) DNB (Cardiac Anes) MNAMS FCICM FCCP Dip Echo
Director, ICU fellowship Programme
Cardiothoracic Intensive Care Unit
National University Heart Centre
Singapore

Ramesh Venkataraman
AB (Internal Medicine) AB (Critical Care Medicine) FCCM FICCM
Senior Consultant
Department of Critical Care Medicine
Apollo Hospitals
Chennai, Tamil Nadu, India

Ranajit Chatterjee
MBBS MRCPI EDICM DA (Gold Medal)
In-charge Intensive Care
Swami Dayanand Hospital
New Delhi, India

Ranvir Tyagi MD FICCM FCCM
Director
Department of Anesthesia and Critical Care
Synergy Plus Hospital
Agra, Uttar Pradesh, India

Ratender K Singh
MD (Medicine) PDCC (Critical Care Medicine) FICCM FACEE
Head
Department of Emergency Medicine
Sanjay Gandhi Post Graduate Institute of Medical Sciences
Lucknow, Uttar Pradesh, India

Ravi Jain
MD (Anesthesia) FNB (Critical Care Medicine)
Assistant Professor
Department of Critical Care Medicine
Mahatma Gandhi University of Medical Sciences and Technology
Jaipur, Rajasthan, India

Raymond Dominic Savio
MD DM EDIC FICCM
Lead Consultant
Department of Critical Care
Apollo Proton Cancer Centre
Chennai, Tamil Nadu, India

Reena Shah MBBS MRCP MSc (ID) FRCP
Associate Professor
Head of Infectious Diseases
Aga Khan University Hospital
Nairobi, Kenya

Reena Sharma
MD (Medicine) Fellow in Rheumatology
Consultant Rheumatologist
Swastik Rheumatology Clinic
Ahmedabad, Gujarat, India

Rekha Das MD FCCS Trainer
Professor and Head
Department of Anesthesia, Critical Care and Pain
Acharya Harihar Post Graduate Institute of Cancer
Cuttack, Odisha, India

Reshu Gupta Khanikar MBBS DA IDCCM
Senior Consultant and Head
Department of Critical Care Medicine
Health City Hospital
Guwahati, Assam, India

Revathi Aiyer
MD DNB (Medicine) IFCCM EDIC
Director
Department of Medical and Surgical ICU
Sterling Hospitals
Vadodara, Gujarat, India

Ridam Pal B Tech
PHD student
Department of Computational Biology
Indraprastha Institute of Information Technology
New Delhi, India

Ripal Patel Shah MBBS DA IDCCM FCCS
Consultant Intensivist
Critical Care Unit
Zydeus Hospital, Orchid ICU and Hospital
Ahmedabad, Gujarat, India

Ripon Choudhary DA MD
Assistant Professor
Department of Anesthesia and Intensive Care
GB Pant Hospital
New Delhi, India

Ritesh Aggarwal
MBBS DNB IDCC EDIC (Europe)
Principal Consultant
Department of Critical Care Medicine
Max Smart Super Speciality Hospital
New Delhi, India

Ritesh Shah MD IDCCM FICCM FIECMO
Director
Department of Critical Care Unit
Sterling Hospitals
Vadodara, Gujarat, India

Ritika Sharma MD FNB EDIC
Associate Consultant
Department of Critical Care Medicine
PD Hinduja Hospital
Mumbai, Maharashtra, India

Riyan Sukumar Shetty MD
Head of ECLS and Consultant
Pediatric ITU
Narayana Institute of Cardiac Sciences,
Narayana Health
Bengaluru, Karnataka, India

Rohit Aravindakshan Kooloth
MBBS MD(Anesthesiology) EDIC(London) IDCCM, Fellowship in Advanced Intensive Care Medicine (University Hospitals Birmingham, UK)
Consultant
Department of Critical Care
Apollo Specialty Hospital
Chennai, Tamil Nadu, India

Roop Kishen MD FRCA
(Retd) Consultant
Anesthesia and Intensive Care Medicine
Salford Royal NHS Foundation
Trust, Salford
Hon Lecturer (Retired)
Translational Medicine and Neurosciences
University of Manchester
Manchester, UK

Rozil Gandhi
DMRD DNB Fellow in Interventional Radiology
Consultant
Department of Interventional Radiology
Sushrut Hospital
Ahmedabad, Gujarat, India

Ruchira Khasne
MBBS DA DNB IDCCM EDAIC and EDIC
Head
Department of Critical Care Medicine
SMBT Institute of Medical Sciences and Research Center
Nashik, Maharashtra, India

Saad Mahdy MBBS MSce FCAI
Department of Anesthesia
Limerick University Hospital
Ireland

Sabina Regmi
MD (Anesthesiology) DM (Neuroanesthesia)
Consultant
Department of Neurosurgery/ Neuroanesthesia
Lok Nayak Hospital
New Delhi, India

Sachin Gupta
MD IDCCM IFCCM EDIC FCCM FICCM
Director
Department of Critical Care
Narayana Superspeciality Hospital
Gurugram, Haryana, India

Sadik Mohammed MD (Anesthesiology)
Associate Professor
Department of Anesthesiology and Critical Care
All India Institute of Medical Sciences
Jodhpur, Rajasthan, India

Sai Praveen Haranath
MBBS MPH FCCP AB (Int Med) AB (Pulmonary Med) AB (Crit Care)
Senior Consultant
Department of Pulmonary and Critical Care
Apollo Hospitals, Apollo Health city
Hyderabad, Telangana, India

Sai Saran MD IDCCM DM EDIC
Assistant Professor
Department of Critical Care Medicine
King George's Medical University
Lucknow, Uttar Pradesh, India

Sambit Sahu MD
Clinical Director
Department of Critical Care
KIMS Hospitals
Hyderabad, Telangana, India

Sameer Jog
MD (Internal Medicine) IDCCM EDIC
Consultant Intensivist
Department of Critical Care and Emergency Medicine
Deenanath Mangeshkar Hospital and Research Center
Pune, Maharashtra, India

Samir Gami MD
ICU In-charge
Unique Hospital
Surat, Gujarat, India

Samir Patel
MD (Internal Medicine) EDIC MRCP2 (UK)
Administrative Head and Senior Consultant Intensivist
Shree Krishna Hospital, Bhaikaka University
Karamsad, Gujarat, India

Samir Sahu MD FICCM
Director
Department of Critical Care, Pulmonology, Quality and Academics
AMRI Hospitals
Bhubaneswar, Odisha, India

Sandeep Kantor MD FCCM FICCM
Consultant Critical Care
Department of Critical Care Medicine
Royal Hospital
Muscat, Oman

Sanjay Dhanuka MBBS MHA EDIC
Intensivist, Physician and CEO
Eminent Hospitals
Indore, Madhya Pradesh, India

Sanjay N Pandya MD DNB (Nephrology)
Consultant Nephrologist
Department of Nephrology
Samarpan Hospital
Rajkot, Gujarat, India

Sanjay Nihalani
MBBS MD (Anesthesia) IDCCM EDIC
Specialist ICU
Department of ICU
Mediclinic Parkview Hospital
Dubai, UAE

Sanjay Shah
MS (Gen Surgery) DNB (Gen surgery) FNB (Trauma Care)
Head (Emergency Department)
Senior Consultant Trauma Surgeon
Apollo Hospitals
Ahmedabad, Gujarat, India

Sanket Shah MD DM PDF
Consultant Hemato Oncologist and Bone Marrow Transplant Physician
HOC Vedanta
Ahmedabad, Gujarat, India

Santhosh Vilvanathan
MD DM (Cardiac Anesthesia)
Consultant
Institute of Heart and Lung Transplant and Mechanical Circulatory Support
MGM Healthcare
Chennai, Tamil Nadu, India

Saswati Sinha MD (Medicine) IDCCM EDIC
Critical Care Specialist
Department of Critical Care
AMRI Hospitals
Kolkata, West Bengal, India

Satish Deopujari MD DCH MNANS
Director, Shree Clinics
Professor Emeritus
Indira Gandhi Government Medical College and Hospital, Nagpur
Adjunct Professor of Practice (Mechanical Engineering), VNIT, Nagpur
Chairman Academics
Nelson Mother and Child Hospital
Nagpur, Maharashtra, India
Former Chairman National (Pediatric Intensive chapter 1998–2000 India)

Saurabh Debnath
MBBS DNB (Anesthesiology) FNB (Critical Care Medicine) IDCCM FCCM
Senior Consultant
Department of Critical Care Medicine
Peerless Hospitex Hospital
Kolkata, West Bengal, India

Saurabh Pradhan
MD (Anesthesiology & Critical Care) DM (Critical Care Medicine)
Senior Consultant
Department of Critical Care Unit, Anesthesiology and Critical Care
Nepal Medical College and Teaching Hospital
Kathmandu, Nepal

Saurabh Taneja
MD FNB EDICM Exec MBA (HCA)
Consultant
Department of Critical Care Medicine
Sir Ganga Ram Hospital
New Delhi, India

Sauren Panja MD FNBE EDIC FICCM FICP
Head and Senior Consultant
Department of Critical Care Medicine
RN Tagore Hospital
Kolkata, West Bengal, India

Shailender Kumar
DA DNB DM (Neuroanesthesia)
Associate Professor
Department of Anesthesiology Pain Medicine and Critical Care
All India Institute of Medical Sciences
New Delhi, India

Shakya Mohanty DrNB
Trainee
Department of Critical Care Medicine
Artemis Hospital
Gurugram, Haryana, India

Shankha S Sen
MD (Gen Medicine) FACP FICP FIACM FISH FIAMS
Consultant Physician
Chairman, ISCCM, SILIGURI Branch

Sharanya Kumar MD
Anesthetist
Institute of Heart and Lung Transplant
Krishna Institute of Medical Sciences Ltd
Secunderabad, Telangana, India

Sharmili Sinha MD DNB EDIC FICCM PGDHM
Senior Consultant
Department of Critical Care Medicine
Apollo Hospitals
Bhubaneswar, Odisha, India

Sheila Nainan Myatra MD FCCM FICCM
Professor
Department of Anesthesiology, Critical Care and Pain
Tata Memorial Hospital, Homi Bhabha National Institute
Mumbai, Maharashtra, India

Shikha Sachan MD (Anesthesia) IDCCM EDIC
Consultant Critical Care Medicine
Regency Hospital
Kanpur, Uttar Pradesh, India

Shilpa Goyal MD MNAMS
Additional Professor
Department of Anesthesiology and Critical Care
All India Institute of Medical Sciences
Jodhpur, Rajasthan, India

Shivangi Khanna
MD (Anaesthesia), FNB (Critical Care Medicine)
Attending Consultant
Critical Care Medicine
EHCC Hospital
Jaipur, Rajasthan, India

Shivaprakash M Rudramurthy
MD PhD ECMM
Professor and In-charge
Department of Medical Microbiology
Postgraduate Institute of Medical Education and Research
Chandigarh, India

Shrikant Sahasrabudhe
MD (Chest)/IDCCM/TDD
Director and Head
Senior Consultant Pulmonologist and Critical Care Specialist
Department of Pulmonology and Critical Care Medicine
Medicover Hospitals
Aurangabad, Maharashtra, India
Examiner and Teacher for IDCCM /CTCCM

Shrikanth Srinivasan
MD DNB FNB EDIC FICCM
Consultant and Head
Department of Critical Care Medicine
Manipal Hospitals
New Delhi, India

Shweta Chandankhede
MBBS MD IDCCM IFCCM
Consultant
Department of Critical Care Medicine
Care Hospitals
Hyderabad, Telangana, India

Shyamsunder Tipparaju MD PDCC FICCM
Chairman
Galen Health Group
Hyderabad, Telangana, India

Siddharth Chand MD
Senior Resident
Department of Medicine
Maulana Azad Medical College
New Delhi, India

Siddharth Verma MBBS DA IDCCM
Department of Critical Care Unit
Care N Cure Multispeciality Hospital
Bilaspur, Chhattisgarh, India

Sidhaant Nangia
Clinical Fellow
Sidhaashray Health Services
New Delhi, India

Simant Kumar Jha
DA DNB (Anesthesiology) PGDHM FIPM (Pain Fellowship) PDCR Certificate Course in Medical Law and Ethics
Senior Consultant
Department of Critical Care Medicine
PSRI Hospital
New Delhi, India
ATLS Instructor, FCCS Consultant, FCCS OBS Instructor

Simran J Singh
MD FRCP (London) EDIC FICCM
Consultant Intensivist and Physician
PD Hinduja Hospital and Medical Research Centre
Mumbai, Maharashtra, India

Sivakumar MN DA DNB IDCCM EDIC FICCM
Head
Department of Critical Care Medicine
Royal Care Super Speciality Hospital Limited
Coimbatore, Tamil Nadu, India

Smita Sharma MD IDCCM
Senior Consultant
Department of Respiratory and Critical Care Medicine
Jaypee Hospital
Noida, Uttar Pradesh, India

Sree Bhushan Raju
MD DM DNB MNAMS MBA FISN FASN FACP FISOT FIACM
Professor and Unit Head
Department of Nephrology
Nizam's Institute of Medical Sciences
Hyderabad, Telangana, India

Srinath Marreddy MD EDIC
Dr NB Resident
Department of Critical Care and Emergency Medicine
Deenanath Mangeshkar Hospital and Research Center
Pune, Maharashtra, India

Srinivas Samavedam
MD DNB FRCP FNB EDIC DMLE FICCM MBA
Head and Medical Director
Department of Critical Care
Virinchi Hospitals
Hyderabad, Telangana, India

Subhajyoti Ghosh MD PhD
Consultant Diabetologist
Apollo Clinic
Dibrugarh, Assam, India

Subhal Dixit
MD (Med) IDCCM FCCM FICCM FICP
Director
Department of Critical Care
Sanjeevan Hospital
Pune, Maharashtra, India

Subhankar Paul MBBS MD MRCEM
DrNB Resident
Department of Critical Care Medicine
BLK-Max Super Specialty Hospital
New Delhi, India

Subhash Todi MD MRCP
Director
Department of Critical Care
Advanced Medicare and Research Institute
Kolkata, West Bengal, India

Sudhir Khunteta MD FCCM FICCM
Director and Chief Intensivist
Department of Critical Care
Shubh Hospital
Jaipur, Rajasthan, India

Sujata Rege
MBBS DNB Fellowship in Infectious Diseases
Consultant Infectious Diseases
Department of Infectious Diseases
Bharati Vidyapeeth University and Medical College
Bharati Hospital and Research Centre
Pune, Maharashtra, India

Sulagna Bhattacharjee
MD (Anesthesiology) DNB DM (Critical Care)
Assistant Professor
Department of Anesthesiology, Pain Medicine and Critical Care
All India Institute of Medical Sciences
New Delhi, India

Suneel Kumar Garg
MD FNB IFCCM EDIC FICCM FCCP FCCM
Senior Critical Care Physician
Founder and MD
Saiman Healthcare Pvt Ltd
New Delhi, India

Sunil Garg
MD (Medicine) FNB (Critical Care Medicine) EDIC SCE-Acute Medicine
Specialist Physician and Critical Care Specialist
NMC Royal Hospital
Dubai Investments Park, Dubai

Sunil Karanth
MD (Internal Med) FNB (Critical Care Medicine) EDIC FCICM (Aus/NZ)
Chairman of Critical Care Services
Manipal Health Enterprises (P) Ltd
Adjuvant Professor in Critical Care Medicine
Manipal University
Manipal, Karnataka, India

Sunil T Pandya
MD PDCC (Cardiac & Neuro Anesthesia), Post Doctorate Fellow— Obstetric Anesthesia
Chief
Department of Anesthesia, Perioperative Medicine and Critical Care
Anesthesia and Obstetric Critical Care
AIG Hospitals, Gachibowli, Hyderabad
Fernandez Hospitals, Hyderabad
Founder Director
PACCS Health Care Pvt Ltd
Hyderabad, Telangana, India

Suresh Kumar Sundaramurthy
MBBS MD (Anesthesia), DNB (Anesthesia) EDAIC FIPM MNAMS
Consultant
Department of Critical Care
Apollo Proton Cancer Centre
Chennai, Tamil Nadu, India

Suresh Rao KG MD
Co-Director
Institute of Heart and Lung Transplant
MGM Healthcare
Chennai, Tamil Nadu, India

Susruta Bandyopadhyay
MD Dip (Cardiology)
Director
Department of Critical Care
AMRI Hospitals
Kolkata, West Bengal, India

Swagata Tripathy MD DNB IDCC EDIC
Additional Professor and I/C ICU
Department of Anesthesia and Critical Care
All India Institute of Medical Sciences
Bhubaneswar, Odisha, India
Fellow Neuro-anesthesia, Walton Centre, Liverpool

Swati Deepak Parmar
MBBS DNB (Anesthesiology)
Clinical Fellow
Department of Cardiothoracic Intensive Care
National University Hospital
Singapore

Syed Moied Ahmed
MBBS MD PhD FICCM FCCP FICM
Professor
Department of Anesthesiology and Critical Care
Jawaharlal Nehru Medical College
Aligarh Muslim University
Aligarh, Uttar Pradesh, India

Tamanna Bajracharya
MD (Anesthesiology) Fellowship in Intensive Care
Associate Professor
Department of Anesthesia and Critical Care
KIST Medical College and Hospital
Lalitpur, Nepal

Tanima Baronia MD IDCCM
ICU In-charge
Ruby Hall Clinic
Pune, Maharashtra, India

Tanmay Jain MD DNB EDRM IDCCM
Associate Consultant
Department of Critical Care Medicine
Reliance Hospital
Navi Mumbai, Maharashtra, India

Tapas Kumar Sahoo
MD FNB FICCM FCCP EDIC MBA
Senior Consultant and Head
Department of Critical Care Medicine
Medanta Hospital
Ranchi, Jharkhand, India

Tavpritesh Sethi MBBS PhD
Associate Professor
Department of Computational Biology
Indraprastha Institute of Information Technology
New Delhi, India

Tejas Karmata MD (Medicine)
Director and Senior Consultant Intensivist
Department of Critical Care
Gokul Hospital
Rajkot, Gujarat, India
Accredited Teacher ISCCM

Tejash Parikh IDCCM
Intensivist
Zydus Hospital
Ahmedabad, Gujarat, India

Tushar Patel MD
Intensivist and Pulmonologist
Jivandeep Critical Care Unit
Vatsalya Hospital
Rajkot, Gujarat, India

Ujwala Mhatre
DA DNB (Anesthesiology) IFCCM IDCCM
Senior Consultant
Department of Critical Care
Ramkrishna Care Hospital
Raipur, Chhattisgarh, India

Unmil Shah MD DNB
Transplant Pulmonologist
Krishna Institute of Medical Sciences
Malkapur, Maharashtra, India

Vaishali Solao
MD (Medicine) FNB (Critical Care)
Director
Department of Liver and Transplant ICU
Sir HN Reliance Foundation Hospital
Mumbai, Maharashtra, India

Vajrapu Rajendra MBBS MD FNB EDIC
Head
Department of Critical Care Medicine
Aware Gleneagles Global Hospitals
Hyderabad, Telangana, India

Vandana Sinha MD
Director and Head
Department of Critical Care Medicine and Internal Medicine
Ayursundra Superspecialty Hospital
Guwahati, Assam, India

Varun Byrappa MBBS MD DNB FNB EDIC
Associate Professor
Department of Emergency Medicine
Kempegowda Institute of Medical Sciences
Bengaluru, Karnataka, India

Vasant Nagvekar
MD (Medicine) Fellowship in Infectious Diseases
Certificate ASTMH
Consultant
Department of Infectious Diseases
Lilavati and Global Hospital
Mumbai, Maharashtra, India

Venkat Kola MD DNB IDCCM EDIC
Clinical Director
Department of Critical Care Medicine
Yashoda Hospital
Hyderabad, Telangana, India

Venkat S Goyal MD DM (Cardiology)
Consultant Cardiologist
Department of Cardiology
Riddhivinayak Multispeciality Hospital
Mumbai, Maharashtra, India

Vetriselvan P MD (Anes) DM (Critical Care)
Assistant Professor
Department of Critical Care
Sri Ramachandra Medical Centre and Sri Ramachandra Institute of Higher Education and Research
Chennai, Tamil Nadu, India

Vijay Mishra MD FRCA FICCM
Director
Department of Critical Care
Bhagwan Mahavir MEDICA Hospital
Ranchi, Jharkhand, India

Vijay Narain Tyagi
MBBS MD (TB & Respiratory Disease) FCCS FCCP EDARM
Head and Consultant
Department of Pulmonary and Critical Care
Metro Hospitals and Heart Institute
Meerut, Uttar Pradesh, India

Vijil Rahulan
MD FCCP (USA) ABIM (Pulmonary & Critical Care)
Chief of Transplant Pulmonology
Department of Heart and Lung Transplant
Krishna Institute of Medical Sciences
Hyderabad, Telangana, India

Vikas Gulia
MBBS MD EDIC EDAIC MBA (Health)
Consultant
Department of Anesthesia and Critical Care
George Eliot Hospital NHS Trust
Nuneaton, West Midlands, UK

Vikas Kesarwani MD FICM DCH
Senior CMO Hospital and Adjunct Senior Lecturer
Auburn Hospital, Western Sydney Local Health District & University of Notre Dame
NSW, Australia

Vikas Marwah
MD (Resp Med) SCE (Resp Med, UK)
Professor
Department of Pulmonary, Critical Care and Sleep Medicine
Army Institute of Cardio-Thoracic Sciences
Pune, Maharashtra, India

Vikas Sikri DNB IDCCM
HOD Critical Care
Senior Consultant Pulmonary and Sleep Medicine
Department of Pulmonary and Critical Care Medicine
Mohandai Oswal Hospital
Ludhiana, Punjab, India

Vimal Bhardwaj MD FNB EDIC
Consultant Intensivist
Department of Critical Care
Narayana Hrudayalaya
Bengaluru, Karnataka, India

Vinay Singhal MD (Anesthesiology) IDCCM
Additional Director and Head
Department of Critical Care Medicine
Fortis Hospitals
Ludhiana, Punjab, India

Vipul Pranlal Thakkar MD IDCCM
Consultant and Head
Department of Critical Care Medicine
CIMS Hospital
Ahmedabad, Gujarat, India

Vishwesh Mehta MBBS FCCCM
Internal Medicine Specialist
Vishesh Jupiter Hospital
Indore, Madhya Pradesh, India

Vivek Gupta DA DNB (Anesth) FIACTA FICCM
Consultant
Department of Cardiac Anesthesia and Intensive Care
Dayanand Medical College and Hospital
Hero DMC Heart Institute
Ludhiana, Punjab, India

Vivek Kakar MD DNB FRCA MA MSc
Staff Physician and Section Head, Cardiothoracic Critical Care
Department of Critical Care Institute
Critical Care Institute
Cleveland Clinic, Abu Dhabi, UAE

Vivek Nangia MD
Principal Director and Head
Institute of Respiratory, Critical Care and Sleep Medicine
Max Hospital
New Delhi, India

Vivekkumar K Shivhare MD (Pediatrics)
Director and Consultant
Department of Pediatrics
Colours Children Hospital
Nagpur, Maharashtra, India

VVSSD Prasanthi MD IDCCM
Consultant
Department of Critical Care Medicine
Continental Hospital
Hyderabad, Telangana, India

William Rodríguez-Cintrón
MD MACP FCCP FCCM
Chief
Department of Pulmonary and Critical Care Medicine
VA Caribbean Healthcare System
San Juan, Puerto Rico

Yash Javeri MBBS IDCCM FICCM
Head
Department of Anesthesiology, Critical Care and Emergency Medicine
Regency Superspecialty Hospital
Lucknow, Uttar Pradesh, India

Yatin Mehta
MD MNAMS FRCA FAMS FICCM FIACTA FTEE
Chairman
Medanta Institute of Critical Care and Anesthesiology
Adjunct Professor, NBE
President, Sepsis Forum of India, The Simulation Society (TSS)
Past President, ISCCM, IACTA, RSACP, SWAC ELSO
Medanta—The Medicity
Gurugram, Haryana, India

Yatindra Dube MD
Intensivist
Department of Medicine and Critical Care
Suyash Hospital
Nashik, Maharashtra, India

YP Singh MD
Senior Director and Head
Max Super Specialty
Patparganj, New Delhi, India

Foreword

Dear Friends,

As President of the ISCCM (2021–2022), it is my proud privilege to present to you the Critical Care Update 2022, on the occasion of the 28th Annual Conference, CRITICARE–2022 at Ahmedabad.

The COVID-19 pandemic has proven to be the ultimate acid-test for critical care professionals in terms of skill, knowledge, practice and above all improvizations in the face of limitations in resources and staff. Notwithstanding, our doctors rose to the challenge and did a fine job worth commending.

The objective and endeavor of the manual remain to enhance knowledge and strengthen clinical practice in critical care. The manual broadly covers depths of scientific topics over all major organ systems and global current critical care practices. It is styled to serve as a ready bedside reference guide to all practitioners of critical care medicine.

The chapters which are authored on wide evidence-based literature and knowledge, have been meticulously sifted, selected, and edited by experts in the discipline. The manual covers the full spectrum of critical care management and practice with contributions from experts in leading institutes across the country and abroad. The emphasis as always has been both on evidence and experience to make the manual more relevant and impactful to our young and upcoming critical care professionals.

I would like to extend my heartiest regards to the authors and section editors of the manual for their dedication and hard work in bringing together this invaluable reference text. A warm thanks to all members of staff of the ISCCM and M/s Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, who have worked silently.

I hope that this manual benefits intensivists, postgraduate trainees, critical care residents, and all allied critical care professionals in strengthening their concept of critical care medicine, and they, in turn, are able to extend that benefit to the patients for whom they care—the ultimate goal and purpose of the manual.

Deepak Govil
President
ISCCM (2021–2022)

Preface to the Fourth Edition

Critical Care Update 2022 will be the 6th consecutive publication of this series which will be released during the Ahmedabad Annual Congress of Indian Society of Critical Care Medicine in April 2022. This congress will be convened in person after a hiatus of two years. It is indeed commendable that the Society has continued to pursue its traditional academic activities and could bring about this edition of the update book during the pandemic with authors' contributing even when hard pressed with clinical work. The digitization of the editorial process has been the highlight of this edition with manuscript submission, review by section editors and corrections by authors all happening seamlessly on a single platform. This process will certainly improve the content and quality of the journal as will be judged by the readers. The digitization process has also enabled timely publication and increase in number of chapters with new sections such as Applied Physiology, Machine Learning and Artificial Intelligence, Medicolegal and COVID-related issues. Increasing the scope of the update book gives opportunities to induct more contributors increasing the scientific base of the society. Review of chapters by section editors who are experts in the field also maintains quality of the manuscripts submitted. The editorial board has been instrumental in selecting the chapters which are relevant to current clinical practice and will be of help to clinicians and trainees in critical care. We hope you enjoy the congress and happy reading.

Editorial Board
Critical Care Update 2022

Preface to the First Edition

Dear Friends,

New Year Greetings from the Editors of Critical Care Update 2019, the Annual Congress book of ISCCM. The latest edition of Critical Care Update will be released during the Silver Jubilee Conference of ISCCM to be held in Mumbai on 1st February 2019. Similar to previous two editions (2017, 2018) this edition comprises of 101 Chapters divided across 13 Sections with a coverage of all the major subspecialties of critical care. The ratio of chapter distribution is in keeping with the relative scientific work done in the respective field. ISCCM has allocated a substantial space to the Quality, Research and Organizational aspect keeping in mind the growing importance of these often neglected areas of critical care. Most of the chapter topics will be covered during the annual congress and will be a ready reckoner for the attendees. The topics have been carefully selected by the ISCCM National Scientific Committee and the contributors are mostly national and international faculty in the congress. Young talents in the field have been encouraged to contribute to the book and the trend will increase in future.

Best Wishes

Subhash Todi
Subhal Bhalchandra Dixit
Kapil Zirpe
Yatin Mehta

Contents

SECTION 14: Transplant/Organ Donation

SECTION 15: Autoimmune Diseases

SECTION 16: Medicolegal and Ethics

SECTION 17: Quality/ICU Organization

SECTION 20: Extracorporeal Membrane Oxygenation and Extracorporeal Cardiopulmonary Support

SECTION 21: Data Science and Artificial Intelligence

SECTION 22: Research Methodology

SECTION 23: COVID-19 Related Issues

SECTION 1

Applied Physiology

CHAPTER 1

Physiology of Cerebral Blood Flow Autoregulation

Bhuvna Ahuja, Sabina Regmi, Ajay Prajapati

INTRODUCTION

The regulation of cerebral blood flow (CBF) is a complex process. Various studies recently tried to elucidate the physiology of CBF autoregulation. Mainly four mechanisms have been proposed for cerebral flow autoregulation, that is, myogenic, neurogenic, metabolic, and endothelial responses. However, it is critical to distinguish cerebral autoregulation from flow metabolism coupling as well as carbon dioxide reactivity.[1]

With deeper understanding of autoregulation, researchers have developed technologies to measure autoregulatory function in real time. An individualized approach to cerebral perfusion pressure (CPP) target based on patients' distinctive hemodynamics might enhance their outcome in acute brain injury. Autoregulation can be assessed by analyzing the changes in CBF, or it substitutes, because of changes in CPP or mean arterial pressure (MAP).[2,3]

This chapter deals in depth with the mechanism of autoregulation, methods to measure it and its use in various clinical scenarios.

MECHANISM OF AUTOREGULATION

Cerebral Blood Flow Regulation and Physiology (Fig. 1)

Cerebral blood flow is directly proportional to CPP and inversely proportional to cerebrovascular resistance (CVR).

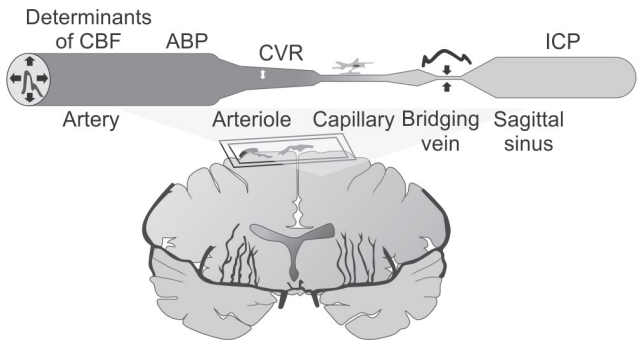


Fig. 1: Diagrammatic representation of regulation of cerebral circulation.

Another concept to explain CPP is via pressure gradient between MAP and cerebral venous pressure, approximately equivalent to intracranial pressure (ICP). **Figure 2** shows the relationship between CBF and MAP. The normal range of MAP is 60–160 mm Hg.

$$CBF = CPP/CVR = (MAP - ICP)/CVR$$

Major contribution to the vascular resistance of the brain is the tone of blood vessels. The smooth muscle tone is moderately influenced by MAP. If CPP increases or decreases, the myogenic reflex will end in vasoconstriction or vasodilation, respectively. This is the classical interpretation of pressure-flow autoregulation. If ICP is stable, CPP and MAP can be used interchangeably. This observation has been exercised to determine changes in brain blood flow for a range of blood pressures (BPs) to determine autoregulation.

Myogenic Response

The myogenic response is produced when arterioles and artery smooth muscle cells contract in response to increased pressure and relaxes in response to decreased pressure.

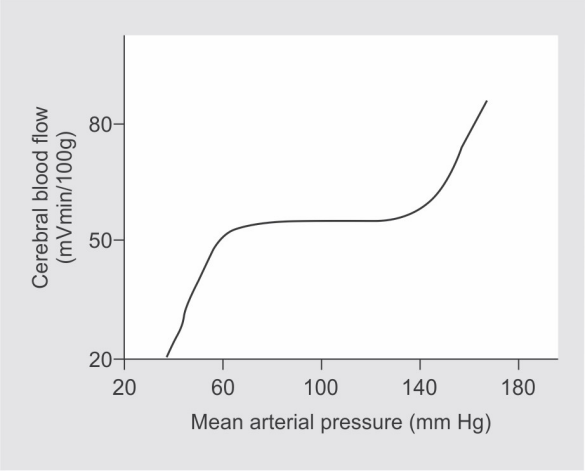


Fig. 2: The relation between cerebral blood flow and mean arterial pressure.

This effect is known as *Bayliss effect*. The myogenic tone is observed in arterioles and in arteries denuded of endothelium. It mainly involves two phenomena: Myogenic tone, which involves partial constriction at constant pressure and myogenic reactivity, in which alteration in tone due to changes in pressure. Also, a third phenomenon is involved called *forced dilatation*. It is a protective phenomenon most likely due to activation of K Ca^{2+} channels in combination with production of reactive oxygen species.

Transmural pressure changes activate mechanically sensitive ion channels and proteins in the vessel wall, triggering various downstream cascades. (R) Increase in pressure causes depolarization of smooth muscle cell membrane followed by opening up of voltage-gated calcium channels and influx of calcium ions. Intracellular calcium activates myosin light chain kinase (MLCK), which activates myosin by phosphorylation. Phosphorylated MLCK increases actin-myosin interaction, causing muscle cell contraction (myogenic tone) and vasoconstriction (myogenic reactivity). With increase in intravascular pressure there may not be significant change in vessel diameter, but further vasoconstriction occurs. The vessel wall stiffens due to enhanced myosin light chain (MLC) phosphorylation and contraction that is further reinforced by actin polymerization.

A rare cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, i.e., CADASIL, is an obvious example of smooth muscle cell myogenic regulation. In CADASIL, patients develop smooth muscle cell degeneration in small cerebral arteries. In CADASIL, mutation in the *NOTCH3* gene is observed and marked by recurrent ischemic strokes, cognitive impairment, subcortical dementia, mood disturbances such as depression, and apathy, as well as premature death.[4]

Neurogenic Response

Neurogenic cerebral vasoreactivity is seen in small and medium size vessels. Neurotransmitters secreted by neurons and other neural cells play a significant role due to their vasoactive properties. Acetylcholine and nitric oxide (NO) are relatively potent vasodilators, while serotonin and neuropeptide Y stimulate vasoconstriction.[5] Infrared videomicroscopy of interneurons and adjacent microvessels in rodents was paramount in displaying that increased depolarizing activity of single cortical interneurons gives rise to precise vasomotor responses in adjoining microvessels.[6]

The transformations in blood flow in response to neuronal activation are discerned as blood oxygen level-dependent (BOLD) signals in functional magnetic resonance imaging (fMRI). The BOLD response has been adapted in many fMRI studies investigating increased cerebral metabolic demand in visual, cognitive, and spatial functioning as well as diseased states of the brain.

There is regional heterogeneity within the brain with anterior circulatory system comprising of denser sympathetic innervation than the posterior circulatory system. The anterior circulation receives sympathetic innervation via the superior cervical ganglion as they run up the carotid artery, whereas the posterior circulation receives its sympathetic innervation via the vertebrobasilar arteries.

In conjunction autoregulation has also exhibited superior efficacy within the brainstem. In one of the studies, it was found that in anesthetized cats with severe hypertension, CBF significantly increased in anterior circulation, whereas there was only moderate increase in CBF in the brainstem.[7] This points to a possible regional inconsistency in cerebral autoregulation within the brain.

Such property may have implications in the development of posterior reversible encephalopathy syndrome (PRES). This syndrome, which incidentally is not always posterior or maybe reversible, is otherwise characterized radiologically by transient bilateral subcortical vasogenic edema within the posterior circulation.[8] Several etiologic theories have been proposed including immunologic dysfunction, vasospasm, and barrier breakdown. One such interesting explanation for the edema's apparent posterior predilection is the relative deficiency of sympathetic tone in the area, resulting in poor autoregulation of blood flow in the setting of abrupt hypertensive episodes.

Metabolic Response

The metabolic response plays a role in autoregulation in small size vessels, wherein local environment causes the changes. Carbon dioxide changes effect vasomotor response, with every 1 mm Hg increase in partial pressure of carbon dioxide, there is 4% increase in CBF.[9] In situation of hypoperfusion due to hypotension below autoregulatory range, partial pressure of cerebral carbon dioxide increases causing vasodilatation and thus anaerobic respiration. The opposite physiology sets in hyperperfusion situation that is decrease in cerebral partial pressure of carbon dioxide, causing vasoconstriction.

One hypothesis states that proton concentration regulation by carbonic anhydrase activity in cerebral vessels smooth muscles plays a role in vasomotor regulation. At severe hypoxemia due to decreased oxygen partial pressures (<50 mm Hg), increase in CBF may occur. Similarly, severe hypoglycemia (<2 mmol/L) may also increase flow to cerebral region.

Endothelial Response

The endothelium produces a variety of signals that affect the vascular tone. NO causes vasodilation, whereas thromboxane A2 and endothelin-1 manufactured at the effect site cause vasoconstriction. Of late, the role of statins has been detected in cerebral autoregulation.

Researchers have recently endeavored the role of statins in autoregulation. Statins can upregulate NO synthase which in turn causes cerebral artery dilatation and further leading to increase in CBF. Rho and Rac, small G proteins are also involved in this mechanism. Rho sends negative feedback to endothelial NO synthase. Statins hinder a process known as geranylgeranylation by inhibiting Rho guanosine triphosphatase (GTPase) activity resulting in the upregulation of NO synthase.

TECHNIQUES TO MEASURE CEREBROVASCULAR AUTOREGULATION (TABLE 1)

The technique assessing the real-time changes in CBF with changes to induce or spontaneous arterial BP fluctuations would be an ideal technique for assessment of cerebrovascular autoregulation. However, measurement of global CBF directly is a challenge.

Therefore, either surrogate of global CBF or regional CBF is measured for the assessment of the cerebrovascular autoregulation. The task of assessing cerebral autoregulation was arduous formerly due to bulky equipment, invasive techniques, and radioactive materials. With the dawn of noninvasive methods such as transcranial Doppler (TCD), assessment of cerebral autoregulation has become simpler.

There are two ways to measure CBF: (1) Static and (2) dynamic.

Static cerebral autoregulation reviews the net adjustment in CBF ensuing the manipulation of CPP during steady state. Phenylephrine test is used for the assessment of static autoregulation. The cerebrovascular reactivity is evaluated in response to manipulation of MAP by the drug. If the CBF varies considerably with either a rise or a fall in arterial BP, cerebral autoregulation is assumed to be impaired.

Dynamic cerebral autoregulation reviews the net adjustment in CBF during rapid changes in BP. In the leg cuff test, the recovery of flow velocity is measured after transient decrease in MAP induced by deflation of a large thigh cuff.

Flow velocity should normalize well within the period of hypotension achieved by cuff deflation before the arterial pressure returns to normalize. The transient hyperemic response test (THRT) utilizes the compression of common carotid artery for 5–8 seconds. The distal cerebrovascular bed dilates in response to decrease in perfusion pressure. When compression is ceased, there is increase in mean flow velocity. This results in transient hyperemia if autoregulation is intact. In more complex methods, fast Fourier transformation (FTT) algorithm is applied to the series of beat-to-beat changes in MAP and mean FV. This is known as the autoregulation index (ARI). An ARI of zero indicates absent autoregulation whereas 9 indicates intact autoregulation. Correlation coefficient between CPP and mean FV is the Mean Index (Mx). Positive coefficient specifies disturbed autoregulation and negative or zero specifies intact autoregulation. The pressure reactivity index (PRx) for the assessment of dynamic autoregulation has gained momentum over the years. It is calculated by correlation analysis of spontaneous waves of MAP and ICP. Positive value indicates disturbed autoregulation. If continuous monitoring of CPP and PRx is performed, plotting CPP against PRx will result in a "U" shaped curve. The optimum CPP (CPPopt) at which there is neither risk of ischemia nor the risk of hyperemia can be found on individual basis. The fourth edition of BTF guidelines recommends 60- and 70-mm Hg CPP for favorable outcome in traumatic brain injury (TBI) patients. Recently, a multicenter randomized controlled trial [CPPopt Guided Therapy: Assessment of Target Effectiveness (COGITATE trial)] tested the feasibility of using CPPopt for patient management in TBI.[10] They included TBI patients in whom CPP was maintained within the range recommended by Brain Trauma Foundation (BTF) guideline in one group and patients where CPP was

TABLE 1: Summary of various methods to assess cerebral autoregulation.

Methods		***Intact autoregulation***	***Impaired autoregulation***
Static	Phenylephrine test %dCVR vs. %dMAP	1	0
Dynamic	Leg cuff test	20%/sec return of FV after drop in MAP	Absent
	Transient hyperemic response test (THRT)	Transient hyperemia (>10%)	Absent
Continuous	Cerebral autoregulation index (ARI) MAP vs. FV	9	0
	Mean index (Mx) CPP vs. FV	0/-ve	+ve
	Pressure reactivity index (PRx) MAP vs. ICP	0/-ve	+ve

(CVR: cerebrovascular reactivity; MAP: mean arterial pressure; FV: flow velocity; CPP: cerebral perfusion pressure; ICP: intracranial pressure, -ve: negative, +ve: positive)

TABLE 2: Summary of changes in cerebral hemodynamic and its effect on prognosis in various diseases.

Conditions	*Changes in cerebral hemodynamics*			*Effect of cerebral hemodynamic parameters on prognosis*		
	Blood flow	*Cerebral autoregulation*	*CO_2 reactivity*	*Blood flow*	*Cerebral autoregulation*	*CO_2 reactivity*
TBI	Initially ↑ Then ↓	↓	↓	Altered flow related to poor outcome	yes	Mostly yes
SAH	↓ due to spasm	↓	↓	Altered	Altered	Altered
Stroke	↓	↓	↓	Altered	Altered	Altered

(CO_2: carbon dioxide; TBI: traumatic brain injury; SAH: subarachnoid hemorrhage; ↓:decrease; ↑: increase)

maintained within the CPPopt derived from the "U"-shaped curve in another group. They concluded that targeting a dynamic optimal CPP six times daily was feasible and safe in TBI patients. They further recommended a phase III outcome study trial that would predict the actual outcome in TBI patients if CPP is maintained at CPPopt values. Any period spent below CPPopt may be detrimental in patients with compromised cerebral autoregulation.[11]

Clinical Significance of Autoregulation

Many recent articles on autoregulation have mentioned significant differences between actual MAP and calculated MAPs.[12] These articles encompass TBI, intracerebral hemorrhage, subarachnoid hemorrhage, ischemic stroke, adult patients undergoing cardiac bypass surgery, children with Moyamoya disease, and neonates with hypoxic-ischemic encephalopathy.[1,13]

Most guidelines recommend, to follow a single, fixed target value for many critically ill patients. American Heart Association (AHA) guidelines recommend systolic BP of <140 mm Hg after intracerebral hemorrhage, systolic pressures <160 mm Hg before aneurysm obliteration and <140 mm Hg after clipping or coiling of the aneurysm following subarachnoid hemorrhage (SAH). AHA also recommends SBP <180 mm Hg after IV recombinant tissue plasminogen activator for large vessel occlusion ischemic stroke.

The recent studies have shown that neurologic patients are well benefitted by use of simpler determination of static autoregulation. For example, patients undergoing carotid endarterectomy, uncontrolled hypertensive patients, and patients with carotid artery stenosis can be managed efficiently if cerebrovascular autoregulation is monitored. **Table 2** shows the alterations in cerebral hemodynamic in various neurocritical conditions.

TRAUMATIC BRAIN INJURY

Traumatic brain injury pathophysiology can be split into two phases:

1. Primary injury: It occurs at the time of ictus.
2. Secondary injury: It occurs in few minutes, days, or weeks following primary injury.

Neuronal injury is caused by a cascade of pathophysiologic events which cause changes in cerebral and systemic physiology, deranged blood glucose metabolism, thermoregulation, respiration, and cerebral circulation. The cerebral circulation is universally compromised after severe TBI; CBF, CO_2 reactivity, and cerebral pressure autoregulation can all be impaired at various stages after TBI.

A combination of low or high CBF and impaired autoregulation have been associated with poor outcome.

In a study conducted by Carmona Suazo et al. wherein parenchymal brain tissue oxygen monitors were used to assess CBF in 90 patients of TBI, it was found that all patients had low CO_2 reactivity on day 1 which it gradually increased over the next 5 days of monitoring. Amazingly, it was also found that CO_2 reactivity on day 5 was higher in those with poor prognosis.

SUBARACHNOID HEMORRHAGE

Severe disturbances of CBF as well as cerebral autoregulation can occur following SAH, which are mostly related to major vessel spasm, but may also be due to dysregulated CBF and other pathological processes, such as cortical spreading depolarizations, acute inflammation, and breach of blood–brain barrier. All of them are related to patient prognosis. In literature it is mentioned that about 60% of SAH shows vasospasm on TCD, accompanied by deranged CBF and cerebrovascular autoregulation. Also 15–30% develop late cerebral ischemia and neurological deficits.

ISCHEMIC STROKE

There is obstruction of arterial lumen by a blood clot in ischemic stroke. This results in a particular territory of brain developing unusually high resistance and low flow. By monitoring the cerebrovascular autoregulation, a propensity for ischemic stroke can be set on; ischemic stroke develops in those patients who develops has impaired CO_2 reactivity. In ischemic stroke, careful consideration of cerebrovascular regulation in the acute phase is of vital importance.[14,15]

In the acute phase of ischemic stroke, patients with the lowest global CBF tend to have worse prognosis,[16] as do those with a greater proportion of penumbral to ischemic tissue.[17]

CONCLUSION

Cerebrovascular autoregulation is a complex process. Though genuine attempt has been made by various studies and trials to understand the mechanism of cerebrovascular autoregulation, deeper analysis is still awaited. With the development of methods to monitor CBF, better therapeutic approaches can be applied to deal with cerebral pathology.

REFERENCES

1. Rivera Lara L, Zorrilla-Vaca A, Geocadin RG, Healy RJ, Ziai W, Mirski MA. Cerebral autoregulation-oriented therapy at the bedside: A comprehensive review. Anesthesilogy. 2017;126(6):1187-99.
2. Wang A, Ortega-Gutierrez S, Petersen NH. Autoregulation in the Neuro ICU. Curr Treat Options Neurol. 2018;20(6):20.
3. Budohoski KP, Czosnyka M, Kirkpatrick PJ, Smielewski P, Steiner LA, Pickard JD, Clinical relevance of cerebral autoregulation following subarachnoid haemmorage. Nat Rev Neurol. 2013;9(3):152-63.
4. Chabriat H, Joutel A, Dichgans M, Tournier-Lasserve E, Bousser MG. Cadasil. Lancet Neurol. 2009;8(7):643-53.
5. Hamel E. Perivascular nerves and the regulation of cerebrovascular tone. J Appl Physiol (1985). 2006;100(3):1059-64.
6. Cauli B, Tong XK, Rancillac A, Serluca N, Lambolez B, Rossier J, et al. Cortical GABA interneurons in neurovascular coupling: relays for subcortical vasoactive pathways. J Neurosci. 2004;24(41):8940-9.
7. Faraci FM, Mayhan WG, Heistad DD. Segmental vascular responses to acute hypertension in cerebrum and brain stem. Am J Physiol. 1987;252(4 Pt 2):H738-42.
8. Tetsuka S, Ogawa T. Posterior reversible encephalopathy syndrome: A review with emphasis on neuroimaging characteristics. J Neurol Sci. 2019;404:72-9.
9. Yoshihara M, Bandoh K, Marmarou A. Cerebrovascular carbon dioxide reactivity assessed by intracranial pressure dynamics in severely head injured patients. J Neurosurg. 1995;82(3):386-93.
10. Beqiri E, Smielewski P, Robba C, Czosnyka M, Cabeleira MT, Tas J, et al. Feasibility of individualised severe traumatic brain injury management using an automated assessment of optimal cerebral perfusion pressure: the COGiTATE phase II study protocol. BMJ Open. 2019;9(9):e030727.
11. Kramer AH, Couillard PL, Zygun DA, Aries MJ, Gallagher CN. Continuous assessment of "optimal" cerebral perfusion pressure in traumatic brain injury: A cohort study of feasibility, reliability, and relation to outcome. Neurocrit Care. 2019;30(1):51-61.
12. Silverman A, Petersen NH. Physiology, Cerebral Autoregulation. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021.
13. Petersen NH, Silverman A, Wang A, Strander S, Kodali S, Matouk C, et al. Association of personalized blood pressure targets with hemorrhagic transformation and functional outcome after endovascular stroke therapy. JAMA Neurol. 2019;76(10):1256-8.
14. Lassen NA. Cerebral blood flow and oxygen consumption in man. Physiol Rev. 1959;39(2):183-238.
15. Donnelly J, Budohoski KP, Smielewski P, Czosnyka M. Regulation of the cerebral circulation: bedside assessment and clinical implications. Crit Care. 2016;20(1):129.
16. Firlik Ad, Rubin G, Yonas H, Wechsler LR. Relation between cerebral blood flow and neurologic deficit resolution in acute ischemic stroke. Neurology.1998;51:177-82.
17. Wintermark M, Reichhart M, Thiran JP, Maeder P, Chalaron M, Schnyder P, et al. Prognostic accuracy of cerebral blood flow measurement by perfusion computed tomography, at the time of emergency room admission, in acute stroke patients. Ann Neurol. 2002;51:417-32.

CHAPTER 2

Hardcore Mathematics in Intensive Care: Alveolar Gas and Shunt Equation

Satish Deopujari, Vivekkumar K Shivhare, Jignesh Shah

INTRODUCTION

Every student of clinical medicine and healthcare professionals come across two important equations of medical science. The equations are the alveolar gas equation and shunt equation. Very few books or articles provide information about the derivation of these equations. Knowing the derivation of equation and its physiological basis gives learners an opportunity to understand the basics and also make a way for modification or redevelopment.[1]

ALVEOLAR GAS EQUATION

The alveolar gas equation uses practically measurable parameters to calculate the partial pressure of oxygen in alveoli. It was first derived in 1946.[2]

Derivation of the alveolar gas equation is based on a few assumptions and Dalton's law as mentioned below.

Assumptions

1. The derivation is done considering the subject is in a steady state.
2. Trace gases such as argon are considered to be inert and as a part of nitrogen.
3. There is a negligible amount of CO_2 in the atmosphere, hence considered absent for calculation purposes. In other words, CO_2 is only expired and not inspired.
4. Through the thin alveolar membrane carbon dioxide is highly diffusible. Hence, $PaCO_2$ and $PACO_2$ will be in close approximation and can be considered as the same (i.e., CO_2 gradient across the alveolar membrane can be considered as zero).[3]
5. For calculation purposes, all gases are considered dry with no humidity.

Dalton's Law of Partial Pressure

Dalton's law of partial pressure states that the total pressure of a mixture of gases is equal to the sum of partial pressure of each individual gas in the mixture, e.g., in a close chamber containing a mixture of gas 1, gas 2, gas 3, and gas 4. The total pressure in the chamber will be equal to the sum of partial pressure of each gas.

$$P_{total} = P_1 + P_2 + P_3 + P_4$$

The partial pressure of each gas can be calculated as follows:

$$\text{Fraction of gas 1 in mixture} = \frac{P_1}{P_{total}}$$

$$P_1 = \text{Fraction of gas 1 in mixture} \times P_{total}$$

where P_{total} stands for total pressure.

Similarly, the equation can be applied to the volume of gas

V_1 (Volume of gas 1) = Fraction of gas 1 in mixture × V_{total} (Total volume of gas)

Fraction of gas 1 = V_1/V_{total}

Applying the above equation for oxygen, we get

Inspired ventilated volume of O_2 = Fraction of inspired O_2 × Inspired alveolar minute ventilation

$$\text{Inspired } O_2 = F_IO_2 \times V_{AI}$$

Expired ventilated volume of O_2 = Fraction of expired O_2 (F_EO_2) × Expired alveolar minute ventilation (V_{AE}). As fraction of expired O_2 (F_EO_2) = Fraction of alveolar O_2 (F_AO_2)

$$\text{Expired } O_2 = F_AO_2 \times V_{AE}$$

In steady-state: Oxygen consumption should be the difference between the inspired volume of oxygen and the expired volume of oxygen.

O_2 consumption (VO_2) = inspired O_2 – expired O_2

$$VO_2 = (F_IO_2 \times V_{AI}) - (F_AO_2 \times V_{AE})$$

The volume of CO_2 production (VCO_2) should be equal to the expired minute ventilation of CO_2.

CO_2 production = Fraction of expired CO_2 × Expired alveolar minute ventilation

$$VCO_2 = F_ECO_2 \times V_{AE}$$

Fraction of alveolar CO_2 (F_ACO_2) =
Fraction of expired CO_2 (F_ECO_2)

$$VCO_2 = F_ACO_2 \times V_{AE}$$

Respiratory quotient:
Respiratory quotient =
Carbon dioxide production/Oxygen consumption

$$RQ = \frac{VCO_2}{VO_2}$$

Applying the above equations for VCO_2 and VO_2, we get

Equation no. 1:

$$RQ = \frac{F_ACO_2 \times V_{AE}}{(F_IO_2 \times XV_{AI}) - (F_AO_2 \times V_{AE})}$$

At RQ of 0.8, for every 10 molecules of O_2 being absorbed by capillary only 8 molecules of CO_2 are released, hence expired alveolar minute ventilation (V_{AE}) must be less than inspired alveolar minute ventilation (V_{AI}).

$$V_{AE} \neq V_{AI}$$

Applying assumption number 3: (There is negligible amount of CO_2 in atmosphere, i.e., = 0). Atmospheric air is a combination of oxygen and nitrogen. Hence,

Inspired alveolar minute ventilation (V_{AI}) =
inspired O_2 + inspired N_2

$$V_{AI} = (F_IO_2 \times V_{AI}) + (F_IN_2 \times V_{AI})$$

Deleting V_{AI} from all sections, we get

$$F_IO_2 + F_IN_2 = 1$$

Equation no. 2:

$$F_IN_2 = 1 - F_IO_2$$

Expiratory alveolar minute ventilation (V_{AE}) = expired O_2 + expired N_2 + expired CO_2

$$V_{AE} = (F_AO_2 \times V_{AE}) + (F_AN_2 \times V_{AE}) + (F_ACO_2 \times V_{AE})$$

Deleting V_{AI} from all sections, we get

$$F_AO_2 + F_AN_2 + F_ACO_2 = 1$$

Equation no. 3:

$$F_AN_2 = 1 - F_AO_2 - F_ACO_2$$

As nitrogen is an inert gas

Alveolar minute ventilation of nitrogen (VN_2) =
Inspired N_2 = Expired N_2

Inspired N_2 =
Fraction of inspired nitrogen (F_IN_2) ×
Inspired alveolar minute ventilation (V_{AI})

$$VN_2 = F_iN_2 \times V_{AI}$$

$$V_{AI} = \frac{VN_2}{F_iN_2}$$

Applying equation no. 2:

$$F_iN_2 = 1 - F_IO_2$$

$$V_{AI} = \frac{VN_2}{(1 - F_iO_2)}$$

Expired N_2 = Fraction of expired nitrogen (F_AN_2) × Expired alveolar minute ventilation (V_{AE})

$$VN_2 = F_AN_2 \times V_{AE}$$

$$V_{AE} = \frac{VN_2}{(F_AN_2)}$$

Applying equation no. 3:

$$F_AN_2 = 1 - F_AO_2 - F_ACO_2$$

$$V_{AE} = \frac{VN_2}{(1 - F_AO_2 - F_ACO_2)}$$

Restarting with equation number 1

$$RQ = \frac{F_ACO_2 \times V_{AE}}{(F_IO_2 \times V_{AI}) - (F_AO_2 \times V_{AE})}$$

(Replacing above equations for V_{AI} and V_{AE})

$$RQ = \frac{F_ACO_2\left(\frac{VN_2}{(1 - F_AO_2 - F_ACO_2)}\right)}{\left[F_IO_2\left(\frac{VN_2}{1 - F_IO_2}\right)\right] - \left[F_AO_2\left(\frac{VN_2}{1 - F_AO_2 - F_ACO_2}\right)\right]}$$

Canceling VN_2

$$RQ = \frac{\frac{F_ACO_2}{1 - F_AO_2 - F_ACO_2}}{\left(\frac{F_IO_2}{1 - F_IO_2}\right) - \left(\frac{F_AO_2}{1 - F_AO_2 - F_ACO_2}\right)}$$

For ease of calculation, let's consider few short forms
RQ = q
F_ACO_2 = c
F_AO_2 = o
F_IO_2 = i
Applying the short form, we get

$$q = \frac{\frac{c}{1 - o - c}}{\left(\frac{i}{1 - i}\right) - \left(\frac{o}{1 - o - c}\right)}$$

$$q.\left[\left(\frac{i}{1 - i}\right) - \left(\frac{o}{1 - o - c}\right)\right] = \left(\frac{c}{1 - o - c}\right)$$

$$q \cdot \left(\frac{i}{1 - i}\right) - q \cdot \left(\frac{c}{1 - o - c}\right) = \left(\frac{c}{1 - o - c}\right)$$

Multiply everything with (1–o–c)

$$q \cdot \left(\frac{i}{1 - i}\right) \cdot (1 - o - c) - q.o = c$$

$$q \cdot \left\{\left[\left(\frac{i}{1 - i}\right) \cdot (1 - o - c)\right] - o\right\} = c$$

$$\left[\left(\frac{i}{1 - i}\right) \cdot (1 - o - c)\right] - o = \frac{c}{q}$$

Divide everything with $\left(\frac{i}{1-i}\right)$

$$1-o-c-\left[o.\left(\frac{1-i}{i}\right)\right]=\left(\frac{c}{q}\right).\left(\frac{1-i}{i}\right)$$

$$1-o-c-\left(\frac{o}{i}\right)+\left(\frac{oi}{i}\right)=\left(\frac{c}{q}\right).\left(\frac{1-i}{i}\right)$$

$$1-o-c-\left(\frac{o}{i}\right)+o=\left(\frac{c}{q}\right).\left(\frac{1-i}{i}\right)$$

$$1-c-\left(\frac{o}{i}\right)=\left(\frac{c}{q}\right).\left(\frac{1-i}{i}\right)$$

Multiply everything with *i*

$$i-i.c-o=\left(\frac{c}{q}\right).(1-i)$$

$$i-i.c-o=\left(\frac{c}{q}\right)-\frac{(i.c)}{q}$$

$$i-o=\left(\frac{c}{q}\right)-\frac{(i.c)}{q}+i.c$$

$$o=i-\left(\frac{c}{q}\right)-\frac{(i.c)}{q}+i.c$$

$$o=i-c.\left(\frac{1}{q}-\frac{i}{q}+i\right)$$

$$o=i-c.\left(\frac{1-i}{q}+i\right)$$

Replacing back the full form we get

$$F_AO_2=F_IO_2-F_ACO_2\times\left(\frac{1-F_IO_2}{RQ}+F_IO_2\right)$$

Rearranging it we get

$$F_AO_2=F_IO_2-F_ACO_2\times\left(F_IO_2+\frac{1-F_IO_2}{RQ}\right)$$

Applying Dalton's law

$$P_AO_2=P_IO_2-P_ACO_2\times\left(F_IO_2+\frac{1-F_IO_2}{RQ}\right)$$

As per assumption no. 5: We considered dry air for calculation

$$P_IO_2=Pb\times F_IO_2$$

(Pb = Atmospheric pressure)

In reality, the air has humidity.

Air has fixed relative humidity at a specific temperature.

At a body temperature of 37°C, water vapor pressure is 47 mm Hg.

Hence,

$$P_IO_2=(Pb-47)\times F_IO_2$$

$$P_AO_2=[(Pb-47)\times F_IO_2]-P_ACO_2\times\left(F_IO_2+\frac{1-F_IO_2}{RQ}\right)$$

As per assumption no. 4: The partial pressure of alveolar CO_2 (P_ACO_2) = Partial pressure of arterial CO_2 ($PaCO_2$)

Equation no. 4:

$$P_AO_2=[(Pb-47)\times F_IO_2]-P_aCO_2\times\left(F_IO_2+\frac{1-F_IO_2}{RQ}\right)$$

Now for clinical utilization, let's evaluate

$$\left(F_IO_2+\frac{1-F_IO_2}{RQ}\right)$$

Rearranging the equation as RQ/RQ = 1

$$=\left(F_IO_2.\frac{RQ}{RQ}+\frac{1-F_IO_2}{RQ}\right)$$

$$=\frac{F_IO_2.RQ+(1-F_IO_2)}{RQ}$$

$$=\frac{1+F_IO_2\times RQ-F_IO_2}{RQ}$$

$$=\frac{1}{RQ}-\left(\frac{F_IO_2-F_IO_2\times RQ}{RQ}\right)$$

$$=\frac{1}{RQ}-F_IO_2.\left(\frac{1-RQ}{RQ}\right)$$

Consider F_IO_2 of 0.21 and RQ of 0.8.

$$F_IO_2.\left(\frac{1-RQ}{RQ}\right)=0.05$$

$$\frac{1}{RQ}-F_IO_2.\left(\frac{1-RQ}{RQ}\right)=1.25-0.05=1.2$$

For the clinical purpose, at F_IO_2 of 0.21, value 0.05 will not affect the integrity of the equation much. Hence for ease of clinical usability

$$\frac{1}{RQ}-\left(F_IO_2+\frac{1-F_IO_2}{RQ}\right)$$

can be replaced with $\frac{1}{RQ}$.

Hence (Equation 4)

$P_AO_2=[(Pb-47)\times F_IO_2]-P_aCO_2\times\left(F_IO_2+\frac{1-F_IO_2}{RQ}\right)$ will become

Equation no. 5:

$$P_AO_2=[(Pb-47)\times F_IO_2)-\frac{P_aCO_2}{RQ}$$

The shortcoming of the equation:

- As F_IO_2 goes above 0.5 the value of $\left[F_IO_2\times\left(\frac{1-RQ}{RQ}\right)\right]$ becomes 0.125.

$$\frac{1}{RQ}-F_IO_2.\left(\frac{1-RQ}{RQ}\right)=1.25-0.125=1.12$$

And as F_IO_2 reached 1, the difference between the value of equations 8 and 9 become significant.

$$\frac{1}{RQ} - F_IO_2 \cdot \left(\frac{1-RQ}{RQ}\right) = 1.25 - 0.25 = 1$$

Let's consider three patients

Name	*$PaCO_2$*	*F_IO_2*	*P_AO_2 by equation 4*	*P_AO_2 by equation 5*	*Difference*
Patient A	40	0.21	102	100	2
Patient B	40	0.5	312	307	5
Patient C	40	1	673	663	10
Patient D	40	0.1	22	21	1

Applied physiology:

- *Relation of partial pressure of alveolar oxygen (PAO_2) with the partial pressure of alveolar (arterial) carbon dioxide ($PaCO_2$)*: Considering other variables such as atmospheric pressure (Pb), a fraction of inspired oxygen (F_IO_2), and RQ as constant, PAO_2 is directly proportional to the negative value of $PaCO_2$.

  $$P_AO_2 \alpha PaCO_2$$

  Hence, as the $PaCO_2$ value increases, PAO_2 value decreases. $PaCO_2 = PACO_2$. Hence, as the alveolar CO_2 level increases, the level of alveolar O_2 should go down.
- *Relation with atmospheric pressure*: Considering other parameters constant, partial pressure of alveolar oxygen (P_AO_2) is directly proportional to atmospheric pressure (Pb).

  $$P_AO_2 \alpha Pb$$

  Hence, as altitude level increases, atmospheric pressure decreases, and as a result, partial pressure of alveolar oxygen decreases.
- *Relation with RQ*: Considering other parameters constant P_AO_2 is inversely related to RQ.

  $$P_AO_2 \alpha \frac{1}{RQ}$$

  Hence, partial pressure of oxygen decreases with an increase in the respiratory quotient. (Note: RQ for fat, protein, and carbohydrate are 0.7, 0.8, and 1.0, respectively).
- *Correlation with a fraction of inspired oxygen (F_IO_2)*: Considering other parameters constant in equation 5, PAO_2 is directly proportional to F_IO_2.

  $$P_AO_2 \alpha F_IO_2$$

Hence partial pressure of oxygen increases with increase in fraction of inspired oxygen.

SHUNT EQUATION

Introduction

Shunt equation is also called as Berggren equation. It was originally described by Sven Berggren in 1942 to determine the oxygen deficit of arterial blood caused by nonventilated parts of lung.[4]

Concept of Shunt and Venous Admixture

Shunt is the blood which enters systemic circulation without participating in gas exchange. Term shunt fraction is used to describe ventilation/perfusion (V/Q) mismatch caused due to percentage of blood flow that is not exposed to inhaled gas.

Venous admixture is the amount of deoxygenated blood from venous circulation which appears to have bypassed lungs, thereby not participating in gas exchange.

Shunt fraction is calculated ratio of venous admixture to total cardiac output.

Shunt and venous admixture are often used interchangeably. However, true shunt is described as V/Q ratio of 0. Venous admixture takes into account contributions from bronchial veins and thebesian veins and alveolar regions with V/Q ratio between 0 and 1.

Classifying Shunt (Table 1)

Qt = Cardiac output (mL/min)
Qs = Pulmonary shunt (mL/min)
Qc = pulmonary capillary blood flow (mL/min)
CcO_2 = End-pulmonary-capillary oxygen content
CaO_2 = Arterial oxygen content
CvO_2 = Mixed venous oxygen content

TABLE 1: Classification of shunt.

Shunt	
Physiological	***Pathological***
• *Anatomical:* – Bronchial veins (<1% of cardiac output) – Thebesian veins (0.12–0.43% of total aortic flow)	• Intrapulmonary shunt (V/Q < 1) • Intracardiac shunts • Pulmonary arteriovenous malformations • Portopulmonary shunts in liver disease
• *Functional*: V/Q mismatch due to lung zones	

(V/Q: ventilation/perfusion)

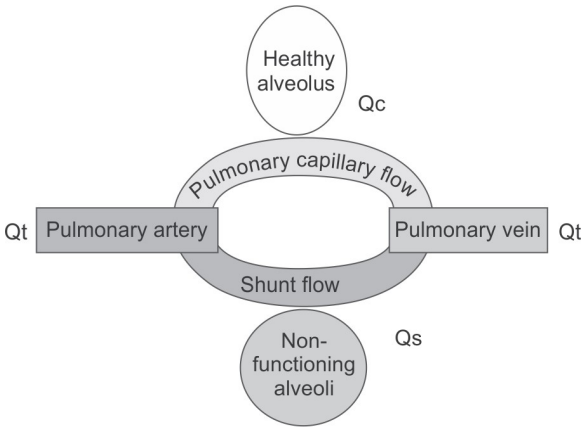


Fig. 1: Represents shunt and flow parameters.

Derivation of Shunt Equation

Conservation of blood flow is given as Qt = Qc + Qs

Whereas total cardiac output is sum of pulmonary capillary blood flow (Qc) and shunt blood flow (Qs).

Oxygen content of blood is given by equation

$$CO_2 = 1.34 \times Hb \times SO_2 + 0.003 \times PO_2$$

CO_2 is oxygen content of blood, 1.34 is oxygen carrying capacity of hemoglobin, SO_2 is oxygen saturation, and PO_2 is partial pressure of oxygen. The fraction ($0.003 \times PO_2$) representing amount dissolved in plasma is negligible and can be ignored in calculations.

Conservation of mass dictates the transport of oxygen through the lungs as is given as below.

$$Qt \times CaO_2 = Qc \times CcO_2 + Qs \times CvO_2$$

Qs is the flow through the shunt fraction, which is returning shunted mixed venous blood back to the systemic arterial circulation.

CaO_2 is the oxygen content of systemic arterial blood. It is measured using arterial blood gas machine. CaO_2 will be lower than the content of pulmonary end capillary blood flow (Qc) as it is mixed with the blood from relatively hypoxic shunt flow (Qs).

CcO_2 is the oxygen content of pulmonary end capillary blood. This fraction of blood is flowing through nonshunted (V/Q = 1) area and is perfectly oxygenated blood. Pulmonary end capillary blood oxygen cannot be measured and is assumed that it is equal to the alveolar oxygen content [CtO_2(A)] as there is no V/Q mismatch. Thus, alveolar oxygen partial pressure can be calculated from alveolar gas equation. The assumption that pulmonary end capillary oxygen content will be same as alveolar oxygen content is based on a two-compartment model, where this nonshunted flow compartment is perfectly oxygenated (i.e., the arterial and alveolar oxygen content is the same).

CvO_2 is the oxygen content of mixed venous blood. It is measured by sampling through pulmonary arterial catheter. As pulmonary artery catheterization is invasive procedure.

(CcO_2 – CvO_2) is the difference in oxygen content between pulmonary end capillary blood and mixed venous blood.

(CcO_2 – CaO_2) is the difference in oxygen content between pulmonary end capillary blood and systemic arterial blood. This drop in oxygen content is due to the venous admixture.

Mathematics of Shunt Equation[5]

$$Qt = Qs + Qc$$

$$Qc = Qt - Qs$$

Adding oxygen content to above equation

$$Qt \times CaO_2 = Qs \times CvO_2 + Qc \times CcO_2$$

Substituting Qc with (Qt – Qc) as derived above

$$Qt \times CaO_2 = Qs \times CvO_2 + (Qt - Qs) \times CcO_2$$

$$Qt \times CaO_2 = Qs \times CvO_2 + Qt \times CcO_2 - Qs \times CcO_2$$

Rearranging

$$Qs \times CcO_2 - Qs \times CvO_2 = Qt \times CcO_2 - Qt \times CaO_2.$$

$$Qs\,(CcO_2 - CvO_2) = Qt\,(CcO_2 - CaO_2)$$

The relationship between the different fractions is a ratio, rather than a real oxygen difference in milliliters. Hence, the shunt fraction is usually represented as Qs/Qt.

$$Qs/Qt = (CcO_2 - CaO_2)/(CcO_2 - CvO_2)$$

Alternative Ways to Estimate Shunt

Isoshunt

Virtual shunt in percentage can be estimated using isoshunt lines nomogram. This nomogram plots alveolar PO_2 (PAO_2) to arterial PO_2 (PaO_2) with assumptions that CvO_2 has a constant value and that partial pressure of carbon dioxide in arterial blood ($PaCO_2$) and hemoglobin are constant. This nomogram-based approach is not applicable in disease states where CvO_2, $PaCO_2$, and hemoglobin are not likely to be in normal ranges.[6]

a/A ratio

a/A ratio is the ratio of partial pressure of oxygen in arterial blood to partial pressure of oxygen in alveolus (representing pulmonary end capillary saturation). a/A ratio is a good measure of shunt only if both PAO_2 and PaO_2 lie along the flat portion of oxygen hemoglobin dissociation curve which correlates to normal lung.

Problems with Shunt Equations

- Assumption CcO_2 is equal to alveolar partial pressure of oxygen.
- Measuring mixed venous oxygen partial pressure and calculating CvO_2 requires pulmonary artery catheterization which is obsolete nowadays being an invasive procedure. Assumption of mixed venous oxygen saturation as 75% will not hold true in disease conditions such as sepsis.
- All shunt calculations use a two-compartment model. However, the lung is a mixture of heterogeneous alveolar units with a varying V/Q ratio. The shunt equation is therefore a very gross estimate of oxygenation defects.

Clinical Application

The effects of shunt on oxygenation: With worsening shunt, arterial oxygenation will decrease proportionately.

The effects of increasing F_IO_2 on shunt: As shunt worsens, increasing F_IO_2 will have minimal effect on improving arterial oxygenation. The Alveolar arterial oxygen gradient (A-a DO_2) will increase. As shunt fraction increases to of 50% or more, increasing the F_IO_2 will have minimal effect on the PaO_2.

The effects of shunt on CO_2 clearance are as follows:

- Shunt has little effect on $PaCO_2$. Compensatory increase in alveolar ventilation associated with hypercapnia will help wash out CO_2. Only in those patients with impaired ability to increase their alveolar ventilation due to obstructive or restrictive lung diseases or as a result of reduced chest wall compliance or neuromuscular weakness, $PaCO_2$ may increase slightly (approximately up to 15–30% with a shunt fraction of 50%).
- Low cardiac output and metabolic acidosis increase the effect of shunt on $PaCO_2$.

REFERENCES

1. Curran-Everett D. A classic learning opportunity from Fenn, Rahn, and Otis (1946): the alveolar gas equation. Adv Physiol Educ. 2006;30(2):58-62.
2. Fenn WO, Rahn H, Otis AB. A theoretical study of the composition of the alveolar air at altitude. Am J Physiol. 1946;146:637-53.
3. Cruickshank S, Hirschauer N. The alveolar gas equation. BJA Educ. 2004;4(1):24-7.
4. Berggren SV. The oxygen deficit of arterial blood caused by non-ventilating parts of the lung. Acta Physiologica Scandinavica. 1942;11:Supplementum 11.
5. Bigeleisen PE. Models of venous admixture. Adv Physiol Educ. 2001;25(3):159-66.
6. Benatar SR, Hewlett AM, Nunn JF. The use of iso-shunt lines for control of oxygen therapy. Br J Anaesth. 1973;45(7): 711-8.

ABBREVIATION

For *alveolar gas equation*

V_E: Expiratory minute ventilation

V_A: Alveolar minute ventilation

V_{AI}: Inspired alveolar minute ventilation

V_{AE}: Expired alveolar minute ventilation

F_{IZ}: Inspired fraction of z gas

F_{EZ}: Expired fraction of z gas (nondead space expiratory alveolar air)

V_D: Dead space minute ventilation

V_T: Tidal volume

V_D: Dead space volume

RR: Respiratory rate

For *shunt equation*,

Qt: Cardiac output (mL/min)

Qs: Pulmonary shunt (mL/min)

Qc: pulmonary capillary blood flow (mL/min)

C_CO_2: End-pulmonary-capillary oxygen content

C_aO_2: Arterial oxygen content

C_VO_2: Mixed venous oxygen content.

CHAPTER 3

Dynamic Airway Collapse and its Clinical Effects

Javier Perez-Fernandez, Arlene Torres, Paola Perez

INTRODUCTION

On the expiratory phase of respiration, the airways and the chest cage are continuously subject to stretching by external forces, elastic recoiling, and the movement of the diaphragm, all of which are influencing the passing of air at maximum flow.

The breathing pattern is determined mostly by pressure gradients and less by mechanical forces. Some areas of the airway are subject to natural dynamic narrowing during normal tidal breathing, specifically those with no cartilaginous structure such as the bronchioles. This phenomenon is better demonstrated at maximum expiratory effort, measured at the peak of the flow–volume curve. As changes in pressure determine the movement of air through the airway, mechanical factors will, sometimes, influence the passage of air and on occasions determine anomalies of the expiratory phase **(Fig. 1)**. Thus, it is of utmost importance to recognize changes in factors affecting ventilation, as they may cue clinicians in identifying a disease process.

Some conditions are associated with an excessive and unnatural narrowing of the airway, determining an obstruction in the airflow, and creating a dynamic airway collapse (DAC). This abnormal closure of the airway is generally associated with a change in the flow–volume pattern on the expiratory limb, and it is also the cause for a variety of clinical manifestations.

In this chapter, we will be addressing some of those manifestations and clinical implications.

DYNAMIC AIRWAY COLLAPSE

Dynamic airway collapse is defined as the pathological narrowing of the airway lumen by 50% or more in the sagittal axis, caused by the collapse of the posterior membrane of the airway during the expiratory phase. The exact degree of the narrowing associated with a clinical significance is subject to discussion as there is evidence of airway collapse with no symptoms. Therefore, some authors have described 70% or more change in airway patency required for the diagnosis.

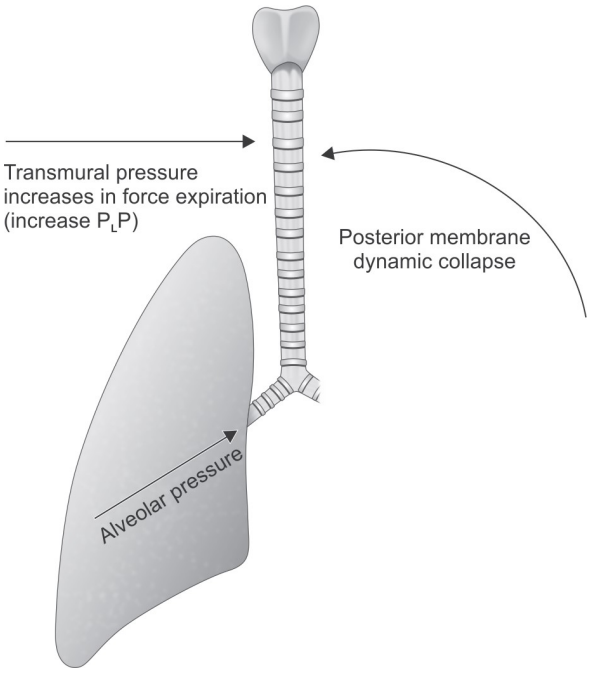


Fig. 1: Mechanical forces determine flow of air at maximum forces. Passing of air through trachea might be limited by narrowing of the posterior membrane (noncartilaginous).
(P_LP: pleural pressure)

Nonetheless, measuring the degree of obstruction becomes useful in guiding different treatment options.

Airway collapse can occur in a variety of diseases. Tracheomalacia is probably the first entity described in its association with airway collapse,[1] a condition resulting from cartilaginous weakening of the tracheal and bronchial walls along with hypotonia of the myoelastic element mostly characterized by an injury resulting in the cartilaginous defect.

The term excessive central airway collapse (ECAC) was later coined to include excessive dynamic closure of the airway (excessive DAC) and tracheobronchomalacia (TBM).[2] The terms DAC, ECAC, or even TBM are used interchangeably in the literature. However, careful consideration should be

given when diagnosing such ailments as tracheomalacia has a poorer prognosis than DAC, and DAC can have better reversible treatment options.[3,4]

Perhaps, the increased diagnostic interest for clinicians to correctly diagnose and treat this condition within the past few years can be presumably attributed to the technological advances in dynamic imaging of the chest and the description of this phenomenon in association with clinical manifestations in otherwise healthy individuals.[5]

PHYSIOLOGY

The collapse of the large airways occurs by the resultant of the increased airway resistance, decreased lung elastic recoil, and increased pleural pressure, all of which naturally occur during the expiratory phase. In the presence of a debilitated smooth muscle, a permanent increase in airflow velocity, or decreased pressure, the muscle surrounding the lumen can become stressed, leading to muscular fatigue, reduced elastic recoil, and greater narrowing of the airway, further resulting in the dynamic collapse of the airway.

Dynamic computed tomography (CT) images have demonstrated invagination of the posterior membrane of the trachea during expiration, a phenomenon previously described by physiologists, which is due to changes in the transmural pressure.[6,7]

ETIOLOGY

The prevalence of DAC or ECAC is unknown but is estimated to be between 13% of the population and more notably seen in patients with chronic obstructive pulmonary disease (COPD) and asthma.[8]

Several conditions have been associated with the presence of DAC. Diseases manifesting with small airway obstruction and decreased expiratory flow such as asthma, COPD, or bronchiectasis are some to consider. Autoimmune diseases with pulmonary manifestations and possible, but rarely, airway involvement such as relapsing polychondritis or Sjögren syndrome have also been associated with DAC. Similarly, trauma can lead to possible impairment of blood supply to vital structures, which eventually weakens the tracheal/bronchial muscle that can spare the lumen. The presence of prior tracheostomy, obesity, or gastroesophageal reflux disease, just to name a few more, has been seen associated with a DAC. In addition, DAC as a diagnosis has indeed recently been associated to the use of inhaled corticosteroids.[9] Chronic inflammatory diseases, prolonged tracheal ischemia, or the inhalation of toxins or certain smokes have also been postulated as etiologic factors for all the same, if not similar mechanisms.[10]

Diseases mentioned above can coexist with DAC as these conditions are not exclusive, making the diagnosis of DAC more difficult for the clinician.

CLINICAL SIGNIFICANCE

Tracheal narrowing is enhanced in the presence of a reduced elastic recoil (i.e., obesity) or in patients with small airways diseases, such as asthma or COPD. However, the presence of airway closure does not always represent airflow obstruction and as mentioned previously, the degree of the narrowing, besides being a diagnostic consideration, might also lead into different treatment options.

A big emphasis has been placed lately on DAC as the cause of clinical manifestations in the absence of diagnosed airflow obstruction.[5,11] Patient's symptoms can mimic those of airflow obstruction but there will be no evidence of such on spirometry or history suggestive of those diseases.

Patients with asthma or COPD can also present with a higher prevalence of DAC. Symptoms might suggest exacerbations of the baseline disease. Stridor, wheezing, cough dyspnea, and difficulty clearing secretions are frequent. Misdiagnosing DAC in the setting of these conditions is very common and only a high suspicion index will help to identify DAC.[11,12]

Dynamic airway collapse can occasionally present in an indolent form and manifest a chronic, and at times productive, paroxysmal cough as persistent airway inflammation and impaired mucociliary clearance can be present.[13]

Dynamic airway collapse does not necessarily demonstrate abnormalities in the pulmonary function test. Symptoms of airflow can be present in some patients without showing features of airflow limitation of the forced expiratory volume in the first second (FEV1) or even in the flow–volume curve. This has been demonstrated in patients with tracheomalacia.[14] On some occasions, patients might only show airflow limitation signs and symptoms during exercise, making it very difficult to differentiate from exercise-induced asthma.[5,11]

In summary, in the presence of respiratory symptoms, clinicians must always have a high index of suspicion for the presence of DAC despite the possibility of those symptoms being produced by other baseline diseases, and even more so if there is an abnormal course of presentation or recovery, hinting to the possible diagnosis of DAC.

DYNAMIC AIRWAY COLLAPSE IN THE CRITICAL CARE SETTING

Asthma or COPD patients can require critical care management in virtue of exacerbations caused by the baseline disease. Multiple causes have been attributed to the presence of COPD or asthma exacerbation. However, and despite the increased prevalence of DAC, albeit sometimes indolent and episodic, among patients with those conditions, its association with those exacerbations is seldom considered in the differential diagnosis by the clinicians.[10] DAC must be considered in the setting of respiratory failure, in patients with sudden deterioration of their baseline conditions, those

presenting unusual challenges in the recovery process or in the presence of repeated failure to wean from the ventilator. Clinicians must exercise a high index of suspicion in those scenarios as a failure to diagnose the presence of excessive airway collapse might lead to mismanagement and poor patient outcomes.

It is also important to consider DAC in patients admitted with autoimmune diseases, such as Sjögren or relapsing polychondritis, as those conditions have also shown increased association with DAC, and are, often, seen in the setting of the intensive care unit.[15]

In some patients, DAC might complicate procedures performed under conscious sedation or light anesthesia as the relaxation of the posterior membrane of the trachea can exacerbate the narrowing of the lumen. In other occasions, manifestations can occur after extubating or decannulating a tracheostomized patient after the removal of the protective plastic tubing.[16]

Dynamic airway collapse could lead to high peak airway pressures in some patients receiving mechanical ventilation, altering the delivery of volumes and target pressures. As in some of these cases, DAC was not previously diagnosed, considering DAC in the presence of high-pressure alarms or in failure-to-wean patients might be challenging.[17] In some instances, episodic DAC has resulted from the administration of some inhalation anesthetic gases.[18]

In the critical care setting, when patients are more challenging and seriously ill with a myriad of pathologic conditions and multiple physiologic abnormalities, DAC can be a cumbersome to recognize, and can contribute to increasing morbidity, prolonging ventilator times, or can be associated with recurrent cardiac arrest.[19]

DIAGNOSIS

Making a definitive diagnosis of DAC is seldom simple. The quantification of tracheal collapse and its clinical significance can be difficult at last. The presence of asymptomatic and nonclinically significant central airway collapse could be common in a significant proportion of the population as demonstrated by dynamic CT scan images. Furthermore, the lack of correlation between the degree of obstruction and symptoms prior or even during the acute dynamic collapse of the airway makes it even more challenging.[20,21]

In patients with acute DAC, bronchoscopy remains the best tool for diagnosis. Bronchoscopy can be done under conscious sedation. Ideally, a spontaneous breathing patient, who can follow instructions, and is subject to a forced expiration maneuver or a Valsalva maneuver, will demonstrate the collapse of the airway and the bronchoscopist will be able to differentiate DAC from TBM.

If CT scan images are used to help to establish the diagnosis, comparison between end-inspiratory and end-expiratory acquisitions might be helpful, as it could demonstrate expiratory posterior compression of the airway. In intubated patients, the right main bronchus could be the territory to observe as the collapse of the posterior lining of the trachea will be obscured by the placement of the endotracheal tube. Impulse oscillometry might be advantageous in ventilated patients.[22]

For both main diagnostic methods, bronchoscopy and dynamic CT, it is recommended to use a predetermined reference point in the airway to facilitate measurement and the grading of the narrowing of the airway.

Pulmonary function tests might be normal in almost one-fourth of patients with DAC. Obstructive or restrictive pattern might be secondary to concomitant diseases and not caused by DAC. Maximum forced expiratory flow might be reduced, although its sole abnormality is not enough to clue clinicians.

TREATMENT

The initial step in the treatment of these patients should consist of managing their baseline and concomitant diseases to achieve their optimal control.

Stent trials, both using uncovered metallic, or silicone stents are typically implemented for a short period of time (5–10 days) to assess the clinical response. This could be measured by quality of life, exercise tolerance, pulmonary function test changes, etc., provided that all or any one of those were measured prior to the treatment and were documented with abnormalities. It has been reported that most patients improve and are then subsequently considered for surgical treatment.[23]

In patients admitted to the critical care unit with acute respiratory failure, mechanical ventilation or noninvasive positive pressure ventilation might exercise similar results and could be used as a temporary treatment until more definitive resolution is feasible.[24] In addition, it is important to consider a presurgical assessment that includes the abovementioned exclusion differential, the degree of the obstruction, and the functional impairment. The FEMOS (functional status, extent of abnormality, morphology, origin, severity of airway collapse) classification system has been described by many as a useful tool to help such evaluation.[25]

Prior to determining surgery as the definitive treatment, a thorough and detailed differential diagnosis, to exclude potential alternative causes of DAC, should be required. This process must happen over weeks of time span to be able to rule out all possible reversible conditions.

Mild-to-moderate cases might be treated with noninvasive positive pressure [continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP)] for long-term management. Compliance and insurance authorization are major factors associated with treatment failure.

Tracheobronchoplasty or surgical central airway stabilization by posterior mesh splinting are the most

permanent treatment options. The treatment requires differentiation between DAC and TBM. In patients with DAC, the transverse diameter of the airway is not large, requiring less downsizing of the trachea. The procedure has an elevated success rate with a perioperative mortality circa 1%.[2,26]

CONCLUSION

Dynamic airway collapse and TBM are both associated with weakening of the central airway walls causing collapse of the lumen during the expiratory phase. Several common conditions such as COPD, asthma, Sjögren syndrome, prolonged ventilation, trauma, and relapsing polychondritis have been associated with the presence of DAC. Patients can exhibit confounding symptoms such as shortness of breath, coughing, stridor, and wheezing making the diagnosis of the condition very challenging and requiring a high index of suspicion for the clinician to suspect it. While CT is helpful, the gold standard for diagnosis is the bronchoscopic evaluation of the airway, which can not only identify the phenomenon but also quantify the degree of narrowing.

In the clinical setting, clinicians should rule out DAC and TBM for those patients that have been difficult to wean from invasive ventilation or those with unusual presentation or course of airflow limiting diseases.

Treatment may only be needed if there is complete or near complete collapse of the airway. For milder cases, it is recommended to use noninvasive positive pressure ventilation. In more severe scenarios, stenting of the airway for a short period of time might reveal improvement of the symptoms. In those cases, surgical intervention is required. Tracheobronchoplasty is the surgical procedure of choice, and it requires presurgical assessment, including ruling out any possible alternative in the diagnosis, as well as determination of the existent condition, dynamic airway collapse, or TBM.

REFERENCES

1. Gross RE, Neuhauser EB. Compression of the trachea by an anomalous innominate artery: an operation for its relief. Am J Dis Child. 1948;75(4):570-7.
2. Kheir F, Fernandez-Bussy S, Gangadharan SP, Majid A. Excessive dynamic airway collapse or tracheobronchomalacia: Does it matter? Arch Bronconeumol. 2019;55(2):69-70.
3. Park JG, Edell ES. Dynamic airway collapse. Different from tracheomalacia. Rev Port Pneumol. 2005;11(6):600-2.
4. Murgu SD, Colt HG. Treatment of adult Tracheobronchomalacia and excessive dynamic dynamic airway collapse: an update. Treat Respir Med. 2006;5(2):103-15.
5. Weinstein DJ, Hull JE, Ritchie BL, Hayes JA, Morris MJ. Exercise-associated excessive dynamic airway collapse in military personnel. Ann Am Thorac Soc. 2016;13(9):1476-82.
6. Javidan-Nejad C. MDCT of trachea and main bronchi. Radiol Clin North Am. 2010;48(1):157-76.
7. Gibson GJ, Pride NB, Empey DW. The role of inspiratory dynamic compression in upper airway obstruction 1, 2. Am Rev Respir Dis. 1973;108(6):1352-60.
8. Wright CD. Tracheobronchomalacia and expiratory collapse of the central airways. Thorac Surg Clinic. 2018;28(2):163-6.
9. Shah V, Husta B, Mehta A, Ashok S, Ishikawa O, Stoffels G, et al. Association between inhaled corticosteroids and tracheobronchomalacia. Chest. 2020;157(6):1426-34.
10. Kalra A, Abouzgheib W, Gajera M, Palaniswamy C, Puri N, Dellinger RP. Excessive dynamic airway collapse for the Internist: New nomenclature or different entity? Postgrad Med J. 2011;87(1029):482-6.
11. Murgu S, Stoy S. Excessive dynamic airway collapse: a standalone cause of exertional dyspnea? Ann Am Thorac Soc. 2016;13(9):1437-9.
12. Hunter JH, Stanford W, Smith M, Grillo HC, Weiler JM. Expiratory collapse of the trachea presenting as worsening asthma. Chest. 1993;104(2):633-5.
13. Aneeskhumar S, Thaha MM, Varun S. Excessive dynamic airway collapse presenting as intractable cough: A case report. Lung India. 2018;35(6):525-6.
14. Loring SH, O'donnell CR, Feller-Kopman DJ, Ernst A. Central airway mechanics and flow limitation in acquired tracheobronchomalacia. Chest. 2007;131(4):1118-24.
15. Ismael S, Wermert D, Dang-Tran KD, Venot M, Fagon JY, Diehl JL. Severe excessive dynamic airway collapse in a patient with primary Sjögren's syndrome. Respir Care. 2014;59(10):e156-9.
16. Lynker MR, Davila VR, Papadimos TJ. Excessive dynamic airway collapse: An unexpected contributor to respiratory failure in a surgical patient. Case Rep Anaesth. 2015. Article ID 596857.
17. Murakami S, Tsuruta S, Ishida K, Yamashita A, Matsumoto M. Excessive dynamic airway collapse during general anesthesia: a case report. JA Clin Rep. 2020;6:73.
18. Katoh H, Saltoh S, Takiguchi M, Yamasaki Y, Yamamoto M. A case of tracheomalacia during isoflurane anesthesia. Anesth Analg. 1995;80(5):1051-3.
19. Acharya S, Avula A, Dusi V, Sharma D, Narula N, ElSayegh D, et al. Excessive dynamic airway collapse as a cause of recurrent cardiac arrest. Am J Respir Crit Care Med. 2020;201:A3412.
20. Boiselle PM, O'Donnell CR, Bankier AA, Ernst A, Millet ME, Potemkin A, et al. Tracheal collapsibility in healthy volunteers during forced expiration: assessment with multidetector CT. Radiology. 2009;252(1):255-62.
21. Boiselle PM, Michaud G, Roberts DH, Loring SH, Womble HM, Millett ME, et al. Dynamic expiratory tracheal collapse in COPD. Correlation with clinical and physiologic parameters. Chest. 2002;142(6):1539-42.
22. Handa H, Huang J, Murgu SD, Mineshita M, Kurimoto N, Colt HG, et al. Assessment of central airway obstruction using impulse oscillometry before and after interventional bronchoscopy. Respir Care. 2014;59(2):231-40.
23. Diaz Milan R, Foley E, Bauer M, Martinez-Velez A, Castresana MR. Expiratory central airway collapse in adults: corrective treatment (Part 2). J Cardiothoracic Vasc Anesth. 2019; 33(9):2555-60.
24. Bastos HN, Teixeira N, Redondo M, Gonçalves M, Sucena M. Mechanical ventilation for the treatment of severe excessive dynamic airway collapse. Respir Care. 2015;60(4):e90-1.
25. Wright CD Mathisen DJ. Tracheobronchoplasty for tracheomalacia. Ann Cardio-Thorac Surg. 2018;7(2):261-5.
26. Murgu SD, Colt HG. Tracheobronchomalacia and excessive dynamic airway collapse. Respirology. 2006;11(4):388-406.

CHAPTER 4

Physiology and Pharmacology of Vasopressor Selection in Septic Shock

Fredrik Olsen, Patrick M Wieruszewski, Ashish K Khanna

INTRODUCTION

Septic shock is a major source of morbidity and mortality globally. The defining trait of septic shock is hypotension or more correctly, the need for vasopressor treatment to treat hypotension [mean arterial pressure (MAP) <65 mm Hg] caused by vasoplegia (in the absence of hypovolemia) and elevated lactate in the presence of sepsis.[1] A major part in the treatment of septic vasoplegia are vasopressors and additional inotropes to ensure circulation, perfusion, and organ function until the underlying cause is treated.[1]

PHYSIOLOGY OF SEPTIC SHOCK

The physiology of septic shock is a complicated dysregulated host response to infection. There is simultaneous hyperinflammation and immune suppression. Innate immunity is responsible for the initial response to an infection recognized through microbial-associated molecular patterns (MAMPs). Our own immune cells display pattern recognition receptors (PRRs), such as toll-like receptors (TLRs). After activation TLR initiates a cascade reaction through nuclear factor kappa B (NFκB), upregulating the production and the release of tumor necrosis factor α (TNFα) and interleukin 1 (IL-1). These substances in turn are responsible for the hallmark traits of sepsis; white blood cell activation and migration, endothelial damage and capillary leakage.[2,3]

Hypoperfusion and hypoxemia leading to cell death are also a source of the signaling substances, damage associated molecular patterns (DAMPs), which over time contributes to the maintenance of the immune response. Nitric oxide (NO) is a major regulator of vascular function. It has a direct effect on vascular tone as well as stimulation of leukocyte adhesion and platelet activation. NO is essential in the regulation of vascular tone in the healthy patient, but can be increased by up to 200% in the presence of PAMPs. Prostacyclin (PGI2) is another product of the endothelium leading not only to vasodilation but also to platelet aggregation. Its production is stimulated by the presence of PAMPs, IL-1, TNFα, hypoxia, and MAMPs.[3] Endothelin 1 (ET1) is a small peptide originating in the vessel endothelium. Although its intrinsic effect is that of a vasoconstrictor, the presence of ET1 during inflammation activates a number of signaling pathways leading to the increased synthesis of IL-1, TNFα, and IL-6, leading to net vasodilatory effect in vivo.[2]

Over time, there may be an underexpression of α1 adrenergic receptors, resulting in a resistance to exogenous adrenergic stimulation. Studies have also shown a reduced receptor expression in severe sepsis.[4] Lactic acidosis accompanying septic shock also has significant consequences on circulatory hemodynamics by relaxation of vascular smooth muscles cells through ATP-K+ channel activation.[5] Additionally, endothelial and vascular smooth muscle expression of inducible NO is potentiated during acidosis, further compounding its profound vasodilatory effects.[6] To make matters even worse, the contractile function of catecholamine vasopressors and inotropes at the level of vascular smooth muscle adrenergic receptors is diminished during acidosis, leading to excessive vasopressor dosages necessary to maintain satisfactory perfusion pressures.[7]

PHYSIOLOGY OF VASOPRESSORS AND INOTROPES

Vasopressors' main effect is vasoconstriction of the arterial system. Inotropes on the other hand aim to increase cardiac contractility. There is a significant overlap between the two and the most common group, catecholamines, includes both effects. Catecholamines bind to α, β, and dopaminergic receptors in arterial circulation, where α-1 receptors on vascular smooth muscle cells induce vasoconstriction through the release of intracellular calcium. α receptors are predominantly located on the tunica media of the vessel wall. *See* **Table 1** for details on receptor affinity of the drugs discussed in this review.

In the arterial circulation, small arterioles are the source of much of the resistance of the arterial circulation.

Venous circulation contains roughly twice the volume of blood as the arterial system. α and vasopressin receptors

TABLE 1: Receptor pharmacology of sympathomimetic agents.

	α_1	α_2	β_1	β_2	DA_1	DA_2
Epinephrine*	+/++	?	+++	+	0	0
Norepinephrine	++	++	++	0	0	0
Ephedrine	++	?	++	+	0	0
Dopamine*	++	++	++	+	+++	+++
Dobutamine	0/+	0	+++	+	0	0
Phenylephrine	+++	+	0	0	0	0

*Dose-dependent pharmacology with greater α_1 stimulation at higher dosages.

are present in the walls of the systemic veins. Their ability to adjust vascular tone is crucial for the venous capacitance vessel's role as a reservoir. An increase in venous vascular tone leads to increased venous return to the heart, which in turn increases the cardiac output of the competent heart.

Cardiac function and vessel tone are tightly bound to another. Catecholamine effect on the heart is mainly from the presence of β receptors on the myocytes, increasing its contractility by cyclic monophosphate (cAMP) signaling and an increase of intracellular calcium. Increased myocyte contractility does not improve cardiac output until the end-diastolic volume is increased, equivalent of a fall in the ejection fraction. β stimulation increases the heart rate/chronotropy (β-1) and enhances relaxation/lusitropy (β-2). Cardiac perfusion is compromised in low pressure states such as septic shock, restoration of systemic pressure improves the diastolic perfusion of the coronary arteries, preserving cardiac output.

Catecholamine or sympathomimetics is the main group of agents used in the treatment of septic shock. Endogenous catecholamines derived from the adrenal gland have a common synthesis pathway originating from phenylalanine, an essential amino acid. Dopamine, norepinephrine (NE), and epinephrine are all in this group. Synthetic catecholamines such as dobutamine, isoproterenol, and phenylephrine utilize the same adrenergic receptors, α and β.

PHARMACOLOGY AND SELECTION OF VASOPRESSORS

Norepinephrine is normally the first choice of sepsis and septic shock,[1,8] with vasopressin and epinephrine as second-line treatment for refractory shock.[1,8]

Norepinephrine/Noradrenaline

Norepinephrine/noradrenaline is an endogenous derivative of dopamine and is produced mainly in the adrenal gland, and it is the first choice of vasopressor in septic shock.[8] The primary effect is the stimulation of α-1 and the absence of β-2 leading to vasoconstriction of both arterial and venous vessels. NE does have a moderate β-1 effect, giving some inotropic effect on the heart. Studies have shown a mortality benefit in septic shock when compared to dopamine, with less risk of arrhythmia.[9] Dosing consists of continuous infusion 0.01 μg/kg/min and up to above 1.0 μg/kg/min in the extreme cases. For patients on high doses, a double syringe driver setup may be needed to avoid gaps in administration. Outside the intensive care unit (ICU), it can be used as a "push-pressor." Weaker solutions can be used in peripheral lines, but a central line is needed to avoid the risk of local tissue hypoperfusion. Over time and at higher doses NE might be toxic to cardiac myocytes, induce arrhythmia, and induce distal vasoconstriction leading to necrosis of digits and the splanchnic structures.[10]

Vasopressin

Vasopressin (antidiuretic hormone, ADH) is a noncatecholamine naturally occurring peptide produced in the pituitary gland with nonspecific vasopressin receptor agonism. Its action is on the V-1 receptors, stimulating the contraction of smooth muscle in the vessels. V-1 receptor activation triggers vasoconstriction through an increase in intracellular calcium in the vascular smooth muscle cells (VSMCs) and are found mainly in the splanchnic and skin vessels. Vasopressin has a stimulatory effect on V-2 receptors in the kidneys, leading to water resorption. Renal circulation is only slightly affected by vasopressin, further promoting kidney function in shock. Vasopressin has no inotropic or chronotropic effects. Only systemic vascular resistance (SVR) and subsequently blood pressure (BP) are increased with vasopressin.[11]

An early increase in endogenous vasopressin from posterior pituitary stores in septic shock gives way to a "vasopressin deficiency" after the first 24 hours leading partly to loss of vascular tone and refractory vasoplegia.

An early increase by a factor of 10 of endogenous vasopressin in septic shock gives way to a deficiency after the first 24 hours. The use of vasopressin as a supplement to NE leads to a catecholamine-sparing effect and the two treatments work synergistically.[12] There is concern of digital ischemia and subsequent necrosis following the use of vasopressin in combination with NE.[13]

Vasopressin has a longer half time (up to 30 minutes) than NE, making it difficult to titrate, and in fact most clinical practitioners will choose not to actively titrate this agent. Dosing can be either set to 0.01 U/min and up to 0.06 U/min as a continuous infusion. As a second-line vasopressor,[8,14] it should be started when NE reaches higher doses of around 0.5 μg/kg/min (20–50 μg/min) without signs of cold extremities or digital ischemia. More data suggests that delayed initiation of vasopressin is associated with a significant increase in ICU mortality.[15]

Synthetic analogs of vasopressin include terlipressin and selepressin. Terlipressin is also a nonspecific vasopressin receptor agonist with greater effects on V-1 compared to V-2 receptors, whereas selepressin is a specific V-1 receptor agonist. Similarly, these agents result in potent contractile effects on vascular smooth muscle cells. The more V-1 receptor specificity of these synthetic analogs have been proposed to potentially exhibit less adverse effects compared to vasopressin.[11]

OTHER TREATMENTS

Phenylephrine

Phenylephrine is a synthetic adrenergic analog with isolated α receptor affinity leading to peripheral arterial vasoconstriction. As there is no β effect, a reflex bradycardia might develop. Phenylephrine increases MAP through an increase in SVR. Dosing is achieved by continuous infusion 0.1 μg/kg/min to 10 μg/kg/min or it can be pushed in 100 μg increments, which can be particularly useful for acute rescues.

Epinephrine/Adrenaline

Through stimulation of β-1, epinephrine raises cardiac output and myocardial oxygen demand due to the increased contractility conveyed by β stimulation. The α-1 stimulation increases with increasing dosage and inhibits renal and splanchnic blood flow giving rise to systolic pressure increase while at the same time β-2 mediated vasodilation results in diastolic pressure decrease leading to increased pulse pressure.

It is available in different concentrations in different markets and indications. For continuous infusion 0.01–0.10 μg/kg/min is a starting dose and titrated to a maximum dose of 1.5 μg/kg/min. It can also be used as a "push-pressor" at doses of 100 μg in unstable or rapidly decompensating patients as a bridge to other treatments.

Ephedrine

Similar to epinephrine, ephedrine stimulates β-1 receptors for increased chronotropy and myocardial contractility, as well as α receptors in the periphery for vasoconstriction. Interestingly, ephedrine stimulates endogenous NE release through indirect mechanisms. Ephedrine's longer half-life and tendency to produce tachyphylaxis limit its value as a titratable vasopressor in shock. More commonly, it can be administered intravenous (IV) push at dosages of 5–10 mg for acute rescues.

Angiotensin II

Renin–angiotensin–aldosterone system (RAAS) activation in addition to NE and vasopressin allows for noncompetitive synergetic treatment of vasodilation. Low perfusion stimulates renin production in the juxtaglomerular cells of the kidneys which serves as a catalyst for angiotensinogen conversion to angiotensin I, following which pulmonary capillary endothelial ectoenzyme angiotensin-converting enzyme (ACE) stimulates the conversion to angiotensin II, which has potent vasoconstrictive effects at angiotensin type 1 receptor in the vascular smooth muscle. When the RAAS is impaired, particularly at the level of ACE (such as ACE inhibitor or pulmonary injury), buildup of angiotensin I substrates leads to the production of profoundly vasodilatory angiotensin1-7 and angiotensin1-9. Similarly, during impairment, ACE is unable to break down bradykinin leading to additional vasodilatory effects. All of these secondary pathways induce a vicious cycle of additional renin production and further vasodilatory mediator generation.[16,17] Indeed, the ATHOS-3 trial showed improvement of MAP and catecholamine-sparing effect in the angiotensin-II group compared to placebo,[18] and post-hoc analyses have identified patients with high-renin shock to experience profound survival benefit when treated with angiotensin II.[19] Angiotensin II has a very short half-life and is a rapidly titratable drug. It is used as an IV infusion, through a central line at doses starting from 2.5 ng/kg/min to up to 40 ng/kg/min. Doses as high as 80 ng/kg/min can also be used, but not >3 hours at a time. Usual therapeutic response is seen at around 20 ng/kg/min for most patients.

Dobutamine

Dobutamine increases CO mostly by its effects on β and α stimulation. Dobutamine has an affinity for β-1 greater than β-2 greater than α. Dobutamine increases contractility and CO with minimal effects on BP. It is profoundly arrhythmogenic and has fallen out of favor in use for septic shock without primary cardiac failure. It has a dose range of 2–20 μg/kg/min, a suitable starting dose is 5 μg/kg/min

Dopamine

Dopamine is more used in cardiogenic shock than in septic shock. Its effect varies by dose. In the 2–5 μg/kg/min range, it is commonly referred to as a renal dose and is believed to selectively target DA1 receptors increasing renal blood flow and upholding diuresis. Increasing the dose shifts the affinity to α and β receptors, inducing more inotropic and vasopressor effects. Dopamine use in septic shock should be discouraged given its high potential for arrhythmogenicity.

Milrinone

Milrinone is a phosphodiesterase inhibitor that causes increased levels of cAMP. In cardiac myocytes, this results in cardiac stimulation and increased CO. cAMP has vasodilatory effects in the smooth peripheral vessels leading to vasodilation and decreased BP. Milrinone is used to treat low CO as in decompensated HF.[20]

Levosimendan

Levosimendan increases sensitivity to Ca^{2+} in the myocytes through troponin binding, thereby promoting muscle contraction. It has inotropic and lusitropic effect which is beneficial in septic cardiomyopathy. In a patient with refractory shock and reduced CO, levosimendan might be an option.[21]

FUTURE PERSPECTIVES

The physiology and pharmacology of vasopressors and inotropes detailed above lends itself to the understanding that the over-reliance on a singular receptor mechanism (for example mono therapy with high-dose NE) is likely to fail. This is similar to the "common sense" analogy of not using 80 g of metoprolol for treating hypertension, or not using high dose opioids for analgesia. While, common clinical practice is reliant on gradual up titration of NE, followed by vasopressin and or epinephrine, we have for ages been fairly "step-wise" in our introduction of vasopressors. This has translated into a physiological disadvantage for the second, third, and fourth pressors and inotrope that is introduced, since the progression of the primary insult leads to further impairment of the physiological milieu, which increases chances of mortality independent of correction of hypotension and makes later introduced pharmacological agents largely inactive. Recently, impressive data has clearly established a nearly 20% increase in the risk of mortality with the delayed introduction of vasopressin beyond every 10 μg/min of NE of at least 10 μg/min or more.[15] Early, multi-modal, or broad-spectrum use of vasopressors is certainly a concept that will need to be appropriately embraced.[22,23] This can only be done while we continue to develop biomarkers that lend specificity to the choice of vasopressors.[24,25] On the other hand, the avoidance of hypotension and prediction modeling based on arterial waveform features, that predicts hypotension defined as mean arterial pressure less than 65 mm Hg for at least 1 min. We therefore tested the primary hypothesis that index guidance reduces the duration and severity of hypotension during noncardiac surgery. We enrolled adults having moderate- or high-risk noncardiac surgery with invasive arterial pressure monitoring. Participating patients were randomized to hemodynamic management with or without index guidance. Clinicians caring for patients assigned to guidance were alerted when the index exceeded 85 (range, 0 to 100 On the other hand, the avoidance of hypotension and prediction modeling based on advanced deep learning while well established in the operating room has not yet been tested appropriately in the ICU, and especially in the setting of septic shock. Early work has been done using large available ICU datasets such as MIMIC-III and eICU using a combination of available vital signs, and other monitoring data.[26-28] While these have produced encouraging results in as far as the prediction of hypotension, hemodynamic instability, and interventions such as the use of vasopressors, prospective interventional trials in septic shock patients with outcomes that show reduction of hypotension and organ system injury have yet to be done. The future, therefore, rests on a combination of a balanced approach to vasopressor pharmacology, necessary biomarkers, adjunctive therapy to decrease reliance on catecholamine therapy, and the further evolution of artificial intelligence into the sphere of the prediction, and prevention of hemodynamic instability ahead of time.

REFERENCES

1. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47(11):1181-247.
2. Russell JA, Rush B, Boyd J. Pathophysiology of septic shock. Crit Care Clin. 2018;34(1):43-61.
3. King EG, Bauzá GJ, Mella JR, Remick DG. Pathophysiologic mechanisms in septic shock. Lab Invest. 2014;94(1):4-12.
4. Burgdorff AM, Bucher M, Schumann J. Vasoplegia in patients with sepsis and septic shock: pathways and mechanisms. J Int Med Res. 2018;46(4):1303-10.
5. Ishizaka H, Kuo L. Acidosis-induced coronary arteriolar dilation is mediated by ATP-sensitive potassium channels in vascular smooth muscle. Circ Res. 1996;78(1):50-7.
6. Fernandes D, Assreuy J. Nitric oxide and vascular reactivity in sepsis. Shock Augusta Ga. 2008;30 (Suppl 1):10-3.
7. Marsh JD, Margolis TI, Kim D. Mechanism of diminished contractile response to catecholamines during acidosis. Am J Physiol. 1988;254(1 Prt 2):H20-7.
8. Scheeren TW, Bakker J, De Backer D, Annane D, Asfar P, Boerma EC, et al. Current use of vasopressors in septic shock. Ann Intensive Care. 2019;9:20.
9. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med. 2010;362(9):779-89.
10. Stratton L, Berlin DA, Arbo JE. Vasopressors and inotropes in sepsis. Emerg Med Clin. 2017;35(1):75-91.
11. Demiselle J, Fage N, Radermacher P, Asfar P. Vasopressin and its analogues in shock states: a review. Ann Intensive Care. 2020;10(1):9.
12. Russell JA, Walley KR. Vasopressin and its immune effects in septic shock. J Innate Immun. 2010;2(5):446-60.
13. Nagendran M, Russell JA, Walley KR, Brett SJ, Perkins GD, Hajjar L, et al. Vasopressin in septic shock: an individual patient data meta-analysis of randomised controlled trials. Intensive Care Med. 2019;45(6):844-55.
14. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43(3):304-77.
15. Sacha GL, Lam SW, Wang L, Duggal A, Reddy AJ, Bauer SR. Association of catecholamine dose, lactate, and shock duration at vasopressin initiation with mortality in patients with septic shock. Crit Care Med. 2021.

16. Paul M, Poyan Mehr A, Kreutz R. Physiology of local renin-angiotensin systems. Physiol Rev. 2006;86(3):747-803.
17. Moreau ME, Garbacki N, Molinaro G, Brown NJ, Marceau F, Adam A. The kallikrein-kinin system: current and future pharmacological targets. J Pharmacol Sci. 2005;99(1):6-38.
18. Khanna A, English SW, Wang XS, Ham K, Tumlin J, Szerlip H, et al. Angiotensin II for the treatment of vasodilatory shock. N Engl J Med. 2017;377(5):419-30.
19. Wieruszewski PM, Wittwer ED, Kashani KB, Brown DR, Butler SO, Clark AM, et al. Angiotensin II infusion for shock: a multicenter study of postmarketing use. Chest. 2021;159(2):596-605.
20. Sato R, Ariyoshi N, Hasegawa D, Crossey E, Hamahata N, Ishihara T, et al. Effects of inotropes on the mortality in patients with septic shock. J Intensive Care Med. 2021;36(2):211-9.
21. L'Heureux M, Sternberg M, Brath L, Turlington J, Kashiouris MG. Sepsis-induced cardiomyopathy: a comprehensive review. Curr Cardiol Rep. 2020;22(5):1-12.
22. Gleeson PJ, Crippa IA, Mongkolpun W, Cavicchi FZ, Van Meerhaeghe T, Brimioulle S, et al. Renin as a marker of tissue-perfusion and prognosis in critically ill patients. Crit Care Med. 2019;47(2):152-8.
23. Jeyaraju M, McCurdy MT, Levine AR, Devarajan P, Mazzeffi MA, Mullins KE, et al. Renin kinetics are superior to lactate kinetics for predicting in-hospital mortality in hypotensive critically ill patients. Crit Care Med. 2022;50(1):50-60.
24. Maheshwari K, Shimada T, Yang D, Khanna S, Cywinski JB, Irefin SA, et al. Hypotension prediction index for prevention of hypotension during moderate- to high-risk noncardiac surgery: A pilot randomized trial. Anesthesiology. 2020; 133(6):1214-22.
25. Wijnberge M, Geerts BF, Hol L, Lemmers N, Mulder MP, Berge P, et al. Effect of a machine learning–derived early warning system for intraoperative hypotension vs standard care on depth and duration of intraoperative hypotension during elective noncardiac surgery: The HYPE randomized clinical trial. JAMA. 2020;323(11):1052-60.
26. Yoon JH, Jeanselme V, Dubrawski A, Hravnak M, Pinsky MR, Clermont G. Prediction of hypotension events with physiologic vital sign signatures in the intensive care unit. Crit Care. 2020;24:1-9.
27. Moghadam MC, Masoumi E, Kendale S, Bagherzadeh N. Predicting hypotension in the ICU using noninvasive physiological signals. Comput Biol Med. 2021;129:104120.
28. Kwak GH, Ling L, Hui P. Predicting the need for vasopressors in the intensive care unit using an attention based deep learning model. Shock. 2021;56(1):73-9.

CHAPTER 5

Cardiac Output, Arterial Elastance, and Transmural Pressure

Swati Deepak Parmar, Ramanathan Kollengode

CARDIAC OUTPUT

Introduction

Cardiac output (CO) is the volume of blood ejected from the left ventricle (LV) in 1 minute. CO is often described in terms of left ventricular ejection; however, right ventricle (RV) is equally important for maintaining the desired cardiac function. CO monitoring is popular in perioperative settings where large amount of fluid shifts is expected. However, its use in intensive care is usually limited to selected indications, given the invasiveness of the procedure and the challenges of additional resources to measure it. In this chapter, we discuss invasive monitors to noninvasive monitors that aid in CO measurement and its usefulness in critically ill patients. This chapter is simplified for the trainees to have more clear idea about the CO measurements, their invasiveness and limitations, and will guide them to choose between the various available modalities.

Physiology

Cardiac output is calculated as the volume ejected from the LV during systole. Stroke volume (SV) multiplied by the heart rate (HR):

$$CO\ (L/min) = HR\ (bpm) \times SV\ (L)$$

Stroke volume of the LV depends on the LV end-diastolic volume (EDV), cardiac contractility, and afterload, making them determinants of CO as well. While there are no precise clinical markers for determining CO at the bedside, mean arterial pressure (MAP) is often used as an indicator for adequate perfusion. It should be borne in mind that MAP is a product of CO and systemic vascular resistance (SVR), and hence MAP may not always reflect CO all the time. CO is about the flow rather than the pressure.

$$MAP = CO \times SVR$$

Other indirect clinical markers pointing out to an adequate CO include normal mentation, urine output, lactate, base deficit, and temperature of extremities. All these clinical markers have many confounding factors and may not be reliable all the time.

Determinants of Cardiac Output[1]

Both LV and RV are equally important for any cardiac cycle. The factors affecting the RV CO and LV CO are outlined in **Table 1**.

The physiological relation between SV, CO, preload, and afterload are depicted in **Figures 1 to 4**.

TABLE 1: Factors affecting the ventricular function.

	RV	*LV*
Heart rate (HR)	HR initially increases SV. If it increases further may hamper CO as it decreases diastolic filling time	
Stroke volume	It is affected by following factors	
Afterload	Increase in afterload is due to increase in intrathoracic pressure, increase in pulmonary artery pressure: • Hypoxic pulmonary vasoconstriction (HPV) • Decreased pulmonary blood flow • Sympathetic stimulation • Increased hematocrit	Increase in afterload: • Thick wall LV • Increase in systemic vascular resistance • Sympathetic stimulation • Age-related arterial compliance
Preload	• Right atrial pressure • Total venous blood volume • Intrathoracic pressure • Pericardial compliance	• Left atrial pressure • Total blood compartment • Intrathoracic pressure • Pericardial compliance
Contractility	• Heart rate (Bowditch effect) • Afterload (Anrep effect) • Preload (Frank–Starling mechanism) • As well as cellular and extracellular calcium concentrations and temperature	
Effect of ventricular interdependence	The compliance of the RV is decreased in systole by the contraction of the interventricular septum	The compliance of LV is decreased in diastole due to RV dilatation

(CO: cardiac output; LV: left ventricle; RV: right ventricle; SV: stroke volume)

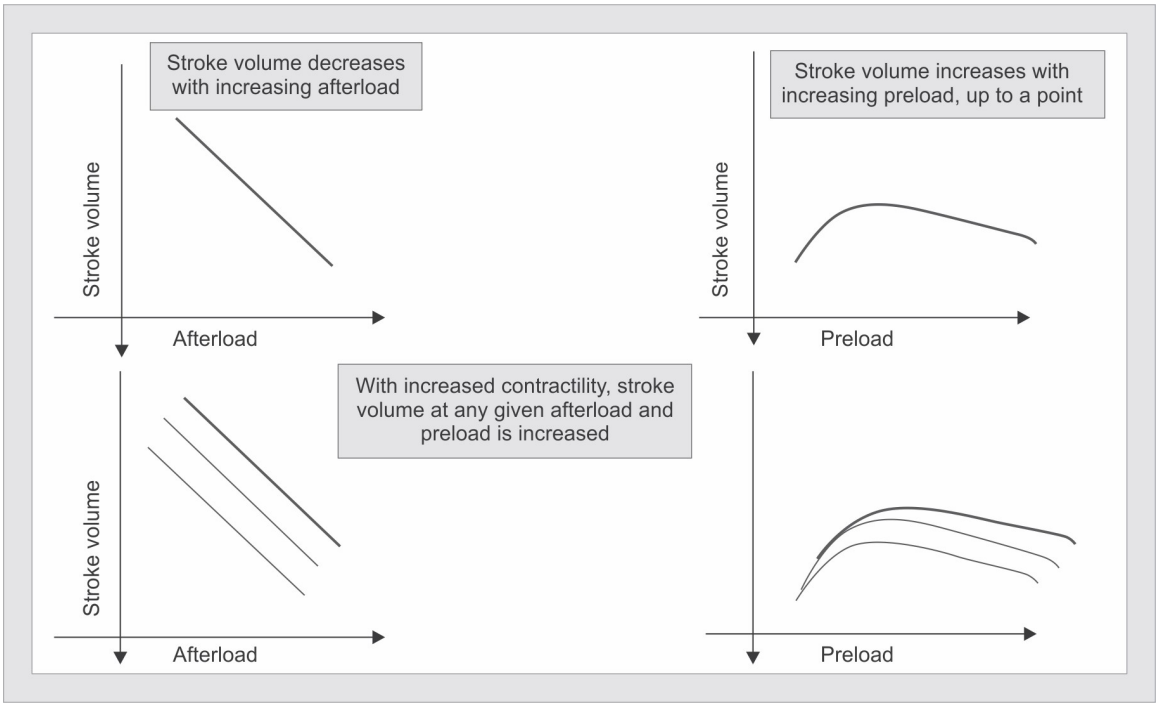


Fig. 1: Graph of stroke volume and relation to cardiac output.

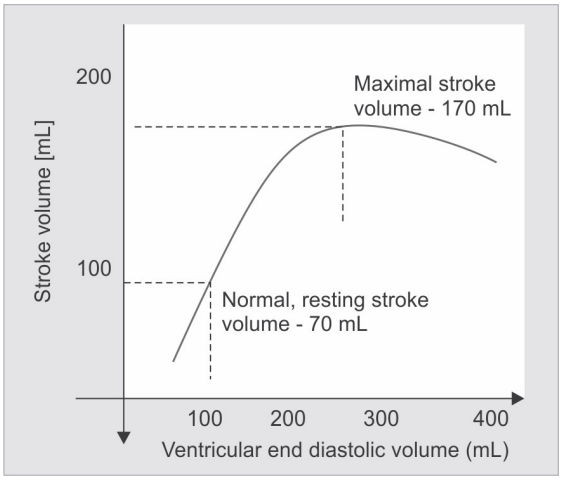


Fig. 2: Graph relation between preload and cardiac output.

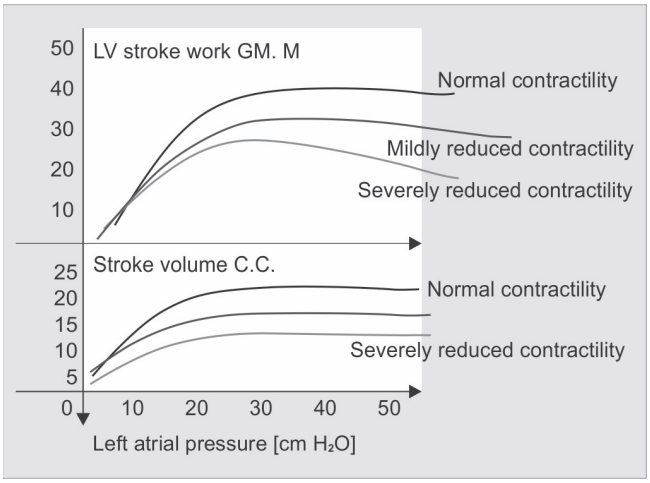


Fig. 4: Graph relation between contractility and cardiac output (CO). (LV: left ventricle)

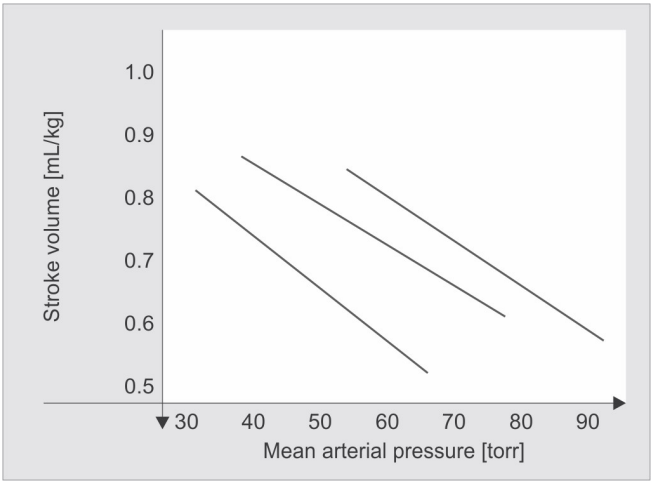


Fig. 3: Graph relation between afterload and cardiac output.

Frank–Starling law represents the relationship between SV and EDV preload. The Frank–Starling law states that *the SV of the LV will increase as the left ventricular volume increases due to the myocyte stretch causing a more forceful systolic contraction*.

Indications of CO Monitoring in Critical Care

Hemodynamic Assessment and Goal-directed Therapy

It is one of the main indications in the intensive care where it enables decisions on fluid resuscitation versus use of inotropes versus diuretics in patients with complicated shock states and mixed shock states.

Hypoperfusion with Impaired Oxygen Delivery

Cardiac output varies dynamically in various physiological and pathological conditions to provide adequate tissue delivery of oxygen.

The goal of adequate CO is the oxygen delivery to the vitals, and which is an important determinant for calculating oxygen delivery.

DO_2 (Oxygen flux) = CO (L/min) × arterial oxygen content (CaO_2)

CaO_2 = Chemical oxygen + dissolved oxygen

$CaO_2 = [1.39 \times (Hb) \times SaO_2] + (0.0225 \times PaO_2)$

CaO_2 is the arterial oxygen content (mL/L)

1.39 is the oxygen-binding capacity of Hb (mL/g) also called as Hefner's number

[Hb] is hemoglobin concentration (g/L)

SaO_2 is the fraction of Hb saturated with oxygen

PaO_2 is the partial pressure of oxygen (kPa) multiplied by its solubility coefficient

Ostwald solubility coefficient for oxygen at 37°C = 0.0225 mL/100 mL of blood/mm Hg.

Defining Cardiogenic Shock and Need for Mechanical Cardiac Support

Principle of cardiac output monitoring

Fick's principle (Adolph Fick, 1970): The amount of blood directed to an organ can be calculated by knowing the content of a substance in the blood supplying an organ, the content of the substance in the blood leaving the organ, and the amount of substance taken up by that organ **(Fig. 5)**.

$VO_2 = (CO \times CaO_2) - (CO \times CvO_2)$

VO_2 is the oxygen consumption

CO is the cardiac output

CaO_2 is the oxygen content of the arterial blood

CvO_2 is the oxygen content of the mixed venous blood

Rearranging: $CO = VO_2/CaO_2 - CvO_2$ (where the CO is equal to the oxygen consumption divided by the arteriovenous difference of oxygen content).

Ideal features of CO monitor:

- Noninvasive, minimally invasive
- Accurate in monitoring CO various physiological conditions
- Continuous
- Rapid response time
- Independent of assessor
- Safe
- Can be used in different set up like labor suite, emergency rooms, inter or intrahospital transfer
- Cost-effective

The recommendations are if intending to use CO monitor, should be used early in the phase of resuscitation when patient becomes critically ill where decision of fluid resuscitation versus ionotropic drugs is in question **(Table 2)**.[2,3]

ARTERIAL ELASTANCE

Introduction

The pressure volume (PV) loop of the ventricles gives a lot of information about the ventricular function particularly of the left. It can be used to understand the contractility, SV, effect of inotropes on the heart in addition to understanding the physiology of valve pathologies, heart failure, and

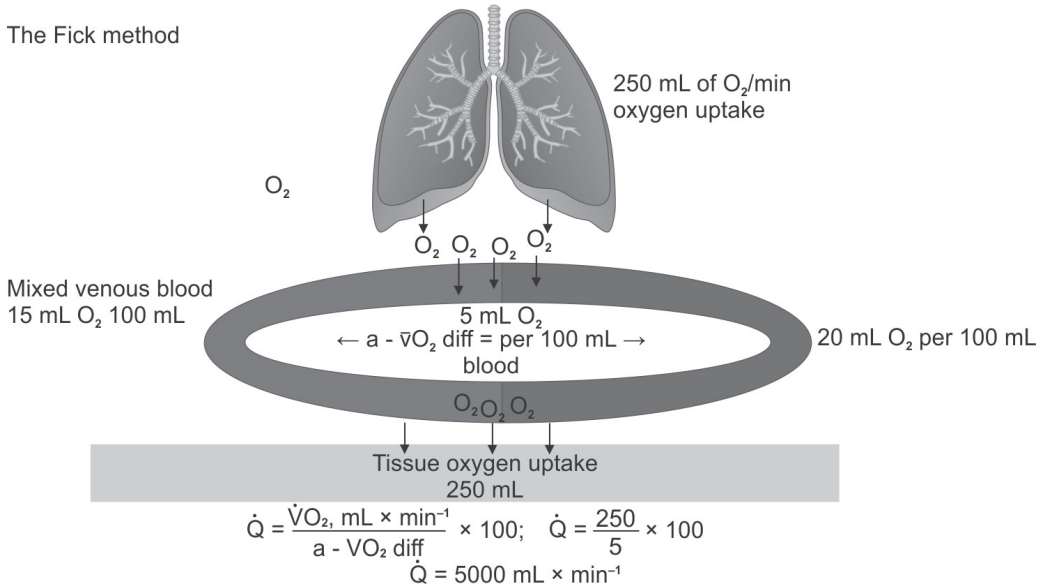


Fig. 5: Fick method (lungs with blood vessel).

TABLE 2: Invasive and noninvasive methods of measuring cardiac output.[4-7]

Principle	*Measurement*	*Invasiveness*	*Limitations*
1. *Fick based*: Indicator dye dilution	Indicator dye dilution	• Invasive • Intermittent	• Difficult to determine concentration • Recirculation of dye • Dye reaction
2. *Fick based*: Thermodilution	Swan Ganz catheter. Gold standard	• Invasive • Continuous/intermittent	• Error due to various pathological conditions • Catheter-related complications
3. *Fick based*: Indicator dilution + pulse contour analysis	Transpulmonary indicator Lithium dilution technique	• Invasive • Intermittent/continuous	Patient with aortic regurgitation and arrhythmia which disrupts the arterial curve have inaccurate readings
4. *Fick based*: Thermodilution+ pulse contour analysis	Transpulmonary PiCCO	• Invasive • Intermittent/continuous	
5. Fick method:	Partial CO_2 rebreathing	Noninvasive continuous	Mechanically ventilated patient
6. Doppler and ultrasounds	Transthoracic echocardiography (TTE)	Noninvasive intermittent	• Need training • Operator dependent • Windows should be good
7. Doppler and ultrasounds	Transesophageal echocardiography (TOE)	Minimal invasive intermittent	• Need training • Operator dependent • Contraindicated in esophageal/ gastric surgery
8. *Doppler*: Aortic velocimetry	Esophageal Doppler	Minimal invasive continuous	• Error in case of aortic coarctation, IABP • Contraindicated if IABP, esophageal pathologies
9. Pulse contour analysis	Pleth variability Index	Noninvasive continuous	Peripheral vascular disease
10. Impedance bioimpedance/ bioreactance	Transthoracic	Noninvasive continuous	• Electrical interference • Extrathoracic fluid interference • Need stable hemodynamic

(IABP: intra-aortic balloon pump; PiCCO: pulse contour cardiac output)

follow-up therapeutic intervention. Beat-to-beat PV analysis has clarified cardiac mechanics in various pathogenic conditions. The aim of this chapter is to understand PV loops to decipher the importance of effective arterial elastance (Ea) of LV and the RV.[8]

Understanding the Pressure and Volume Loop

Pressure volume loop is either rectangular or trapezoidal depicting four phases of cardiac cycle, i.e., isovolumic relaxation, diastolic filling, isovolumic contraction, ejection. In above PV loop, LV pressure changes are described. The similar changes can also be done for RV. The information gathered from a PV loop of the LV includes the following mentioned next **(Fig. 6)**.

Volumes

- EDV (where the mitral valve opens)
- End-systolic volume (ESV) (where the aortic valve closes)
- SV (the difference between the end-diastolic and end-systolic volumes)
- Ejection fraction (EF), which is the ratio of SV to EDV.

Pressures

- Systolic blood pressure (SBP) (peak of the curve)
- Diastolic blood pressure (BP) (where the aortic valve opens)
- End-systolic BP (where the aortic valve closes) (Pes) which is 0.9 × SBP.

Pressure volume relationships

- Systolic ejection, which has fast and slow phases
- Diastolic filling
- Isovolumetric contraction and relaxation
- The end-diastolic pressure volume relationship (EDPVR), which describes ventricular Ea
- The end-systolic pressure volume relationship (ESPVR), which describes contractility

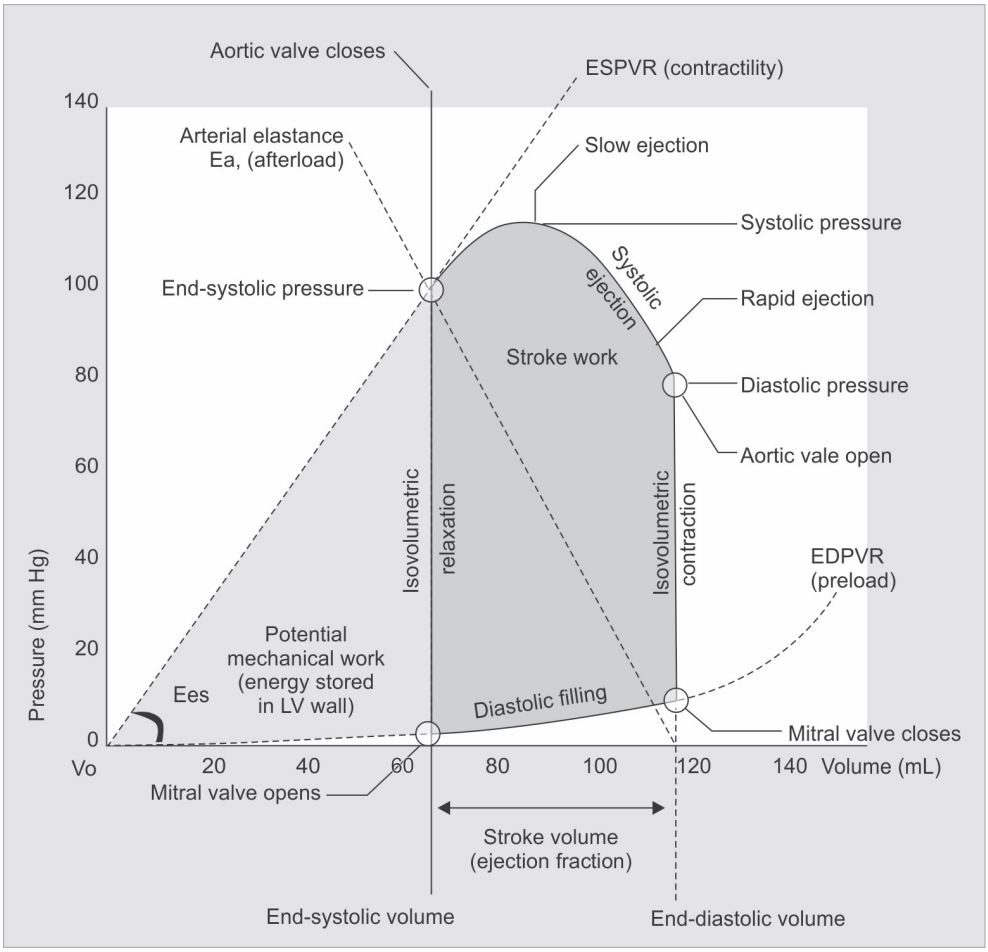


Fig. 6: Understanding the pressure and volume loop: left ventricle (LV).
(EDPVR: end-diastolic pressure volume relationship; ESPVR: end-systolic pressure volume relationship)

- The effective arterial Ea line which connects the point of EDV to the point of ESV, and which approximates afterload[9]
- End-systolic elastance (Ees) is determined at the slope of ESPVR.

Areas

Total mechanical energy [stroke work (SW)], which consists of:

- SW, which is the total area of the P-V loop
- Stored "potential" mechanical energy (PE) (in the LV wall), which is the area under the ESPVR line

Equations

- Pes = 0.9 × SBP
- Ea = Pes/SV
- Ees = Pes/ESV – Vo
- Ea/Ees = (Pes/SV)/(Pes/ESV – Vo)
- Ea/Ees – ESV – Vo/SV
- Ea/Ees = (1/EF) – 1
- SW = MAP × SV
- PE = Pes × [ESV – Vo]/2
- P V area = SW + PE.

What is Arterial Elastance?

- Elastance (Ea) is change in pressure (P) per unit change in volume (V). While compliance on the other hand is the inverse of Ea, i.e., change in volume per unit change in pressure.
  Ea = P/V
- The Ea of LV is described as resistance to deformation or an ability to recoil back after distention. The line connecting the end-diastolic pressure and volume to ESV as described in **Figure 6**.
- In normal condition, the change in pressure per unit change in volume for LV is not much as described above in **Figure 7**. The Ea of the LV is low and that is the reason it can accommodate large amount of volume without much change in LV pressure.
- However, in a condition where there is injury to the LV wall in the form of ischemia, the walls may not recoil normally leading to stiff ventricle. The Ea of the LV increases which increases left ventricular end-diastolic pressure (LVEDP). This may lead to increase in intraventricular pressure. This will lead to increase in left atrial (LA) pressure and pulmonary edema.[10]

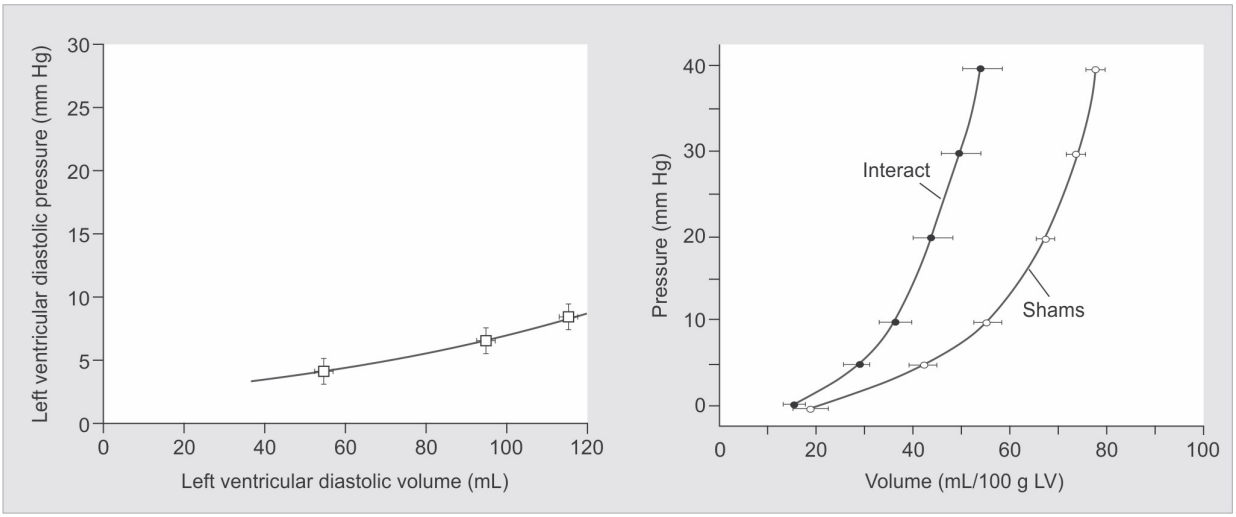


Fig. 7: LV pressure volume curve.

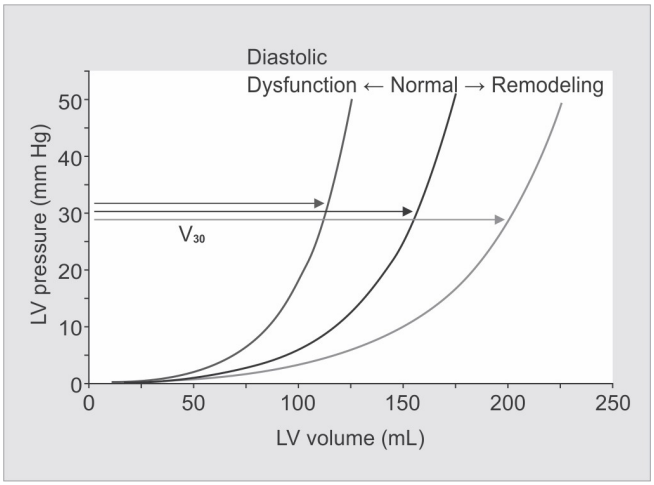


Fig. 8: V30 of left ventricle.

End-diastolic Pressure Volume Relationship (Fig. 8)

- EDPVR is a nonlinear graph. This explains about the LV stiffness and relaxation mechanism of LV. The compliance of LV should be high to accommodate large amount of blood.
- If there is any pathology with LV such as ischemia, cardiomyopathy, hypertrophy increase in LVEDP will cause increase in LA pressure and pulmonary edema.
- V30, i.e., the LV volume at 30 mm Hg, is often described in terms of EDPVR. The rightward shift happens during remodeling of the heart, while leftward shift happens during diastolic dysfunction. V30 is another way to describe compliance.

End-systolic Pressure Volume Relationship

- ESPVR is a linear within physiological range.
- ESPVR curve determines the cardiac contractility. The end-systolic pressure (ESP) depends upon the EDV. ESPVR can be represented by the succession of several PV loops at different volumes, which produces a linear relationship of several ESP/volume points. As the EDV increases, the slope also increases.
- As the contractility of LV increases, the slope of the curve increases despite same EDV.
- The End systolic elastance (Ees) reflects the ventricular compliance when the maximum number of contractile units are formed. Ees increases with ionotropic drugs while decreases with sympatholytic drugs such as β-blockers.

Effective Arterial Elastance

- The effective arterial Ea as described in **Figure 6** is the slope of line joining EDV to Pes.
- Ea is also calculated as a ratio of Pes/SV. Ea is also directly proportional to total peripheral resistance and HR.
- The mere statement as diastolic heart failure may not guide us for the treatment. The therapy tailored with the help of these PV loops gives us better treatment in patients with ischemia, heart failure, ongoing vasopressors, and inotropes. These PV loop analyses can be used for all the chambers.
- The arterial Ea which is equivalent of afterload is best denoted as effective arterial Ea.
- The *effective arterial Ea* is an index comprising of peripheral vascular resistance, total arterial compliance, characteristic impedance, HR, and systolic and diastolic time intervals. Ea can be estimated at the bedside preferably using the femoral artery.
- Effective arterial Ea is the ratio of ESP/SV.
- Ea along with ESPVR also describes cardiac contractility which is an integral part of studies researching ventricular arterial coupling which determines cardiac performance and energetics.

Ventricular Arterial Coupling (VAC)[11]

- The ventricular arterial coupling is the ratio of effective arterial Ea to Ees and it determines how LV interacts with the arterial system. This is a better indicator than EF.
- The arterial system affecting LV function is the core determinant of cardiovascular performance and myocardial energetics.
- Aging, hypertension, and cardiac failure affect structure and function of LV plus major arterial system.
- Ea/Ees is 0.6 under normal physiological condition. While aging, hypertension increases both the values and Ventricular arterial coupling (VAC) being normal.
- In HEART failure with reduced ejection fraction (HFrEF), the Ea increases while Ees decreases, hence ratio is increased suggesting mismatch. While exercise causes overall decrease in ratio as it increases Ees and decreases Ea.

End-systolic Elastance

- It is determined by the slope of the ESPVR.
- The increase in preload and thus contractility will shift the slope to the left which allows LV to generate enough pressure with given volume.
- The Ees = Pes/ESV – V_0 [V_0 = volume at the x-axis intercept]
- The Ees at rest can be calculated at the bed side by echocardiography. Pes corresponds with 0.9 × SBP very well. If V_0 considered minimal than ESV is calculated with echocardiography. Other method is derivation from PV loop. This method requires the measurement of systolic and diastolic BPs, EF, and SV, pre-ejection period, and total systolic ejection period on Doppler echocardiography.

Myocardial Energetics and PV Area

- Ea/Ees is an important determinant of cardiac energetics. In PV loop area which is composed of SW and potential energy (PE) **(Fig. 6)**.
- The SW refers to the work done by LV to eject blood in aorta. Therefore, ventricular SW is the product of SV and mean systolic pressure during ejection.
- PE is the residual stored energy in the myocardium at the end of contraction.
- PVA correlates well with the myocardial oxygen consumption per beat.

Dynamic Elastance[12]

- Dynamic elastance (Edyn) is the real time indicator, ratio between pulse pressure variation (PPV) and stroke volume variation (SVV).
- LV efficiency (LVeff) was defined as the ratio between SW and the LV PV area.

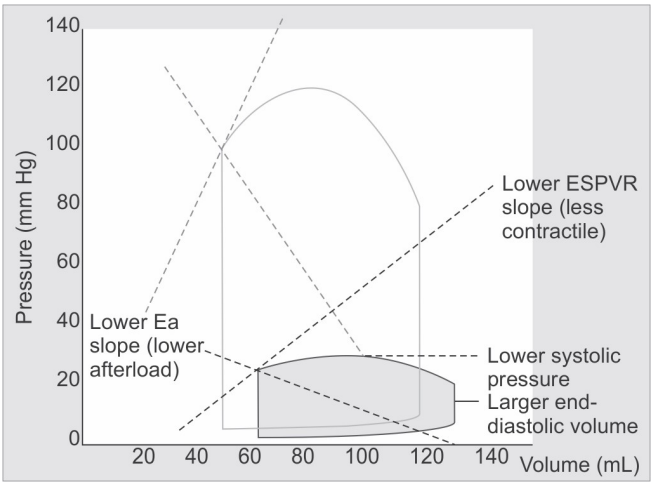


Fig. 9: Right ventricle and left ventricle pressure volume loop comparison of effective arterial elastance.
(ESPVR: end-systolic pressure volume relationship.

- Edyn is used to assess the various parameters such as fluid responsiveness and effect on increase in afterload with use of vasopressors. Edyn < 0.89 indicates use of vasopressors, while >0.89 indicates use of fluid boluses.
- For the PPV and SVV measurement, pulse contour uncalibrated as well as echocardiography is used.

Difference of PV Loops between the RV and LV (Fig. 9)

The difference is not only based on size, shape but is also based on most important characteristics of afterload and effective Ea.

Clinical application of PV loops:[8]

- Percutaneous revascularization
- Transcatheter aortic valve implementation
- Percutaneous edge-to-edge mitral repair
- *Heart failure*: Diagnosis and treatment
- Cardiac resynchronization therapy
- Ventricular reconstruction and partitioning
- *Mechanical circulatory support (MCS)*: impact on LV venting
- Weaning of MCS

TRANSMURAL PRESSURE

Introduction

Transmural pressure (PTM) is the pressure inside a cavity relative to the outside of any compartment. It is pressure gradient across any closed space such as a sphere or a tube. The term is often used in context with the lungs however can also be used for the cardiac chambers and blood vessels. The various PTMs described in terms of respiratory physiology, transpulmonary pressure (TPP) is of utmost importance in critical care. It not only guides us to adjust our ventilator parameters but also helps to decrease ventilator-associated lung injury such as barotrauma and

atelectotrauma. The various pressures of heart chamber are constantly interacting with the lung pressures. We shall discuss these cardiopulmonary interactions in spontaneously as well as mechanically ventilated patients. These interactions are often difficult to understand in patients with cardiopulmonary pathology.

Transmural Pressure

The pressure across the wall of any structure is called as transmural pressure, which is the difference between the intramural pressure (PIM) and extramural pressures (PEMs). PTM of any chamber along with the chamber compliance defines not only filling but also dimensions of the chambers and blood vessels.

Transmural pressure of various structures can be defined if we know their surrounding pressure. The transmural right atrial pressure is the difference between right atrial pressure and pleural pressure. For heart, the PTM is the difference between the intracavity pressure and pericardial pressure. In normal physiology, the pericardial pressure corresponds to intrathoracic pressure, so it is often not considered during calculations.

In respiratory mechanics, the transpulmonary pressure (TPP) is also a PTM, which is of utmost importance.

Transpulmonary Pressure (TPP)

Alternatives

Transalveolar pressure and alveolar distending pressure.

Definition

Regarding definition of TPP, various definitions are described in literature. The TPP is the net distending pressure of the entire lung.

In past decade, lot of importance is given to TPP. It does not take into consideration the compliance of the chest wall in its definition. The respiratory mechanics are better adjusted with the help of TPP. The TPP is the drop in pressure at the airway opening and drop in pressure at the lung surface (also called as elastic recoil).

Thus, TPP = (Paw – Palv) + (Palv – Ppl).

Paw—airway pressure

Palv—alveolar pressure

Ppl—transpleural pressure

Most of the time these pressures are measured when patient is on mechanical ventilation and thus airway opening pressure is equivalent to airway pressure (Paw).

Pressure Flow Relationship

Hagen–Poiseuille Equation

The flow is assuring in any system if difference in pressures exists at both the ends. The blood flow or the ventilation depends on the difference in the pressures. This equation is thus of utmost importance. However, the lung mechanics are more complex than this simple equation.

$$Q = \frac{\pi R^4}{8\eta L}\Delta p$$

Q: Blood flow
P: Pressure gradient
R: Vessel radius
L: Vessel length
n: Viscosity

The equation above states that the flow of any substance directly depends upon the diameter of tube, and the pressure gradient and inversely proportional to the viscosity and length of the tube.

$$R \propto \frac{\eta L}{r^4}$$

Vessel resistance (R) is directly proportional to the length (L) of the vessel and the viscosity (η) of the blood, and inversely proportional to the radius to the fourth power (r^4).

Importance of these Equations: Waterfall Concept[13]

The physiology of blood flow is not as simple as Bernoulli–Poiseuille equation. The collapsible nature of vessels differs from the fixed diameter of the tube mentioned in the equation. The blood flow is highly dependent not only on the upstream pressure but also on the PTM. When the downstream pressure is greater than the PEM of the vessel, the flow is directly proportional to the difference between the upstream and downstream pressure and external pressure has no influence on the vessel flow. When the PEM is greater than the downstream pressure of the vessel, the flow is dependent on the difference in pressure of the upstream pressure and PEM and changes in downstream pressure have no influence on the flow.

Compartment Model of the Cardiorespiratory System[14]

The circulatory system is divided into various compartments and influenced by various external and internal pressures.

Inspiratory Changes to Transmural Pressures in the Cardiac Chambers and Blood Vessels (Fig. 10)

During inspiration, the diaphragm contracts and the intrapleural pressure becomes much more negative and this expands the lungs. It also expands the major vessels in the lungs whereby the pressure falls in superior vena cava (SVC) and right atrium (RA). Although the intramural right atrial pressure (RAIM) depends upon the difference in pressure between intracardiac chamber pressure and intrapericardial pressure. The intrapericardial pressure in normal physiology is same as intrathoracic pressure and varies

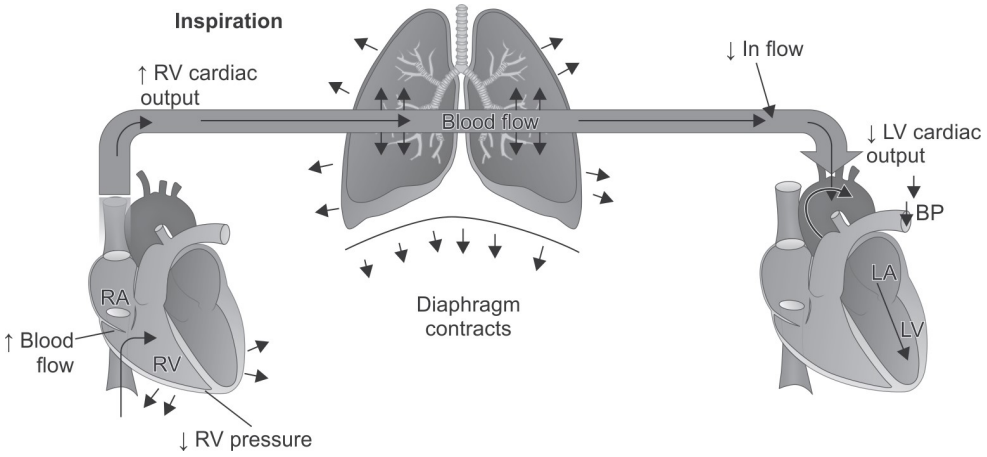


Fig. 10: Inspiratory changes to transmural pressures in the cardiac chambers and blood vessels. (BP: blood pressure; LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle)

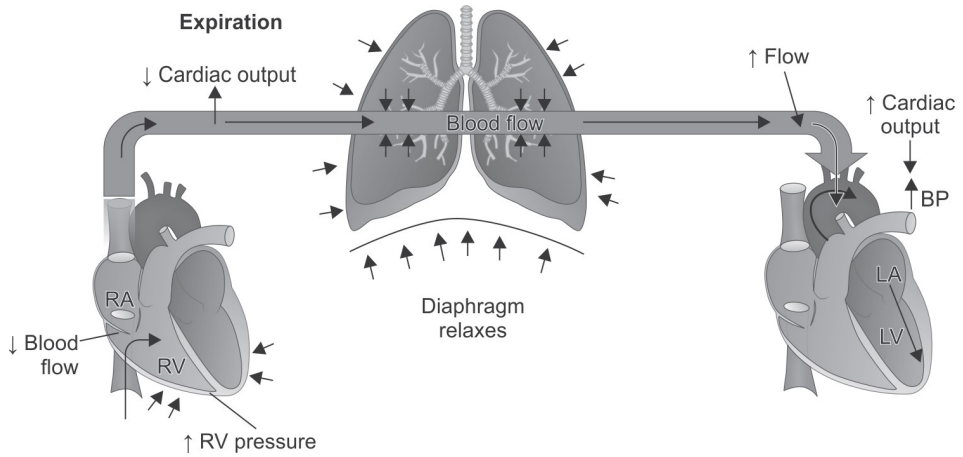


Fig. 11: Expiratory changes to transmural pressures in the cardiac chambers and blood vessels. (BP: blood pressure; LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle)

from +5 to −5 mm Hg during spontaneous inspiration and expiration. The lower thoracic vessels generate much higher pressure than the intrathoracic vessels and acts as a diastolic suction and drives the blood inside the ventricle. As a result, blood gushes inside the RA and flow increases and systemic venous return increases and increases RV CO. This causes increase in PTM. The blood must pass through the lungs and lung receives more blood which also increases pulmonary vascular resistance. The blood flow to the left heart decreases CO and momentarily BP. This drop in BP causes increases in HR. LV afterload is increased due to diaphragm contraction which increases intra-abdominal pressure (PABD). During RV filling, it also pushes the intraventricular septum to the left side which is also one of the causes of decreased LV filling. The relationship between ventricular filling, septal motion, and respiratory variation is referred to as ventricular interdependence.

Changes

Right ventricular preload increases, RV SV increases, LV preload decreases, LV SV decreases, and BP decreases.

The excessive fall in pressure is observed in cardiac tamponade, pulmonary edema, cardiac failure, hypovolemia, and seen as pulsus paradoxus.

Expiratory Changes to Transmural Pressures in the Cardiac Chambers and Blood Vessels (Fig. 11)

During expiration, the diaphragm relaxes and intrapleural pressure changes to its resting negative pressure. The pressure in the right heart increases; however, it is still lower than great vessels and thus the systemic venous return decreases. The lung recoil squeezes the blood from pulmonary circulation to the left side of the heart by increasing flow in the pulmonary veins. This transiently increases the CO and thus BP.

Changes

Right ventricular preload decreases, RV SV decreases, LV preload increases, LV SV increases, and MAP increases.

We must make a note of the PEM of neck veins (extrathoracic) and abdominal vessels. The PEMs are influenced by atmospheric (PATM) and abdominal pressures (PABD), respectively for neck and abdomen.

Of interest to the intensivist is the pressure changes in thoracic cavity during respiration. These changes in pressure alter various PTM of the heart and the lungs and the effect of mechanical ventilation in critically ill patients is further discussed below.

Factors

- Interaction of preload, afterload, contractility
- Ventricular compliance
- *Ventricular interdependence*: The RV and LV sharing the same pericardiac sac and interventricular septum makes the estimation of intra- and PEMs challenging. The compliance of one ventricle affects volume of the other.

Mechanical Ventilation, Positive Pressure Ventilation to Transmural Pressures in the Cardiac Chambers and Blood Vessels (Fig. 12)

The use of positive pressure ventilation (PPV) is associated with many interactions with cardiac physiology.[15,16] During PPV, the airway pressure (Paw) becomes positive and intrapleural pressure becomes much more positive (Ppl). This increases PTM of pleura. As increase in plural pressure expands lungs and pushes diaphragm downward increasing the abdominal pressure (PABD). The intrapleural pressure acts as a PEM for the cardiac chambers. Thus, any increase in intrapleural pressure impedes the filling of cardiac cavity. The fall in PTM of right heart and drop in thoracic pump causes decrease in venous return and decrease in right ventricular filling and SV. The pulmonary pressure increases due to positive intra-alveolar pressure which increases RV afterload and decrease CO from RV. The rise in TPP with increased transpulmonary flow causes increase in LV preload and thus SV and CO. In addition, there is decrease in LV afterload due to increase in PTM of LV. The BP and SV increase at the end of inspiration. The rise in Ppl during inspiration increases LVEDP. This reduces the amount of pressure that the ventricle must generate to pump blood against the MAP, and LV afterload falls. The interventricular septum also shifts to the right side when LV preload increases and thus impedes RV filling. Also, PTM of intrathoracic aorta decreases while that of abdominal aorta increases decreasing afterload. Afterload rises during expiration as Ppl returns to baseline. Reverse effects are observed when patient is in expiratory phase of mechanical ventilation. The LV SV and BP are decreased in expiration because of decrease in LV preload due to prior decrease in RV preload.

Changes

Right ventricular preload decreases, RV SV decreases, LV preload increases, LV afterload decreases, and thus LV SV is improved. The mechanisms explained are mechanical, neural, and humoral mechanism. The most important mechanism considered to influence cardiothoracic pressure is mechanical.

Patients on Mechanical Ventilation with Positive End Expiratory Pressure (PEEP, Extrinsic)

The effects seen with PEEP are same as observed in mechanical ventilation. The application of PEEP increases Ppl and PTM and decreases venous return. The PEEP helps in recruiting alveoli and keeps it open throughout the respiratory cycle. These recruited alveoli are more stable and helps in equal ventilation distribution and thus improving oxygenation. The application of PEEP causes increase in RV afterload shifts interventricular septum to the left causing decrease in LV preload. Recruitment maneuvers needs to be used in caution with pre-existing RV failure patients.

Cardiopulmonary Interaction: Applied Physiology[17]

Right Heart Failure

COVID-19 and several other lung infections are responsible for acute respiratory distress syndrome (ARDS). ARDS

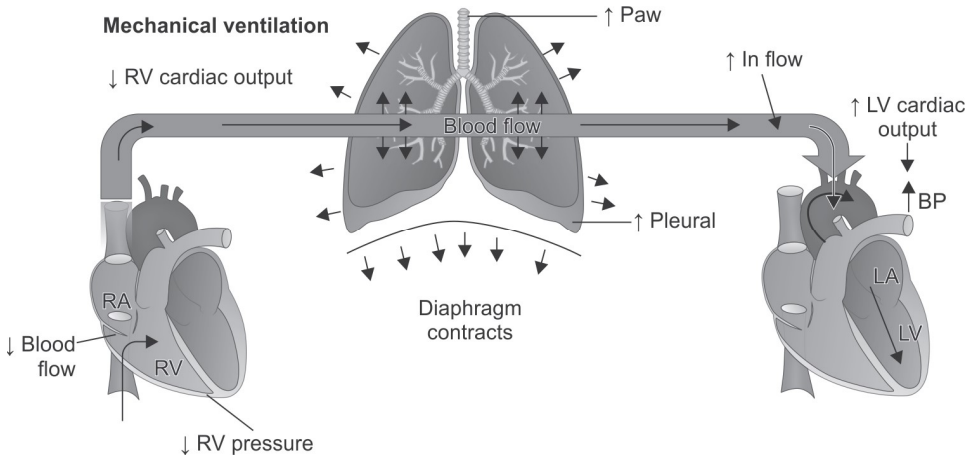


Fig. 12: Mechanical ventilation (MV), positive pressure ventilation to transmural pressures in the cardiac chambers and blood vessels. (BP: blood pressure; LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle)

patients on mechanical ventilation, have increase in pulmonary pressure. Hypoxic environment further aggravates pulmonary vasoconstriction and leads to increase in RV afterload. Another consequence of mechanical ventilation with PEEP in ARDS is decrease in venous return and RV preload. RV function is preload dependent and RV is not used to with the high pulmonary pressure as pulmonary vascular resistance is a low-pressure system. Cyclical changes during mechanical ventilation affect pulmonary vasculature may cause RV failure and more susceptible in cases of RV dysfunction or ARDS. However, in ARDS, the mechanical ventilation is necessary due to the requirement of oxygenation and preventing further lung collapse. The advantage of mechanical ventilation outweighs its risk and harmful effects. Recently, the importance is given to ARDS patient on mechanical ventilation. ARDS patients should have optimum ventilator settings to prevent barotrauma. The TPP is measured with the esophageal probe and peak airway pressure and PEEP are guided through this PTM.[18]

Left Heart Failure

The LV pressure changes in spontaneous breathing patients are not favorable. During spontaneous breathing, increase in intrathoracic pressure increases venous return and increase in LVEDP causing drop in CO. In patients with lung compliance issues such as acute pulmonary edema, the large amount of negative pressure is required to generate, which increases LV PTM and causes increase in afterload. PPV is thus favorable for LV SV as it decreases afterload. The continuous positive pressure ventilation [continuous positive airway pressure (CPAP)] also improves oxygenation with LV function.

Hemodynamic Assessment and Goal-directed Therapy

The end point measure of adequate CO for an individual patient is normal lactate, normal mentation, adequate urine output, and peripheral temperature. The passive leg raise test, or the fluid challenge can be done to check for fluid responsiveness. However, all these bedside tests are not always reliable and thus need more invasive approach to assess CO. In patients on mechanical ventilation, these changes are exaggerated, and we need bedside echocardiographic evaluation at times to guide fluid therapy versus vasopressor therapy. PPV and SVV[19] change with the respiration. If the pulse pressure decreases with inspiration, then this is a preload-responsive pattern, whereas if it increases with inspiration, this reflects interdependence and may be a marker of either cor pulmonale or heart failure. The PPV can guide us for fluid therapy in hypovolemic patient. The normal PPV cannot rule out fluid deficit completely. The effect of vasopressors causes vasoconstriction which shifts the volume of blood in central compartment from peripheral. In such cases, the fluid bolus may help to decrease requirement of vasopressors.

Pericardial Tamponade[20]

The PTM of the heart is the pressure difference between the intracardiac chamber pressure and pericardial pressure. Under normal physiological condition, the pericardial pressure is lower than right cardiac chamber pressure and is equivalent to intrathoracic pressure. The venous return is determined by the PTM of RV and the pressure gradient between the systemic venous circulations with RV chamber. In the case of acute pericardial tamponade, the normal physiological changes of cardiopulmonary interactions are exaggerated. RV is small with thin walls and less muscle, and is first to get compromised than LV. As the intrapericardial pressure increases, RV filling pressure increases, the gradient from systemic venous return decreases, shifts the interventricular septum, and LV filling pressure also increases. During inspiration, LV filling pressures are low which is exaggerated with tamponade physiology, and pulsus paradoxus is observed.

Obstructive Sleep Apnea

In obstructive sleep apnea (OSA) patient, they attempt to inspire against the closed upper airway. The negative intrathoracic pressure increases venous return with shift in intraventricular septum. The RV preload increases, however, the negative intrapleural pressure increases LV pressure and decreases afterload. Hypoxic condition for prolong time also causes increase in pulmonary pressure (hypoxic pulmonary vasoconstriction). CPAP is used in OSA patients. This might improve the cardiopulmonary interaction and prevent LV dysfunction.

REFERENCES

1. Vincent JL. Understanding cardiac output. Crit Care. 2008;12(4):174.
2. Harvey S, Harrison DA, Singer M, Ashcroft J, Jones CM, Elbourne D, et al. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. Lancet. 2005;366(9484):472-7.
3. Morris CG, Pearse RM. Pro-con debate: We should not measure cardiac output in critical care. J Intensive Care Soc. 2009;10(1):8-12.
4. Funk DJ, Moretti EW, Gan TJ. Minimally invasive cardiac output monitoring in the perioperative setting. Anesth Analg. 2009;108(3):887-97.
5. Nguyen LS, Squara P. Non-Invasive monitoring of cardiac output in critical care medicine. Front Med (Lausuanne). 2017;4:200.
6. Lund-Johansen P. The dye dilution method for measurement of cardiac output. Eur Heart J. 1990;11 Suppl I:6-12.

7. Kupersztych-Hagege E, Teboul JL, Artigas A, Talbot A, Sabatier C, Richard C, et al. Bioreactance is not reliable for estimating cardiac output and the effects of passive leg raising in critically ill patients. Br J Anaesth. 2013;111(6):961-6.
8. Bastos MB, Burkhoff D, Maly J, Daemen J, den Uil CA, Ameloot K, et al. Invasive left ventricle pressure-volume analysis: overview and practical clinical implications. Eur Heart J. 2020;41(12):1286-97.
9. Kelly RP, Ting CT, Yang TM, Liu CP, Maughan WL, Chang MS, et al. Effective arterial elastance as index of arterial vascular load in humans. Circulation. 1992;86(2):513-21.
10. Glantz SA, Parmley WW. Factors which affect the diastolic pressure-volume curve. Circ Res. 1978;42(2):171-80.
11. Chantler PD, Lakatta EG, Najjar SS. Arterial-ventricular coupling: mechanistic insights into cardiovascular performance at rest and during exercise. J Appl Physiol. 2008;105(4):1342-51.
12. Monge García MI, Jian Z, Hatib F, Settels JJ, Cecconi M, Pinsky MR. Dynamic arterial elastance as a ventriculo-arterial coupling index: An experimental animal study. Front Physiol. 2020;11:284.
13. Badeer HS, Hicks JW. Hemodynamics of vascular 'waterfall': is the analogy justified? Respir Physiol. 1992;87(2):205-17.
14. Kreit J, Kreit J. Cardiovascular–Pulmonary Interactions. In: Mechanical Ventilation: Physiology and Practice, 2nd edition. Oxford, UK: Oxford University Press; 2017-11.
15. Duke GJ. Cardiovascular effects of mechanical ventilation. Crit Care Resusc. 1999;1(4):388-99.
16. Cassidy SS, Eschenbacher WL, Robertson CH, Nixon JV, Blomqvist G, Johnson RL Jr. Cardiovascular effects of positive - pressure ventilation in normal subjects. J Appl Physiol. 197;47(2):453-61.
17. Grübler MR, Wigger O, Berger D, Blöchlinger S. Basic concepts of heart-lung interactions during mechanical ventilation. Swiss Med Wkly. 2017;147:w14491.
18. Loring SH, Topulos GP, Hubmayr RD. Transpulmonary pressure: the importance of precise definitions and limiting assumptions. Am J Respir Crit Care Med. 2016;194(12):1452-7.
19. Pinsky MR. Heart-lung interaction. Curr Opin Crit Care. 2007;13(5):528-31.
20. Madhivathanan PR, Corredor C, Smith A. Perioperative implications of pericardial effusions and cardiac tamponade. BJA Education. 2020;20(7):226-34.

CHAPTER 6

Immune Dysregulation in Sepsis

Andrew Conway Morris

INTRODUCTION

The ability of severe infections to kill patients has been recognized for millennia and across ancient cultures from China to India, Egypt to Greece. What classical physicians described as sepsis (σηψις), from the Greek term for rotting or putrefaction (sepo/σηπω), has gradually evolved into our modern conception of sepsis. Whilst the ancient physicians understood contagion, it was not until germ theory emerged in 17th century that the causative organisms were identified. Inflammation had long been recognized as part of the syndrome of infection, however it took several hundred years and the development of immunology as a scientific discipline, for the true nature of sepsis to be uncovered. As defined in the most recent definition ("Sepsis-3"), it is "life-threatening organ dysfunction arising from a dysregulated immune response to infection."[1]

It is the immune dysregulation which both defines and characterizes sepsis, distinguishing it from uncomplicated infection. In normal, homeostatic function, the immune system is critical to the identification of and clearance of infecting microorganisms. Cells recognize the presence of infecting organisms via pathogen-associated molecular pattern (PAMP) receptors, initiating and amplifying a response, with recruitment and activation of immune cells, localized vasodilatation, plasma extravasation, and microbial killing, followed by resolution **(Fig. 1)**.[2] When key parts of the immune system are absent or defective, such as following myeloablative chemotherapy, infection can rapidly spread with lethal effect. However, most patients with sepsis have a more-or-less intact immune system, and therefore the question arises how infection generates the systemic immune insult which leads to organ failure and sepsis.

IMMUNE-MEDIATED ORGAN DYSFUNCTION

Systemic inflammation is pathognomonic of sepsis, with evidence of altered circulating immune cell number and function as well as elevated levels of plasma cytokines (sometimes termed a "cytokine storm") with activation of complement and coagulation cascades. At the clinical level, this manifests as pyrexia, diaphoresis, tachypnea, and tachycardia, with emerging evidence of organ impairment and failure. In some organs, most notably the lungs, sepsis-induced organ failure is marked by the infiltration of immune cells, predominantly neutrophils, into the tissues with an accompanying proteinaceous exudate. This produces the histopathological features of early acute respiratory distress syndrome, a common and frequently lethal complication of sepsis.[3] Strikingly, in other tissue beds such as the kidneys, liver, and brain, dysfunction is often not accompanied by marked histological change. However, exposure to plasma containing inflammatory mediators is sufficient to produce impaired cellular function, potentially mediated by mitochondrial dysfunction in the face of a systemic inflammatory insult.[4] Other mechanisms of immune-mediated organ damage are set out below.

One of the critical questions in sepsis is how inflammation transitions from a localized response to infection to a systemic reaction. Although incompletely understood, it is likely to arise from a combination of genetic susceptibility, physiological and microbial factors. Bacteria and other microorganisms which can co-exist harmoniously with the host in one niche (consider *Staphylococcus aureus* or *Streptococcus pneumoniae* in the nasopharynx), induce a potent response in others (for instance the alveolar space). Bacterial invasion into the bloodstream, producing bacteremia, is associated with more severe sepsis and worse outcomes but is not a prerequisite nor a guaranteed precipitant of sepsis.

Key to the establishment and maintenance of sepsis are self-reinforcing feedback loops **(Fig. 2)**. For instance, microbes can trigger both the complement and coagulation pathways, with both these capable of self-amplification and crosstalk. Vasodilation arising from the release of complement components, and other vasoactive compounds such as nitric oxide, along with localized disruption of the endothelial glycocalyx, allow for extravasation of plasma fluid and proteins into the tissues. This, combined with vascular microthrombi, results in heterogenous blood flow,

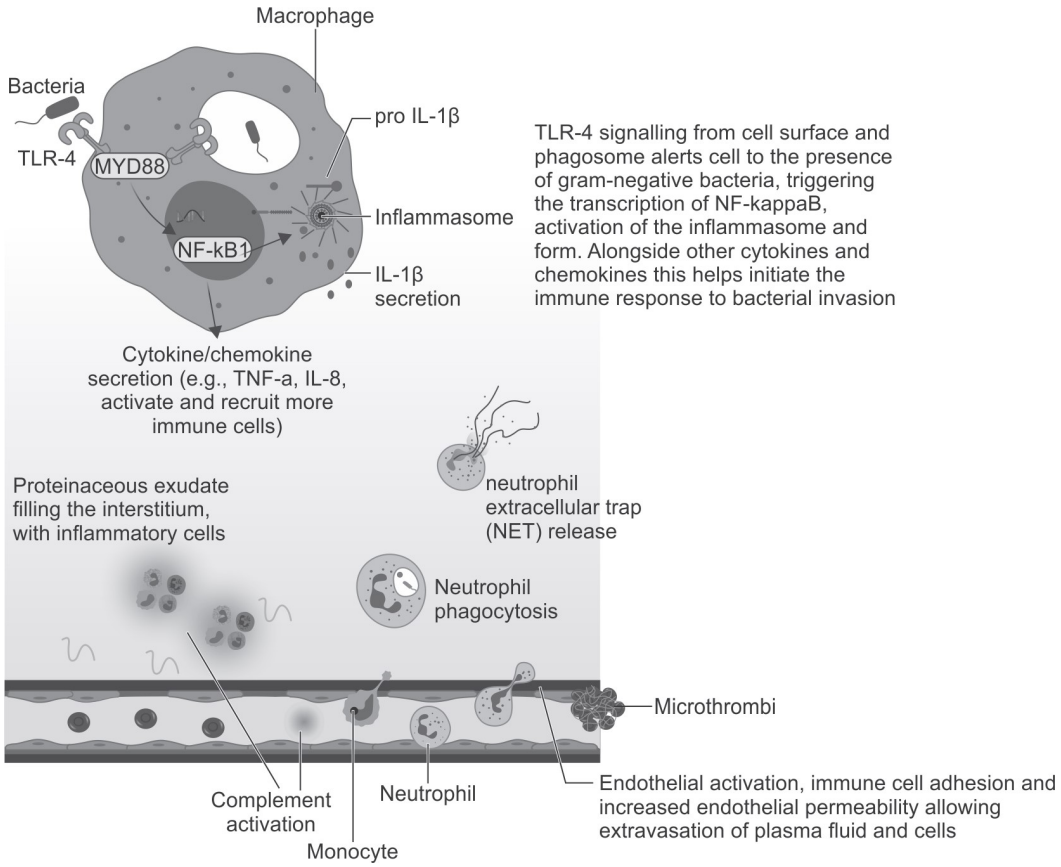


Fig. 1: Simplified diagram illustrating the early innate immune response to bacterial infection (made with Biorender.com). (IL: interleukin; NFKB: nuclear factor kappa B; TNF: tumor necrosis factor; TLR: toll-like receptor)

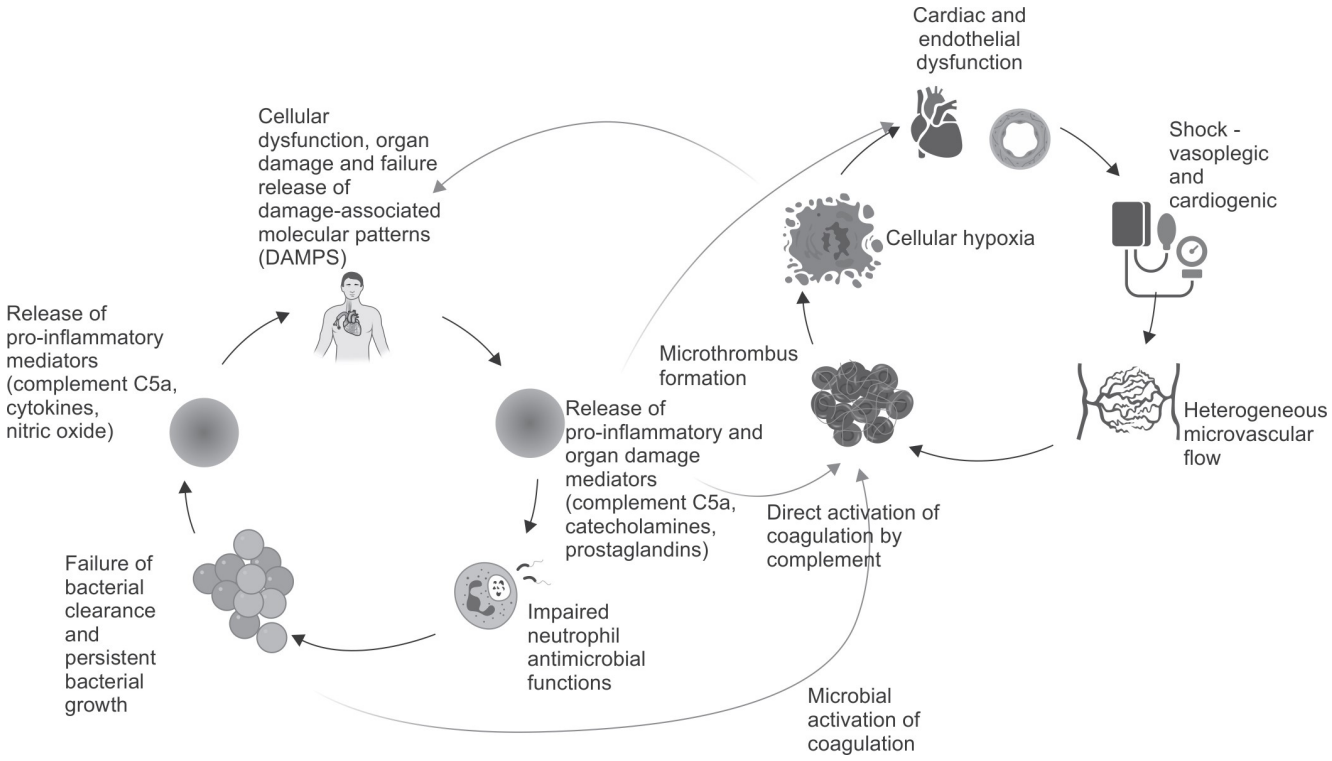


Fig. 2: Self-reinforcing and interacting pathways in sepsis as a route to persistent and worsening organ failure (made with Biorender.com).

cellular hypoxia, and impaired cell function. When cells become stressed or die, they release danger signals which are detected by damage-associated molecular pattern (DAMP) receptors which activate similar pathways to those triggered by PAMPs, further inducing immune cell activation and recruitment. Endothelial impairment can lead to further endothelial dysfunction, with inappropriate regulation of vascular smooth muscle function and systemic dilation leading to redistributive shock, whilst dysfunction of cardiomyocytes can lead to cardiogenic shock.[5] As will be discussed in more detail in the next section, various factors combine to *impair* host antimicrobial functions, which reduces bacterial clearance and allows persistent growth and tissue invasion, setting off further rounds of the maladaptive processes outlined in **Figure 2**. The combined effect is an uncontrolled, self-reinforcing and interacting cycles which if left unchecked results in the death of the patient.

IMMUNOPARESIS IN SEPSIS

One of the counterintuitive aspects of sepsis is the evidence of impaired immune cell antimicrobial functions, despite the clear evidence that immune *activation* and *hyperactivity* are critical to the generation and maintenance of this syndrome. The first indication that sepsis may not be simply a proinflammatory condition came via the disappointing performance of anti-inflammatory therapies in undifferentiated sepsis **(Table 1)**.[6] This led researchers, most prominently Roger Bone who had popularized the concept of "systemic inflammatory response syndrome," to propose a countervailing "compensatory anti-inflammatory response syndrome."[6] Further evidence for the presence of an immunoparetic phase or phenomena comes from heightened vulnerability to nosocomial infections encountered by patients in intensive care unit (ICU) with sepsis. Although not specific to sepsis, rather found across a range of critically ill patients,[7,8] this susceptibility points to a potentially generalizable feature of systemic inflammation.

IMMUNE CELL FUNCTION IN SEPSIS

Sepsis is marked by alterations in the numbers, activation, and functional capacity of various immune cells.

TABLE 1: Summary of existing human trial data in anti-inflammatory and immunostimulatory therapies for sepsis, most trials have recruited all patients with sepsis with the vast majority being bacterial or culture-negative (presumed bacterial).

Immunomodulatory therapies	
Anti-inflammatory	
TLR4 blockade	No survival benefit in phase III trials
TNF-α blockade	No survival benefit (some signal to harm) in phase II/III trials
IL-1 blockade	No survival benefit in phase III trials
Hydrocortisone	Survival benefit in two trials of septic shock and faster shock resolution in two further trials, however vascular rather than immunosuppressive mechanism thought to be dominant
Plasma exchange, cytokine absorption, and polymyxin hemoperfusion	No signal to benefit where large trials have been conducted, some signal to harm with some devices
Macrolides (immunomodulation)	Possible benefit in small scale trials, larger scale trials awaited
Intravenous immunoglobulin (IVIg)	Mixed immunomodulatory and antimicrobial effect (dependent on specific antibody titers)—trials have inconsistent effect with meta-analysis indicating no benefit. Specific products (IgM enriched and high antimicrobe titers) are being tested but remain at early phase trials
Immunostimulatory	
G-CSF	No survival benefit in unselected patients with pneumonia
GM-CSF	Small phase II studies show improvement in biological endpoints in patients with markers of dysfunction (monocyte responsiveness, neutrophil phagocytosis), phase III trials awaited
INF-gamma	Small scale studies show improvement in biological endpoints, no phase II/III RCTs published
IL-7	Phase II trial indicated safety and restoration of lymphocyte counts, phase II/III trials awaited
Anti-PDL1	No clinical trials in patients with sepsis yet reported

(G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; IL: interleukin; INF: interferon; PDL: programmed death-ligand; TNF: tumor necrosis factor; TLR: toll-like receptor)

Neutrophils

In most cases, sepsis is accompanied by a rapid and sustained neutrophilia. Already the most abundant immune cell in the circulation, they can rise to over 80% of total leukocytes. This increase is both relative (as sepsis is frequently accompanied by lymphopenia and eosinopenia) and absolute—with increased total numbers of circulating neutrophils. Neutrophil numbers increase as cells which had previously been loosely bound to the endothelial wall "demarginate" and enter the circulation, as well as increased bone marrow production and release.[9]

Although neutrophils in sepsis take on an "activated" phenotype, with increased expression of adhesion molecules and enhanced tendency to degranulate, several of their antimicrobial functions are impaired. These impaired functions include chemotaxis toward microbial targets, so impairing recruitment to sites of infection. Also prominently impaired is phagocytosis, with recent characterization of defects in phagosomal maturation as well,[10] leading to impaired microbial ingestion and killing. Perhaps because of being unable to effectively ingest and kill microorganisms, there is an increase in the production of neutrophil extracellular traps (NETs) which contain both nuclear material and lytic enzymes which are capable of damaging host tissues. A failure of neutrophil functioning has been associated with increased susceptibility to secondary infections, which may then in turn drive further inflammation.

Interestingly, one of the key drivers of neutrophil dysfunction in sepsis appears to be the proinflammatory complement component C5a.[10,11] As noted above **(Fig. 2)**, this is released in large quantities during sepsis following complement activation and has a range of deleterious effects beyond impairing neutrophil bacterial clearance.[12] This finding provides potential insight into how immune activation and organ damage can co-exist with immunoparesis. Further mechanisms of impaired neutrophil function include increased release of immature neutrophils from the bone marrow, as well as tissue-specific inhibitors such as increased levels of elastase in the lungs.

Monocytes

Monocytes are circulating mononuclear innate immune cells which play critical roles in the orchestration of immune cell recruitment to injured and infected tissues. They also present antigen from ingested microbes to lymphocytes to induce an adaptive immune response. Notably, circulating monocytes from patients with sepsis demonstrate diminished production of proinflammatory cytokines following challenge with microbial PAMPs such as lipopolysaccharide.[13] This so-called "monocyte deactivation" is also associated with the development of secondary infections. The surface expression of the class II human leukocyte antigen (HLA), HLA-DR, correlates with the ability to mount a cytokine response, and this has become the most well-established marker of immunoparesis in critical illness.[8] A similar phenomenon of downregulated HLA-DR predicting subsequent secondary infection has also been noted in the related cell type, dendritic cells.

Macrophages

Macrophages are tissue resident innate immune cells which are amongst the first to be encountered by invading pathogens. They remain relatively understudied amongst patients with sepsis as they are harder to access compared to circulating cell types such as neutrophils and monocytes, however evidence from animal models points to impaired antimicrobial functioning and reduced phagocytosis.[14] The long-lived nature of macrophages mean they present a plausible mediator for the persistent immunoparesis and susceptibility to infection which can persist long after the original insult has resolved.[15] Macrophages are not only important in clearance of microbes, but also play a key role in orchestrating the recruitment of immune cells from the circulation to the infected tissues. For reasons that remain incompletely understood, microbial infection can lead to profound macrophage activation with massive production of cytokines including IL-6 and IL-1β, which spill over into the circulation and lead to secondary macrophage activation syndrome (MAS), also termed hemophagocytic lymphohistiocytosis (HLH). Hemophagocytosis may be seen in this syndrome, although whether this is the key driver or a secondary effect of microbial stimulation remains uncertain.[16] Features of MAS/HLH are seen in a minority of sepsis cases, but in certain situations, this may be a key driver of the systemic immune activation which leads to organ failure. Importantly, MAS/HLH may be triggered by sterile insults such as malignancy and autoimmune disease and differentiating this from sepsis can be key to effective management.[16] Trials targeting specific therapies at the subset of sepsis patients with MAS/HLH features are ongoing.

Lymphocytes

Lymphocytes form the adaptative arm of the immune system, capable of generating immunological memory and thus providing long-lasting immunity. Consisting of B and T-cells, they subsume a number of specialized functions which are critical to immune defenses against microbial infection. B cells generate the various classes of immunoglobulins which demonstrate a degree of selectivity for their targets that is not seen in the more generic pattern-recognition receptors employed by the innate immune system. Immunoglobulins can impair microbial growth and facilitate killing by activating complement, opsonizing bacteria (making them more susceptible

to phagocytosis) and aggregating them. Production of immunoglobulins requires effective presentation of antigen by antigen-presenting cells (monocytes, dendritic cells, and macrophages, outlined above), B-cell binding, and costimulation by helper T-cells. Where one or more of these processes is missing or impaired, B-cell immunoglobulin production may be reduced, and reduced levels of at least immunoglobulin G (IgG) are frequently seen in sepsis.[17] Although attractive as a potential therapy, the administration of exogenous immunoglobulin has not been proven to be effective in trials to date **(Table 1)**.

Lymphopenia is a common feature of sepsis, and encompasses both B- and T-cells, the mechanisms which underpin this include enhanced lymphocyte apoptosis, reduced bone marrow production, and impaired proliferation, as well as some tissue infiltration.[18] Whilst lymphopenia is common, it does not affect all subsets of lymphocytes equally. It is notable that in some patients with sepsis, there is an increase in the relative frequency of the immunosuppressive regulatory T cells (T_{reg}). An increased proportion of T_{reg} is associated with reduced proliferative capacity for effector T-cells, and associated with adverse outcomes of mortality and risk of secondary infections.[8,19] Both T_{reg} and effector T cells show enhanced expression of negative costimulatory molecules such as programmed cell death protein 1 (PD1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). These act as "immune checkpoint" proteins, restraining B and T-cell proliferative responses, and have been associated with both impaired responses in sepsis and other diseases such as solid and hematological malignancies.

TREATMENT OF IMMUNE DYSREGULATION IN SEPSIS

So far there have been no successful immunomodulatory therapies delivered for fungal, bacterial, and almost all viral sepsis syndromes. The notable exception to this is the effectiveness of immunosuppressive treatments for COVID-19, which meets the conceptual definition of viral sepsis. This striking dichotomy illustrates the problems inherent in using broad syndromic categories to encompass a range of heterogeneous diseases, where the heterogeneity arises from the pathogen, the host response (and underlying genetics), and the temporal and pathological trajectory at time of attempted intervention. In COVID-19, it appears that peak viral replication occurs at some time prior to peak hyperinflammatory response and therefore dampening the immune response dose not lead to impaired viral control (although it may increase an already heightened risk of secondary bacterial and fungal infections). This contrasts with bacterial and fungal infection, where active growth continues at the time of organ failure and presentation to intensive care. For this reason, coupled with the earlier negative trials, we must not directly translate practice from COVID-19 to other forms of sepsis.

As noted above, the immune dysfunction of sepsis encompasses both hyperactivation and impaired antimicrobial responses,[20] and various immunostimulatory treatments have shown promise in-vitro and early phase II trials **(Table 1)**. To date there have been no large phase II trials demonstrating efficacy, and there remain understandable concerns about the risks of exacerbating immune-mediated organ damage, although no such exacerbation has been recorded in clinical trials to date. As immunoparesis is not a binary state, but rather a variable degree of impaired function across the range of immune cells and their subsets, which varies over time, a potentially attractive approach would be to target patients with an appropriate therapy at a time when they are most likely to benefit. Cell surface markers have been trialed in various settings as proxy measures of functional capacity[8] and show promise. Whilst standardized techniques for measurement are possible, devices which can reliably do this with the availability and timeframe required for critical care trials are not yet readily available. It is likely that both immunophenotyping tools and therapeutics will need to develop in parallel for successful treatment to be delivered.

CONCLUSION

Immune dysfunction is pathognomonic of and drives the organ failure that distinguishes sepsis from uncomplicated infection. Although immune hyperactivity and immune-mediated organ damage are prominent features, sepsis is also accompanied by impaired antimicrobial functions. These two facets, hyperactivity and impaired microbial clearance combine to drive maladaptive and self-reinforcing cycles of infection and organ damage. Developing disease modifying interventions for sepsis will have to address this complex and rapidly varying pathophysiological situation.

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Baueret M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-23.
2. Morris AC, Wilson J, Shankar-Hari M. Immune activation in sepsis. Crit Care Clin. 2018;34(1):29-42.
3. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA. 2016;315(8):788-13.
4. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet. 2002;360(9328):219-23.
5. Lelubre C, Vincent JL. Mechanisms and treatment of organ failure in sepsis. Nat Rev Nephrol. 2018;14(7):417-27.

6. Bone RCM. Sir Isaac Newton, sepsis, SIRS, and CARS. Crit Care Med. 1996;24(7):1125-8.
7. Vught LA van, Klouwenberg PMCK, Spitoni C, Scicluna BP, Wiewel MA, Horn J, et al. Incidence, risk factors, and attributable mortality of secondary infections in the intensive care unit after admission for sepsis. JAMA. 2016; 315(14):1469-2.
8. Morris AC, Datta D, Shankar-Hari M, Stephen J, Weir CJ, Rennie J, et al. Cell-surface signatures of immune dysfunction risk-stratify critically ill patients: INFECT study. Intensive Care Med. 2018;44(5):627-35.
9. Summers C, Rankin SM, Condliffe AM, Singh N, Peters AM, Chilvers ER. Neutrophil kinetics in health and disease. Trends Immunol. 2010;31(8):318-24.
10. Wood AJ, Vassallo AM, Ruchaud-Sparagano M-H, Scott J, Zinnato C, Gonzalez-Tejedo C, et al. C5a impairs phagosomal maturation in the neutrophil through phosphoproteomic remodeling. JCI Insight. 2020;5(15):93.
11. Ward PA. The dark side of C5a in sepsis. Nature reviews Immunology. 2004;4(2):133-42.
12. Wood AJ, Vassallo A, Summers C, Chilvers ER, Morris AC. C5a anaphylatoxin and its role in critical illness-induced organ dysfunction. Eur J Clin Invest. 2018;48(12):e13028-18.
13. Delano MJ, Ward PA. Sepsis-induced immune dysfunction: can immune therapies reduce mortality? J Clin Invest. 2016;126(1):23-31.
14. Roquilly A, Jacqueline C, Davieau M, Mollé A, Sadek A, Fourgeux C, et al. Alveolar macrophages are epigenetically altered after inflammation, leading to long-term lung immunoparalysis. Nat Immunol. 2020;21(6):636-48.
15. Arens C, Bajwa SA, Koch C, Siegler BH, Schneck E, Hecker A, et al. Sepsis-induced long-term immune paralysis – results of a descriptive, explorative study. Crit Care. 2016;20(1):93.
16. Bauchmuller K, Manson JJ, Tattersall R, Brown M, McNamara C, Singer M, et al. Haemophagocytic lymphohistiocytosis in adult critical care. J Intensive Care Soc. 2020;21(3):256-68.
17. Shankar-Hari M, Madsen MB, Turgeon AF. Immunoglobulins and sepsis. Intensive Care Med. 2018;44(11):1923-5.
18. Hotchkiss RS, Monneret G, Payen D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. Nat Rev Immunol. 2013;13(12):862-74.
19. Venet F, Chung C-S, Kherouf H, Geeraert A, Malcus C, Poitevin F, et al. Increased circulating regulatory T cells (CD4+CD25+CD127–) contribute to lymphocyte anergy in septic shock patients. Intensive Care Med. 2009;35(4):678-86.
20. Steinhagen F, Schmidt SV, Schewe J-C, Peukert K, Klinman DM, Bode C. Immunotherapy in sepsis - brake or accelerate? Pharmacol Therapeut. 2020;208:107476.

SECTION

2

Infections/Sepsis/Infection Control

CHAPTER 7

Approach to Sepsis in Immunocompromised Patients

Khalid Khatib, Mritunjay Kumar

INTRODUCTION

Sepsis, which is a life-threatening organ dysfunction caused by a dysregulated host response and systemic inflammation to infection[1] affects millions of people worldwide with significant mortality and morbidity. Patients who are immunocompromised because of their medical conditions or medications are at high risk for developing and dying from severe sepsis.[2] Recent advances in the antiretroviral, antineoplastic, antibiotics, and other adjuvant therapy; the use of newer and safer immunosuppressive agents; and increased and successful organ and bone marrow transplants, together with improved surgical techniques and intensive care have led to increased survival and numbers of immunocompromised patients in the last decades.

Since, immunosuppression alters manifestations of inflammation, the clinical and laboratory findings of sepsis in the immunocompromised patient can be different. The population of immunocompromised patients includes patients on immunosuppressive drugs following solid organ transplantation (SOT) or hematopoietic stem cell transplantation (HSCT); those with hematological or other malignancies, autoimmune diseases, inflammatory bowel diseases, or acquired immunodeficiency syndrome like in human immunodeficiency virus (HIV) infection. The diagnosis of sepsis in the immunocompromised patient should be done after ruling out noninfectious causes of fever and organ dysfunction [e.g., allograft rejection or thrombosis; immunosuppressive agents' toxicity; graft versus host disease (GVHD); as manifestations of vasculitis, oncological conditions like tumor lysis syndrome, neutropenic fever, and hyperleukocytosis; relapse of autoimmune disease; radiotherapy, etc.]

HOW SEPSIS IN THE IMMUNOCOMPROMISED IS DIFFERENT?

- Altered clinical manifestations, laboratory, and radiological findings
- Increased spectrum of pathogens, opportunistic infections, reactivation/resurgence of latent infections.
- Increased susceptibility to the nosocomial and community-acquired infections.
- Increased risks of infection during acute illnesses, intensive phase of immunosuppressive therapy, etc. warranting greater aseptic precautions and isolation.

Because of all these reasons a prompt diagnosis of sepsis or infections in such patients should be followed by early and aggressive therapy. Empirical therapy based on the local epidemiological factors/exposure and available scientific evidences should also be carried out.[3,4]

Factors which can determine the susceptibility, intensity, and timing of infections are:

- Type of the immunosuppressive agent, their dose, duration, and time sequence
- Chemotherapy, radiotherapy, and antimicrobials use
- Presence or absence of neutropenia
- Presence or absence of breached mucocutaneous surfaces, anatomic barriers, or tissue devitalization—peripheral or central vascular access, urinary or dialysis catheters, surgical drains, implants, wound or decubitus ulcers, etc.
- Presence or absence of immunodeficiency—malnutrition, humoral deficiency states (e.g., lymphoma, leukemia, myelosuppression, hypogammaglobulinemia, post-splenectomy state or functional asplenia), autoimmune disease, uremia, hyperglycemia, hepatic insufficiency or frank cirrhosis, iron overload states, etc.
- Infection by immunomodulating viruses [HIV, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and hepatitis B and C virus].

Along with systemic signs of infection, manifestations of dissemination to pulmonary, gastrointestinal, central nervous systems; cutaneous, joint, bone, ocular, and hepatosplenic invasion; opportunistic infections (e.g., *Mycobacterium avium* complex, nocardia, aspergillosis, cryptococcosis, histoplasmosis, candidiasis, CMV/EBV infections, etc.) can be seen in immunocompromised patients.

TIMELINE OF INFECTION

There are characteristic time windows in which the likelihood of infection with some pathogens becomes greater in immunocompromised patients.[5,6]

- *0–4 weeks*: Nosocomial infections—donor or recipient-derived infections and infections with antimicrobial resistant species are common.
- *1–6 months*: It is period of intense immunosuppression. In this period, opportunistic infections, activation of latent infection, and relapse are common.
- *>6 months*: Community-acquired infections are common, which depends on net state of immunosuppression.

MANAGEMENT

General Measures/Universal Management[7-9]

- *Initial resuscitation*: Taking care of airway and breathing should be followed by fluid resuscitation guided by dynamic parameters like response to a passive leg raise or a fluid bolus, using stroke volume (SV), stroke volume variation (SVV), pulse pressure variation (PPV), or echocardiography, serum lactate levels, and capillary refill time.[9]
- *Source control*: Drainage of an abscess, debriding infected necrotic tissue, removal of a potentially infected device, or definitive control of a source of ongoing microbial contamination like intra-abdominal abscesses, perforation or infections, soft tissue or deep space infections (e.g., empyema or septic arthritis), and implanted device infections. Cessation of high doses of immunosuppression and optimization of disease or medications causing immunosuppression should also be taken care of to break the vicious cycle.
- Monitoring and expert supportive care in the intensive care unit
- Antimicrobial therapy

The following principles should be kept in mind when deciding on initiation of empiric antimicrobial treatment:

- Allow the local antibiogram to guide primary empiric therapy. Keep in mind susceptibility patterns of the healthcare setting and current antibiotics being used.
- Start therapy targeting broad spectrum of organisms known to cause the specific disease. If aerobic gram-negative bacilli are a concern, start treatment with broad-spectrum bactericidal drug like antipseudomonal beta-lactam (BL) drug (cefepime) or a beta lactam/beta-lactamase inhibitor (BL/BLI) combination (piperacillin/tazobactam) or a carbapenem (meropenem). If the clinical case scenario indicates presence of multidrug resistant (MDR) organisms or patient is seriously ill (septic shock), add a fluoroquinolone, aminoglycoside, or colistin/polymyxin B.

  Similarly, even though antibiotic coverage against MDR gram-positive organisms like methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant enterococcus (VRE) may not be routinely started, they must be utilized in clinical scenarios where their presence is a possibility or if grown in culture. These scenarios include skin and soft tissues infections (SSTIs) and infected central or peripheral intravenous catheter-related bloodstream infection (CRBSI).
- Optimize pharmacokinetic and pharmacodynamic principles to increase antimicrobial activity of the drugs. BL antibiotics may be used as infusions rather than bolus to optimize activity against offending bacteria.
- Where appropriate (intra-abdominal infections or if culture indicates anaerobic organisms) add antibiotic with activity against anaerobes.
- Send appropriate biomarkers (galactomannan, beta-D-glucan) and fungal culture for suspected systemic invasive fungal infections. Patients who have received broad-spectrum antibiotics are on long-term steroids, total parenteral nutrition, have prolonged neutropenia (>10 days), have previous history of invasive fungal disease, or chest computed tomography suggestive of mucorales related lung infiltrate should be considered candidates for systemic antifungal therapy. Echinocandins (caspofungin, micafungin, and anidulafungin) should be first choice of antifungal drug in these patients except where mucorales are suspected. Voriconazoles is to be used for suspected or confirmed aspergillosis while liposomal amphotericin B is preferred for mucormycosis.
- Viral infections are rarely (<4%) the cause of sepsis and septic shock.[10] Influenza and severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) (in current pandemic scenario) are known to cause sepsis and organ dysfunction. Appropriate drug therapy for these viruses should be started early. Other viral infections are common in immunocompromised patients including herpes simplex virus (HSV), EBV, CMV, adenoviruses, tropical disease-causing viruses (dengue, chikungunya, viral hemorrhagic fever causing viruses). Unfortunately, antiviral drugs are available for very few of these diseases [acyclovir for varicella-zoster virus (VZV) or HSV and ganciclovir for CMV].

Role of intravenous immunoglobulin (IVIG) therapy in sepsis: Recent guidelines recommend against the use of IVIG in patients with sepsis.[9] These guidelines considered evidence from recent meta-analyses.[11-13] Though there was a trend toward reduced mortality (RR: 0.73; 95% CI: 0.51–0.91)

following administration of IVIG, the studies included were riddled with problems (small size, inherent high risk of bias, imprecise study design, etc.).

Role of granulocyte-macrophage colony-stimulating factor (GM-CSF): Immunoadjuvant therapy by GM-CSF stimulates the production of neutrophils and monocytes by the bone marrow. This cytokine also potently stimulates the activation and survival of monocytes and accelerates bacterial clearance, leading to faster recovery, decreased duration of hospital stay, earlier ventilator weaning, and decreased medical costs without deleterious adverse effects.[14]

Role of stem cell transplantation therapy in sepsis: Use of stem cell transplantation in the management of sepsis is still restricted to animal models and occasional preclinical study. Studies in animals have demonstrated efficacy of stem cells in mice model of sepsis. There is reduced inflammation, increased phagocytosis, decreased apoptosis, and reduced mortality.[15,16] But studies in humans are still premature (phase 1 studies) and a bit in the future.[17]

Targeted gene therapy against nuclear factor-κB and activator protein-1[18] and specific adoptive T-cell therapy for primary immunodeficiency and viral and fungal infections have also shown promise for the management of sepsis, especially in immunocompromised host.

Prophylactic and time to time administration of vaccines (with the exceptions of live vaccines in immunocompromised) against vaccine preventable diseases can also prevent or at least decrease mortality or severity of infections and thus sepsis.

SEPSIS IN SPECIFIC IMMUNOCOMPROMISED POPULATION

Cancer and Neutropenic Patients

Patients with sepsis and septic shock should follow treatment principles as outlined above under universal management. Treatment with antibacterial antiviral and antifungal drugs should adhere to these principles. Along with third-generation cephalosporin a neutropenic patient may require initiation of an antipseudomonal carbapenem and an aminoglycoside; addition of vancomycin for MRSA; linezolid or daptomycin for VRE and candida coverage.

Hematopoietic stem cell recipient: While, cell-mediated and humoral deficiencies related issues are more common in neutropenic pre-engraftment phase (2–4 weeks) and early post-engraftment (4 weeks to 3 months), late post-engraftment phase (>3 months), and later period is characterized by chronic GVHD and severe community acquired infections.[3]

Sepsis in organ transplant recipient: The treatment of sepsis does not differ majorly from nontransplant patients. But the duration of treatment may vary depending on factors such as adequacy of source control, penetration of antibiotics at infected site, and severity of the infection. Carbapenems will be the mainstay of treatment in these classes of patients.[19] Addition of colistin/polymyxin B should be done as for nonorgan transplant patients.

For kidney transplant patients with sepsis, early radiological investigations to rule out anatomical complications (e.g., ureteral or vascular anastomotic leakage, ureteral stenosis) and aggressive and early source control (e.g., perinephric collection) is important and often lifesaving. For patients with liver transplant presenting with, if the source of sepsis is a hepatic abscess in the presence of vascular thrombosis, factors like prolonged duration of antibiotic treatment (due to poor tissue levels of antibiotics) as well as drainage of abscess (percutaneous or surgical) and control of biliary leak, if any, need to be factored in the management plan. In the heart transplant patient with sepsis due to sternal wound infection or mediastinal infection, appropriate source control (wound debridement, thoracotomy) will be needed. Pulmonary infections are most common after lung transplantation, because of allograft exposure to external environment and donor lung flora, impaired lymphatic drainage and mucociliary clearance, and diminished cough reflex.[20] Sepsis due to fungal infections also needs to be kept in mind when dealing with these patients and appropriate antifungal drugs should be started.

Transplant patients with CMV infection should be treated with IV ganciclovir 5 mg/kg twice a day for 2 weeks. Transplant patients with Pneumocystis carinii pneumonia (PCP) infection should receive trimethoprim-sulfamethoxazole (TMP-SMX) with the trimethoprim component being 20 mg/kg/day in 3–4 divided doses for 2 weeks. If these patients develop hypoxia, steroids (prednisone 1 mg/kg/day) should be added for 1 week. If transplant patients develop infective diarrhea and sepsis with septic shock, consider treatment with carbapenem (meropenem 2 g IV TID) + ganciclovir 5 g/kg BD IV and vancomycin 125 mg PO QID (if risk factors for *Clostridium difficile* infection present).[21]

Sepsis in HIV-infected patients: If these patients present with respiratory tract infections leading to acute respiratory failure (ARF), treatment should be as for other patients with severe pneumonia and ARF (IV beta-lactams and macrolide).[22] If there are no clinical and chest X-ray signs suggestive of lobar involvement and CD$ count is <200/mm^3 then PCP should be suspected and treated with TMP-SMX (TMP 15–20 mg/kg/day plus SMX 75–100 mg/kg/day given q6h or q8h). Hypoxic patients should receive adjunctive steroids.

Human immunodeficiency virus-infected patients who develop respiratory tract infections and ARF and have risk factors for getting infected with pseudomonas or MRSA should receive appropriate therapy for these infections.

Those patients with CD4 count <100/mm^3 should be investigated aggressively for disseminated tuberculosis (TB) and treated on finding evidence of TB infection. Empirical antituberculous treatment (ATT) should be avoided.

If the HIV-infected patient presents with meningitis-like picture, they should be started on ceftriaxone 2 g IV BD plus vancomycin intravenously. Cryptococcal meningitis should be treated with liposomal amphotericin B (3–5 mg/kg IV OD) plus flucytosine (100 mg/kg/day orally in four divided doses) for a minimum of 2 weeks.[23] If flucytosine is unavailable, add fluconazole (800 mg OD orally). If toxoplasmosis is suspected combination of pyrimethamine plus sulfadiazine plus leucovorin should be started.

Sepsis-induced immunosuppression: Sepsis causes apoptosis (programed cell death) and marked reduction of immune cells in various organs, including CD4+ and CD8+ T cells, B cells, and follicular dendritic cells.[24-26] This reduction in immune cells occurs in various organ systems, including the gut. This allows for easy translocation of bacteria into the bloodstream. This leads to continued systemic inflammatory response and also causes secondary infections. Sepsis not only causes reduction of the immune cells but also causes dysfunction of the remaining cells (compromised T-cell effector activity, exhaustion of the T cells, dysregulated cytokine activity and reactivation of latent viruses). Therefore, targeting immunosuppression provides a logical approach to treat protracted sepsis. If this sepsis-induced immunosuppression can be corrected it may lead to improvement in morbidity and mortality due to sepsis. Agents such as interleukin-7 (IL-7), anti-programed cell death 1 (anti-PD-1) antibody, and anti-programed cell death 1 ligand (anti-PD-L1) antibody have shown promise in preclinical tests. If patients, who will benefit from such therapy, can be identified (by biomarker studies) then it will be of great help to these patients.

CONCLUSION

Sepsis commonly affects and complicates the course of all immune-compromised patients. Clinicians should have a low threshold of suspicion when it comes to sepsis in such patients. Urgent steps are needed in the management of these patients, as their very survival is at stake. Precise and directed care including diagnostic procedures and targeted therapy is required for improving the survival rate of these patients. Moreover, further research directed toward solving clinical dilemmas which arise in the management of these patients is the need of the hour.

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801-10.
2. Tolsma V, Schwebel C, Azoulay E, Darmon M, Souweine B, Vesin A, et al. Sepsis severe or septic shock: outcome according to immune status and immunodeficiency profile. Chest. 2014;146:1205-13.
3. Linden PK. Approach to the immunocompromised host with infection in the intensive care unit. Infect Dis Clin North Am. 2009;23:535-56.
4. Kalil AC, Opal SM. Sepsis in the severely immunocompromised patient. Curr Infect Dis Rep. 2015;17:487.
5. Fishman JA. Infection in Solid-Organ Transplant Recipients. N Engl J Med. 2007;25:2601-14.
6. Gabrielli A. Critical Care, 4th edition. Philadelphia: Lippincott Williams and Wilkins; 2009.
7. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases' society of America. Clin Infect Dis. 2011;52(4):e56-93.
8. Penack O, Becker C, Buchheidt D, Christopeit M, Kiehl M, von Lilienfeld-Toal M, et al. Management of sepsis in neutropenic patients: 2014 updated guidelines from the Infectious Diseases working party of the German Society of Hematology and Medical Oncology. Ann Hematol. 2014;93(7):1083-95.
9. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47(11):1181-247.
10. Vincent JL, Sakr Y, Singer M, Martin-Loeches I, Machado FR, Marshall JC, et al. Prevalence and outcomes of infection among patients in intensive care units in 2017. JAMA. 2020;323(15):1478-87.
11. Alejandria MM, Lansang MA, Dans LF, Mantaring JB 3rd. Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock. Cochrane Database Syst Rev. 2013;9:CD001090.
12. Busani S, Damiani E, Cavazzuti I, Donati A, Girardis M. Intravenous immunoglobulin in septic shock: review of the mechanisms of action and meta-analysis of the clinical effectiveness. Minerva Anestesiol. 2016;82(5):559-72.
13. Cui J, Wei X, Lv H, Li P, Chen Z, Liu G. The clinical efficacy of intravenous IgM enriched immunoglobulin (pentaglobin) in sepsis or septic shock: a meta-analysis with trial sequential analysis. Ann Intensive Care. 2019;9(1):27.
14. Mathias B, Szpila BE, Moore FA, Efron PA, Moldawer LL. A Review of GM-CSF therapy in sepsis. Medicine (Baltimore). 2015;94:e2044.
15. Lombardo E, van der Poll T, DelaRosa O, Dalemans W. Mesenchymal stem cells as a therapeutic tool to treat sepsis. World J Stem Cells. 2015;7(2):368-79.
16. Gonzalez-Rey E, Anderson P, González MA, Rico L, Büscher D, Delgado M. Human adult stem cells derived from adipose tissue protect against experimental colitis and sepsis. Gut. 2009;58(7):929-39.
17. Perlee D, van Vught LA, Scicluna BP, Maag A, Lutter R, Kemper EM, et al. Intravenous infusion of human adipose mesenchymal stem cells modifies the host response to lipopolysaccharide in humans: a randomized single blind parallel group placebo-controlled trial. Stem Cells. 2018;36(11):1778-88.

18. Hattori Y, Hattori K, Suzuki T, Palikhe S, Matsuda N. Nucleic-acid based gene therapy approaches for sepsis. Eur J Pharmacol. 2018;833:403-10.
19. Dizdar OS, Ersoy A, Akalin H. Pneumonia after kidney transplant: Incidence, risk factors, and mortality. Exp Clin Transplant. 2014;12:205-11.
20. Avery RK. Infections after lung transplantation. Semin Respir Crit Care Med. 2006;27:544-51.
21. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of clostridium difficile-associated diarrhea, stratified by disease severity. Clin Infect Dis. 2007;45:302-7.
22. Barbier F, Coquet I, Legriel S, Pavie J, Darmon M, Mayaux J, et al. Etiologies and outcome of acute respiratory failure in HIV-infected patients. Intensive Care Med. 2009;35: 1678-86.
23. Tan IL, Smith BR, von Geldern G, Mateen FJ, McArthur JC. HIV-associated opportunistic infections of the CNS. Lancet Neurol. 2012;11:605-17.
24. Hotchkiss RS, Swanson PE, Freeman BD, Tinsley KW, Cobb JP, Matuschak GM, et al. Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction. Crit Care Med. 1999;27:1230-51.
25. Felmet KA, Hall MW, Clark RS, Jaffe R, Carcillo JA. Prolonged lymphopenia, lymphoid depletion, and hypoprolactinemia in children with nosocomial sepsis and multiple organ failure. J Immunol. 2005;174:3765-72.
26. Kasten KR, Prakash PS, Unsinger J, Goetzman HS, England LG, Cave CM, et al. Interleukin-7 (IL-7) treatment accelerates neutrophil recruitment through gamma delta T-cell IL-17 production in a murine model of sepsis. Infect Immun. 2010;78(11):4714-22.

CHAPTER 8

Newer Biomarkers in Sepsis: What after Procalcitonin?

Ashit V Hegde

INTRODUCTION

A biomarker has been defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes or pathogenic processes."[1]

The ideal features of sepsis biomarkers according to G Lippi are:[2]

- Should be present early enough (before or at symptom onset)
- Should be highly sensitive and specific for infections.
- Should be capable of identifying the causative organism
- Should help predict the clinical course
- Should provide information on the prognosis
- Should help in guiding therapeutic decisions.

Of course there is no ideal bio marker yet.

The biomarkers that are most often used in the management of patients with sepsis are C-reactive protein (CRP) and procalcitonin (PCT).

C-reactive protein is a very sensitive marker of sepsis but is not very specific because CRP levels rise in a variety of noninfectious inflammatory conditions.

Procalcitonin seems to perform better than CRP but is more expensive. A meta-analysis of three trials seemed to suggest that PCT did not make a significant difference in patient outcomes. On the basis of these three trials and the subsequent meta-analysis, the Surviving Sepsis Guidelines 2021 recommend against the routine measurement of PCT for the diagnosis of sepsis.[3]

Therefore, the search for the ideal biomarker continues.

The immune response to infection involves a variety of proteins, soluble receptors, and cytokines. Some of these chemicals are being evaluated as potential biomarkers. Potential biomarkers may be useful in diagnosis or in prognostication or both.

NEWER DIAGNOSTIC BIOMARKERS[4,5]

Presepsin

Presepsin is the soluble form of CD14 which is a glycoprotein expressed on the membrane of immune cells when they are stimulated by lipopolysaccharides. The exact role of presepsin is not yet clear. It is probably involved in the phagocytosis and in the cleavage of microorganisms by lysosomes. Presepsin levels rise during bacteremia before PCT. It is therefore a potential early biomarker of sepsis. Several studies and meta-analyses have concluded that it probably performs better than PCT in the diagnosis of sepsis.[6]

The value of presepsin in determining the prognosis in patients with sepsis is however debatable. There have been conflicting reports from different studies.

In conclusion presepsin is clearly amongst the front runners in the race to replace PCT in the diagnosis of sepsis. Its role in the prognostication of sepsis is not yet established however

Soluble Triggering Receptor Expressed on Myeloid Cells 1

Soluble triggering receptor expressed on myeloid cells 1 (sTREM-1) is a soluble form of triggering receptor expressed on myeloid cells 1 (TREM-1) which is present on the surfaces of neutrophils and monocytes. It actively participates in the inflammatory response. It is involved in the activation of toll-like receptors and in the stimulation of the production of proinflammatory cytokines. Many studies have suggested that sTREM-1 levels might be a useful biomarker for the diagnosis of sepsis. However, in a recent systematic review, the conclusion was that sTREM was a moderate diagnostic marker with a sensitivity (pooled) of 79% and specificity of 80%.

However, sTREM levels in body fluids might be of value in separating infections from noninfections.

CD64

CD64 is an immunoglobulin receptor that is usually expressed at low levels on neutrophils. Its levels rise considerably in response to stimulation by endotoxin or proinflammatory cytokines.

Several studies have suggested that the CD64 index is a reasonable diagnostic marker of sepsis. A large meta-analysis involving 3,944 patients surmised that CD64 had a mean sensitivity of 0.76 [95% confidence interval (CI) 0.74–0.78] and specificity of 0.85 (95% CI 0.83–0.86). The quality of some of the studies included in this meta-analysis has however been questioned. CD64 has potential but it is a costly and laborious test. Its utility therefore is not firmly established yet.

Pentraxins

Pentraxins (PTXs) are a kind of soluble pattern recognition molecules (PRMs). Depending on the length of the N-terminal region, they are divided into long and short PTXs. Pentaxrin-3 (PTX-3) is one of the long PTXs.

Pentaxrin-3 is released from several cells involved in inflammation after they have been stimulated by toll-like receptor agonists. PTX-3 is an immune modulator and has antimicrobial properties. The diagnostic value of PTX-3 in sepsis has been demonstrated in several studies. It is reasonably sensitive for predicting 28-day mortality but is not very specific. Combining PTX-3 with other biomarkers may improve its performance but this needs to be proven.

Calprotectin[7]

Calprotectin is a calcium-binding protein. Calprotectin has two subunits—calgranulin A and calgranulin B. Calprotectin is released from activated cells following exposure to a microbe and takes part in the inflammatory processes. It also inhibits the growth of microbes. It is also involved in the metabolism of calcium, zinc, and manganese.

Calprotectin has been shown to be a specific marker for bacterial infection in several studies. A cohort study in an intensive care unit concluded that serum calprotectin was more accurate than PCT for the diagnosis of bacterial infection [area under the curve (AUC) 0.76, 95% CI 0.65–0.86] versus (AUC 0.63, 95% CI 0.49–0.77).

More studies are needed before measurement of calprotectin can be recommended routinely in ICU patients with sepsis.

NEWER PROGNOSTIC BIOMARKERS[8,9]

Adrenomedullin and the Mid-regional Fragment of Proadrenomedullin

Endothelial cells and vascular smooth muscle cells produce adrenomedullin (ADM) which is one of the vasodilatory peptides. It also plays an important role in the amplification of the inflammatory response. ADM however is removed from circulation very quickly and it is not practically possible to measure its level. The mid-regional fragment of proadrenomedullin (MR-proADM) is more stable than ADM and its levels correlate with the levels of active ADM.

Several studies have indicated that MR-proADM levels may be useful prognostic markers in sepsis. This needs further validation.[10]

suPAR

Many immunologically active cells express urokinase type plasminogen activator receptor (uPAR). Bacterial infections cause the release of soluble urokinase type plasminogen activator receptor (suPAR).

Soluble urokinase type plasminogen activator receptor levels do not have any diagnostic utility in sepsis but might be of prognostic value. An increase in the levels of suPAR is associated with a higher mortality. In a study of 273 ICU patients, a level of >8 ng/mL predicted high mortality with a moderate degree of specificity and sensitivity.

Monocyte Chemoattractant Protein-1

When the proinflammatory pathway is stimulated, monocyte chemoattractant protein-1 (MCP-1) which is a soluble chemokine is secreted by several immune cells. MCP-1 enables the recruitment of these cells to the site of injury. Increased levels of MCP-1 may predict a poor prognosis in patients with sepsis.

MicroRNAs

MicroRNAs (miRNAs) are one of the small noncoding RNAs. They comprise about 1% of the human genome, but regulate up to 50% of all human protein-coding genes. miRNAs play an important regulatory role in the pathophysiology of sepsis.

Studies seem to suggest that the levels of miRNAs might serve as prognostic markers in sepsis. In one study, the AUC of miR-125b for predicting 28-day mortality was 0.699 (95% CI 0.603–0.795), similar to the SOFA score or the APACHE II score.

Long Noncoding RNAs

These are a class of noncoding RNAs with transcripts of >200 nucleotides. They play a role in the innate and adaptive immune responses. An increase of lnc-NEAT1 levels in patients with sepsis correlated with APACHE II and SOFA scores and was associated with worse outcomes according to a few studies.

There is still much to be learnt about the functions of these noncoding RNAs however and measurement of their levels cannot be recommended at present.

Angiopoietins

Angiopoietins (Angpts) belong to the family of angiogenic growth factors. Vascular endothelial cells secrete these growth factors under the conditions of stress. Angpt-1 and Angpt-2 bind to the endothelial cell-specific Tie2 receptor.

In septic patients, higher levels of Angpt-2 or an increased Angpt-2/1 ratio have been be associated with a poor prognosis.

Therefore a number of potential biomarkers for the diagnosis of sepsis have been developed. These molecules are mainly involved in the initial pathogenesis of the innate immune response to infection, and in many cases, they show prognostic value as well as diagnostic value.

An ideal biomarker for sepsis has not been developed yet and is unlikely to be discovered in the near future. A strategy that uses a combination of biomarkers might be the best possible way forward.

For example, it was shown in a study that sepsis could be ruled out with confidence when the levels of sTREM-1, PCT, and PMN CD64 were all below the cut-off value and could be diagnosed with near certainty when the levels of all the three biomarkers were above the cut-off. Measurement of suPAR, sTREM-1, and MIF in combination has also been shown to be more useful than the level of any of the individual biomarkers.[9,11]

SUMMARY

PCT and CRP have their limitations and there is a need for better biomarkers. Though presepsin (for diagnosis) and adrenomedullin (for prognosis) are the most promising of all the potential new biomarkers, a combination of biomarkers are likely to be more useful (though more expensive) than any single biomarker. It is unlikely however that biomarkers will ever replace clinical judgment.

REFERENCES

1. Doherty M, Wallis RS, Zumla A; WHO-Tropical Disease Research/European Commission joint expert consultation group. Biomarkers for tuberculosis disease status and diagnosis. Curr Opin Pulm Med. 2009;15(3):181-7.
2. Lippi G. Sepsis biomarkers: past, present and future. Clin Chem Lab Med. 2019;57(9):1281-3.
3. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith C, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021;49(11):e1063-143.
4. Kim M, Choi J. An update on sepsis biomarkers; Infect Chemother. 2020;52(1):1-18.
5. Larsen FF, Petersen JA. Novel biomarkers for sepsis: A narrative review. Eur J Int Med. 2017;45:46-50.
6. Zhang X, Liu D, Liu YN, Wang R, Xie LX. The accuracy of presepsin (sCD14-ST) for the diagnosis of sepsis in adults: a meta-analysis. Crit Care. 2015;19(1):323.
7. Jonsson N, Nilsen T, Gille-Johnson P, Bell M, Martling CR, Larsson A, et al. Calprotectin as an early biomarker of bacterial infections in critically ill patients: an exploratory cohort assessment. Crit Care Resusc. 2017;19(3):205-13.
8. Henriquez-Camacho C, Losa J. Biomarkers for sepsis. Biomed Res Int. 2014;2014:547818.
9. Raveendran AV, Kumar A, Gangadharan S. Biomarkers and newer laboratory investigations in the diagnosis of sepsis. J R Coll Physicians Edinb. 2019;49(3):207-16.
10. Önal U, Valenzuela-Sánchez F, Vandana KE, Rello J. Mid-regional pro-adrenomedullin (MR-proADM) as a biomarker for sepsis and septic shock: narrative review. Healthcare (Basel). 2018;6:E110.
11. Gibot S, Béné MC, Noel R, Massin F, Guy J, Cravoisy A, et al. Combination biomarkers to diagnose sepsis in the critically ill patient. Am J Respir Crit Care Med. 2012;186(1):65-71.

CHAPTER 9

Infection Prevention: Why Still a Nightmare?

Prasanna Kumar Mishra, Samir Sahu

INTRODUCTION

Nosocomial infection, also called hospital-acquired infection, is defined by World Health Organization (WHO) as follows: "An infection acquired in a hospital by a patient who was admitted for a reason other than that infection."[1] With rising antibiotics resistance all over the world, hospital deaths being high in intensive care units (ICUs), infection control has become an essential part of ICU management and priority at many institutions. But that's never been an easy task particularly in India. It is a nightmarish situation on which we have tried to put some light.

WHAT IS THE NEED FOR INFECTION PREVENTION?

Healthcare-associated infections (HAIs) increase hospital stay, mortality, and costs. The frequency of infection varies in different parts of world. A prevalence survey conducted by WHO in eight countries and 33 hospitals showed higher incidence of infection in South Asian countries compared to Europe. Accurate estimates of HAIs in India are limited. Routine and reliable surveillance data is absent. HAI publications are mostly from individual hospitals consisting of short-term prospective studies and point prevalence surveys from some units of large hospitals. The prevalence of HAIs in these studies range from 7 to 18%.[2] HAIs in India is high and is more than double of that in Europe and the US.[3] In a study in 2006, it was found device associated infection is >14%.[4] Infection prevention will therefore reduce healthcare costs and improve patient safety. HAI is also a major safety concern for both healthcare workers and the patient.

HOW TO PREVENT INFECTION IN THE INTENSIVE CARE UNIT?

Five basic principles of infection control and prevention is universally accepted which are as follows:

- Hand hygiene
- Use of personal protective equipment
- Safe handling and disposal of sharp, chemical waste, blood and body fluid secretion
- Standard precaution based on risk assessment, make use of common sense practices
- Prevention of patient to patient infection spread (transmission-based precaution).

Infection prevention and control (IPC) programs have been instituted in many settings in an effort to decrease HAIs and has been standardized irrespective of place and person. Core components relevant to the facility-level infection prevention and control program include the following:[5]

- IPC programs
- Evidence-based guidelines
- Education and training
- Healthcare-associated infection surveillance
- Multimodal strategies
- Monitoring and audit of IPC practices and feedback
- Workload, staffing, and bed occupancy
- Built environment, materials, and equipment for IPC.

The first step in an IPC is to form a Hospital Infection Control Committee (HICC). The HICC should consist of a dedicated infection control nurse (ICN), one for each 100 beds, a clinical microbiologist as its head, a hospital administrator, clinicians, nursing, housekeeping, and members from ancillary departments necessary for infection control. HICC should develop evidence-based guidelines. Indian Society of Critical Care Medicine (ISCCM) in their guidelines on Infection control have commented and suggested various aspects of care based on evidence.[6] Isolation, body fluid exposure, alcohol based hand rub, changing gloves between tasks, avoiding re-use of single use items, daily washing with chlorhexidine, skin care before insertion of central venous catheter (CVC), filtering of air in ICU, education and training of staff, and audit of antimicrobial use. Many other guidelines have or less strength of evidence.[6]

All the healthcare professionals should be trained. Written policies should be available. The backbone of infection control is written policies and education. Surveillance of hospital-acquired infections should be done according to

standardized definitions. Multimodal strategies need to be tried for implementation of infection control. By monitoring specific HAIs such as surgical site infections (SSIs), catheter-associated urinary tract infections (CAUTIs), ventilated-associated pneumonia (VAP), and central line associated blood stream infections (CLABSIs), the problem areas can be identified. Areas of improvement can be assessed by gathering initial data and continuous monitoring. Areas that require improvement after implementation of the program can be identified. Audit of the infection control practices and giving feedback to the stakeholders improves compliance and implementation. For implementing the above adequate staff, infrastructure (office space, computers, etc.), materials, and equipment should be available. HICC members should meet regularly and discuss the data and areas of concern.

Infection control includes general hygiene and cleanliness, standard precautions, equipment cleaning, sterilization and disinfection, and laundry management. It also includes wide availability of hand hygiene, gloves, masks, soaps, and disinfectants. There should be provision for pre- and postexposure prophylaxis and proper biomedical waste management.

National Accreditation Board of Hospitals (NABH) is an autonomous body. The certification process includes infection prevention and control, and surveillance of healthcare-associated infections. Hospital accreditation is not mandatory in India. Therefore, very few private hospitals have sought NABH accreditation. These hospitals have an HICC and an infection prevention programs. Some institutes use infection prevention and control bundles to prevent surgical site infections and infections from indwelling devices.[7] Implementation of bundles to reduce infection rates is feasible in India.[8]

WHAT ARE THE BARRIERS TO INFECTION CONTROL IN INDIA?

There are around 70,000 hospitals in India. Most of the healthcare facilities in India do not have adequate systems and infrastructure for infection prevention and control. Only around 800 NABH accredited private hospitals have an HICC. What is the level of implementation in these hospitals is not known.

There are many issues why infection control is a nightmare in India. First hospitals are poorly designed. The ventilation is poor. There is lack of isolation facilities, especially for respiratory isolation. Negative pressure isolation is almost unheard off. Overcrowding, shortage of well-trained staff, very poor nurse/patient ratio, rampant, and indiscriminate use of antimicrobial agents that contribute to drug resistance are a hindrance to infection control. The COVID-19 pandemic brought out these deficiencies.

Hand hygiene is the most common and effective method of reducing HAIs. 80% of infections transmitted in a hospital is due to poor hand hygiene practices. Compliance with hand hygiene by healthcare workers is poor due to several constraints such as knowledge, attitude, workload, and availability.[9] The first step is to make hand rubs widely available. It is the cheapest way of reducing HAIs. Most of the public hospitals did not have this provision before the COVID-19 pandemic. Some awareness about hand hygiene was brought about during the H_1N_1 pandemic in 2009–2010 but everyone forgot it quickly after the pandemic subsided. Apart from making hand rubs available, the ease with which it can be used is also important. Hand rubs should be placed in a transparent bottle so that when it is empty it can be identified and refilled promptly. The bottle should have plunger dispensing system. The place where they are placed should be easily accessible and frequent reminders should be put at prominent places to use hand rub. Hanging a hand rub bottle at the foot end of the bed is the best place for increasing compliance of hand hygiene among healthcare professionals. All healthcare professionals should be taught about the technique of hand rub and the five moments for using hand hygiene. Once this is implemented, the ICN needs to monitor hand hygiene compliance.

The next step is to start surveillance of HAIs. HICC is not present in majority of the hospitals in India. Therefore, there is no data regarding HAIs in majority of the hospitals. The extent of the problem of HAIs is not known, therefore measures to address it are nonexistent. Through surveillance the rates of HAIs can be known and areas which have problem can be addressed. Gathering initial data and continued surveillance can assess areas which need improvement after program implementation. Prospective clinical surveillance is expensive. Each facility has to start at some stage with repeated point prevalence, laboratory, and prescription surveillance and work toward prospective clinical surveillance.[10]

THE WAY FORWARD

Infection control program is not present in most public hospitals. Policy and guidelines are needed at the national level. In 2016, the Indian Council of Medical Research released guidelines on infection prevention and control.[11] *Kayakalp* (clean hospital initiative) was launched by the National Health Mission under the *Swachh Bharat Abhiyan* (clean India mission). The aim was to promote and reward cleanliness, hygiene, and infection control practices in public healthcare facilities.[12]

There are many challenges for successful implementation of an infection prevention and control program in Indian healthcare settings. Funding is insufficient, human resources are not there, hospitals are overcrowded, and low nurse-to-patient ratios in ICUs.[3,8]

Concerted efforts and long-term implementation of recommended procedures will be needed to strengthen

infection prevention and control capacity among staff in healthcare settings. Ways have to be found to support standardized surveillance of healthcare-associated infections in India. Surveillance data has to be linked to the implementation of infection control policies, interventions, and indicators according to local needs. Once improvements are seen in infection control practices and reduction of healthcare-associated infections it will be easier to get the commitment and funding to sustain these infection prevention and control programs.

Surveillance methodology is necessary to understand preventive strategy that helps in effective infection control. Surveillance in the Indian Council of Medical Research network is coordinated by the All India Institute of Medical Sciences. It has been started in the medical, surgical, and pediatric ICUs of 20 network sites. It will be expanded in the coming years. Healthcare-associated infection surveillance data will provide estimates of the resistant pathogens among these infections. Surveillance data of infection prevention and control practices for insertion and maintenance of devices also needs to be collected. Use of central lines in ICUs, infection prevention, and control practices differ according to the characteristics of the institutions, availability of clinical supplies, and whether patients' families have to buy the supplies for device insertion. Information from different sites, input of clinicians, microbiologists, and infection control staff on the wards have been used to develop appropriate bundle for central line insertion and maintenance. Adherence to these bundles can be assessed, measured, and reported. Surveillance data will be used to monitor the progress and effect of these interventions.[13]

Institutional capacity building for infection prevention and control is a priority. Each network facility has completed a self-assessment using a standardized WHO tool to collect information on administrative and staff support and laboratory and monitoring capacity.[14] Data collected till now suggest there is a need for additional capacity building of infection prevention and control staff. This is one of the main goals of the networks. Training will strengthen knowledge and practice of infection prevention and control among healthcare professionals. Trained teams of infection control staff will improve and sustain implementation of infection prevention and control interventions and surveillance healthcare-associated infections. They will help in detection of potential outbreaks of healthcare-associated infections and its response.[15]

For having an IPC program, there has to be adequate funding for which the hospital administration has to be onboard. Separate budget has to be allocated for IPC program. Hospitals who are seeking NABH accreditation are setting out resources to achieve the NABH requirements. The public and other private hospitals should budget for IPC program like having an ICN, supporting surveillance, hand hygiene, disinfection and biomedical waste management, education, and training.

In an IPC program, the microbiologist is usually the team leader. The ICN reports to the microbiologist. All infection control surveillance data is presented regularly and action is taken to see there is consistent decrease in HAIs in the hospital and improvement in the compliance of infection control practices.

To have a successful antibiotic stewardship program, the microbiologist has to share his local antibiogram at least once a year.

WHY INFECTION CONTROL IS A NIGHTMARE?

The elements of surveillance, a key factor in infection control, like administrative control of medical equipment that establishes and recommends various procedures in handling it, administrative control of healthcare personnel that involves training and evaluation at intervals and administrative control of patient which defines policy for hospital admission, patient isolation, epidemiological surveillance with reporting by concerned personnel, are perceived negatively by the healthcare workers.

Majority of the hospitals do not have an HICC. There are inadequate trained staff for infection control. All healthcare professionals should be trained in infection control. There are very few educational programs on infection control. Infection control does not find a place in the undergraduate syllabus. Microbiologists are not trained or exposed to infection control.

There are very few hospital architects in India. Therefore, the hospitals are not designed for controlling infectious diseases. There are inadequate isolation beds both positive pressure and negative pressure isolation beds. Ventilation is not taken into account while planning hospitals.

The cheapest method of infection control like hand hygiene is nonexistent in most hospitals. In spite of this pandemic, hand hygiene is still suboptimal. In the best of ICUs in the world, the compliance to hand hygiene is around 60%. Therefore, human behavior and culture of hand hygiene has to be improved by innovative ways. National guidelines and standards for infection control are not there in India. We do not have any regulation to collect and report surveillance data. Without surveillance data, no intervention can be planned to reduce it.

A WORD ON COVID-19 NIGHTMARE

Looking at COVID-19 pandemic, the infection prevention and control was a nightmare as little was known about the virus, the way it spreads, to whom it affects. As it was a pandemic, the infection spread from public to healthcare workers and vice versa. Standard infection prevention of hand hygiene, putting a mask, and social distancing was advised and it was a difficult task to implement, particularly in

India, as many did not care. Severe and regular containment of public places and vaccination was helpful at last. It was a nightmarish situation as death occurred in most unexpected cases.

More over during the pandemic, the HAIs all over the developed countries have increased by 30–40%.[16] It must be worse in India. Our hospital surveillance data shows that there has been increase in HAIs in 2020.

CONCLUSION

To reduce HAIs and improve infection control in the healthcare settings in India, we need to have national guidelines and standards of infection control. These should be mandatory for hospital registration. Until these are implemented we need to educate and train staff and implement hand hygiene to start with.

REFERENCES

1. Ducel G (Ed). Prevention of Hospital Acquired Infection, A Practical Guide, 2nd edition. Switzerland: World Health Organization; 2002.
2. Kumar A, Biswal M, Dhaliwal N, Mahesh R, Appannanavar SB, Gautam V, et al. Point prevalence surveys of healthcare-associated infections and use of indwelling devices and antimicrobials over three years in a tertiary care hospital in India. J Hosp Infect. 2014;86(4):272-4.
3. Allegranzi B, Bagheri Nejad S, Combescure C, Graafmans W, Attar H, Donaldson L, et al. Burden of endemic health care-associated infection in developing countries: systematic review and meta-analysis. Lancet 2011;377(9761):228-41.
4. Rosenthal VD, Maki DG, Saloma R Moveno CA, Mehta Y, Higguera F, et al. Device-associated nosocomial infections in 55 intensive care units of 8 developing countries. Ann Int Med. 2006;145:582-91.
5. World Health Organization. Improving infection prevention and control at the health facility: Interim practical manual supporting implementation of the WHO Guidelines on Core Components of Infection Prevention and Control Programmes. Geneva: World Health Organization; 2018.
6. Mehta Y, Gupta A, Todi S, Mytra SN, Samadar DP, Patil V, et al. Guidelines for prevention of Hospital Infection: Ind J Crit Care Med. 2014;18(3):149-63.
7. Kumar A, Biswal M, Dhaliwal N, Mahesh R, Appannanavar SB, Gautam V, et al. Point prevalence surveys of healthcare-associated infections and use of indwelling devices and antimicrobials over three years in a tertiary care hospital in India. J Hosp Infect. 2014;86(4):272-4.
8. Mehta Y, Jaggi N, Rosenthal VD, Kavathekar M, Sakle A, Munshi N, et al. Device associated infection rates in 20 cities of India, data summary for 2004-2013: Findings of the International Nosocomial Infection Control Consortium. Infect Control Hosp Epidemiol. 2016;37(2):172-81.
9. Kennedy AM, Elward AM, Fraser VJ. Survey of knowledge, beliefs and practices of neonatal Intensive Care Unit health care workers regarding nosocomial infections, central venous catheter and hand hygiene. Infect Control Hosp Epidemiol. 2004;25(9):747-52.
10. Maki G, Zervos M. Healthcare-acquired infections in low- and middle-income countries and the role of infection prevention and control. Infect Dis Clin N Am. 2021;35(3):827-39.
11. Indian Council of Medical Research. Hospital infection control guidelines. 2016. [online] Available from: http://icmr.nic.in/guidelines/Hospital Infection control guidelines-2. [Last accessed January, 2022].
12. National Health Mission. Clean hospital initiative. 2015. [online] Available from: http://www.kayakalpindia.com/. [Last accessed January, 2022].
13. Swaminathan S, Prasad J, Dhariwal AC, Guleria R, Misra MC, Malhotra R, et al. Strengthening infection prevention and control and systematic surveillance of healthcare associated infections in India. BMJ. 2017;358: j3768.
14. World Health Organization. Core components of infection prevention and control programmes: assessment tools for IPC programmes. WHO, 2011.
15. Walia K, Ohri VC, Mathai D. Antimicrobial Stewardship Programme of ICMR. Antimicrobial stewardship programme (AMSP) practices in India. Indian J Med Res. 2015;142(2):130-8.
16. Weiner-Lastinger LM, Pattabiraman V, Konnor RY, Patel PR, Wong E, Xu SY, et al. The impact of coronavirus disease 2019 (COVID-19) on healthcare-associated infections in 2020: A summary of data reported to the National Healthcare Safety Network. Infect Control Hosp Epidemiol. 2022;43(1):12-25.

10

CHAPTER

Acinetobacter Sepsis: What do We have?

Reshu Gupta Khanikar, Reena Shah, Rakhee Baruah

INTRODUCTION

More than 50 species have been identified in the genus *Acinetobacter*, out of which *A. baumannii* (AB), *A. calcoaceticus*, and *A. lwoffi* are the species most frequently reported in the clinical literature. The term *A. calcoaceticus–A. baumannii* complex (ACB) is comprised of genospecies 1 (*A. calcoaceticus*), genospecies 2 (*A. baumannii*), genospecies 3, and genospecies 13TU. *A. baumannii* (genospecies 2 of the ACB complex) is the most resistant of the genospecies and has the greatest clinical importance. This organism has become a global menace because of its antimicrobial resistance and its propensity to cause nosocomial outbreaks. A. *baumannii* has also been identified as an ESKAPE pathogen (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species), a group of pathogens with a high rate of antibiotic resistance that are responsible for the majority of nosocomial infections. According to World Health Organization (WHO), AB is considered as one of the critical priority pathogens amongst the resistant organisms. It can cause serious infections such as pneumoniae, meningitis, urinary tract infections, bacteremia, skin, and soft tissue infections. It can be spread by direct person to person, contact with contaminated surfaces or equipment, contaminated hands of healthcare providers.

ACINETOBACTER—THE MICROBIOLOGY, EPIDEMIOLOGY, AND RISK FACTORS

Acinetobacter spp. are aerobic, nonmotile, gram-negative coccobacilli that are catalase positive, oxidative negative, and glucose nonfermenting, indole negative organism **(Figs. 1 to 3)**. *Acinetobacter* infections are most frequently seen in humid temperate climate, the most likely explanation may be that the humid air favors the growth of the organism. It preferentially colonizes in aquatic environment. In humans, they colonize in organs with high fluid content such as respiratory tract, cerebrospinal fluid (CSF), peritoneal fluid, and urinary tract. It is a natural inhabitant of soil, water with pets and arthropods being the other possible reservoirs.

Fig. 1: Colonies of *Acinetobacter baumannii* on MacConkey agar plate.

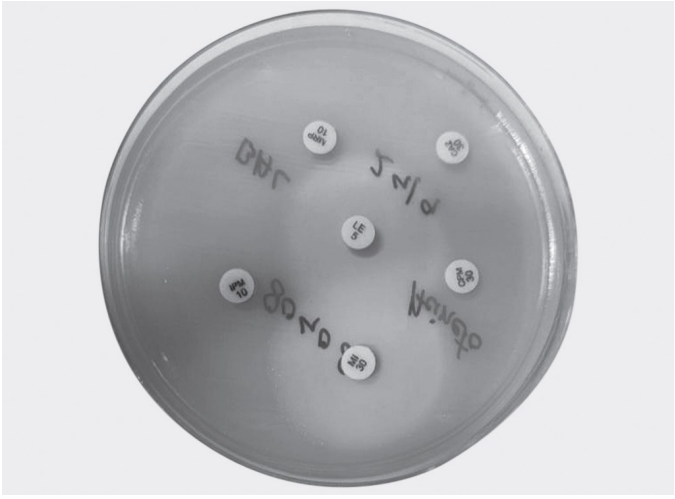


Fig. 2: Antibiotic sensitivity testing on Mueller–Hinton agar plate.

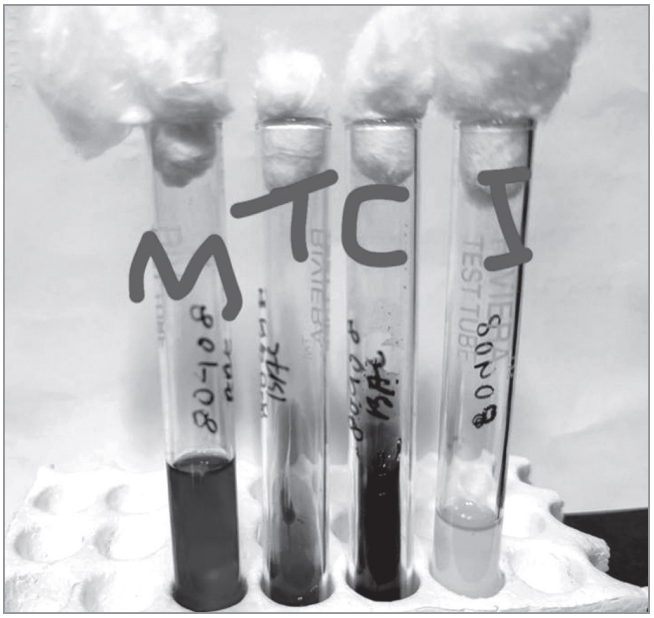


Fig. 3: Biochemical testing—indole, citrate, triple sugar iron, and mannitol.

CLINICAL IMPACT

Acinetobacter alone has been associated with nosocomial infections, especially in intensive care unit (ICU), community-acquired infections, and infections associated with natural disasters and war causalities and neonatal infections.

- Nosocomial infections:
  - Ventilator-associated pneumonia (VAP) isolates
  - Surgical site infection isolates
  - Catheter-associated urinary tract infection isolates
  - Bloodstream infections
  - CLABSI (central line-associated bloodstream infection) isolates
  - Wound infections
  - Secondary meningitis
- *Community-acquired infections:* It is mostly reported from Asia and Australia during the wet season. It manifested as a clinical entity with incidence of bacteremia. Patients with chronic obstructive pulmonary disease (COPD), diabetes mellitus, cancer, alcoholism, and tobacco use were more prone to have community-acquired infections.
- *Infection associated with natural disasters and war causalities*: The prevalence is usually high following exposures to natural disasters and wars.
- In the neonatal intensive care unit (NICU), AB contributes to 0.2–6.9% of all bacteremia[1] and 8–25% of all late-onset sepsis caused by gram-negative bacilli.[2] Bacteremia caused by imipenem-resistant *A. baumannii* (IRAB) has been associated with a higher mortality (46.0%) than bacteremia by imipenem-susceptible *A. baumannii* (ISAB) (28.3%) and other diagnoses of *A. baumannii* infection.[3]

RISK FACTORS

- Host factors—severe underlying disease:
  - Major surgeries
  - Major trauma
  - Newborn (prematurity)
- Exposure-related—exposure to contaminated equipment:
  - Length of hospital stay
  - Previous stay in ICU
- Invasive procedures—mechanical ventilations, catheters, and drainage tubes
- Hemodialysis
- Previous antimicrobial treatment (third-generation cephalosporins, carbapenems, and fluoroquinolones)
- Glucocorticoid therapy.

DEFINITIONS[4]

Specific definitions have been proposed by The European and United States Centers for Disease Control and Prevention (ECDC and CDC) according to the extent of their antibiotic resistance.

- *Multidrug-resistant*: Isolate is nonsusceptible to at least one agent in three or more antibiotic classes.
- *Extensively drug-resistant*: Isolate is nonsusceptible to at least one agent in all but two or fewer antibiotic classes.
- *Pandrug-resistant*: Isolate is nonsusceptible to all agents.

PROGNOSIS

According to studies, the 28-day mortality of patients with carbapenem-resistant *Acinetobacter* (CRAB) bacteremia on inappropriate treatment is around 70%.[5] The overall mortality rate with either carbapenem resistant or susceptible *Acinetobacter* infection was 33%. Some of the independent risk factors for mortality include the following:

- SOFA (sequential organ failure assessment) score >10
- Immunocompromised states
- Vasopressor use
- Platelet count <50,000/μL
- Mechanical ventilation

PATHOGENESIS (FIG. 4)

There are five main pathogenic mechanisms which are as follows:

1. *Biofilm production*: *Acinetobacter* survive well in dry conditions so it has the ability to form biofilm on a wide range of surface as they are less sensitive to desiccation. Biofilm-associated protein (BaP) is needed for biofilm maintenance and maturation. BaP is also important for colonization as it facilitates adherence to cells.
2. *Outer membrane protein A (ompA)*: OmpA is essential for making an intact biofilm, adherence to epithelial cells, binding to Factor H and cell apoptosis.

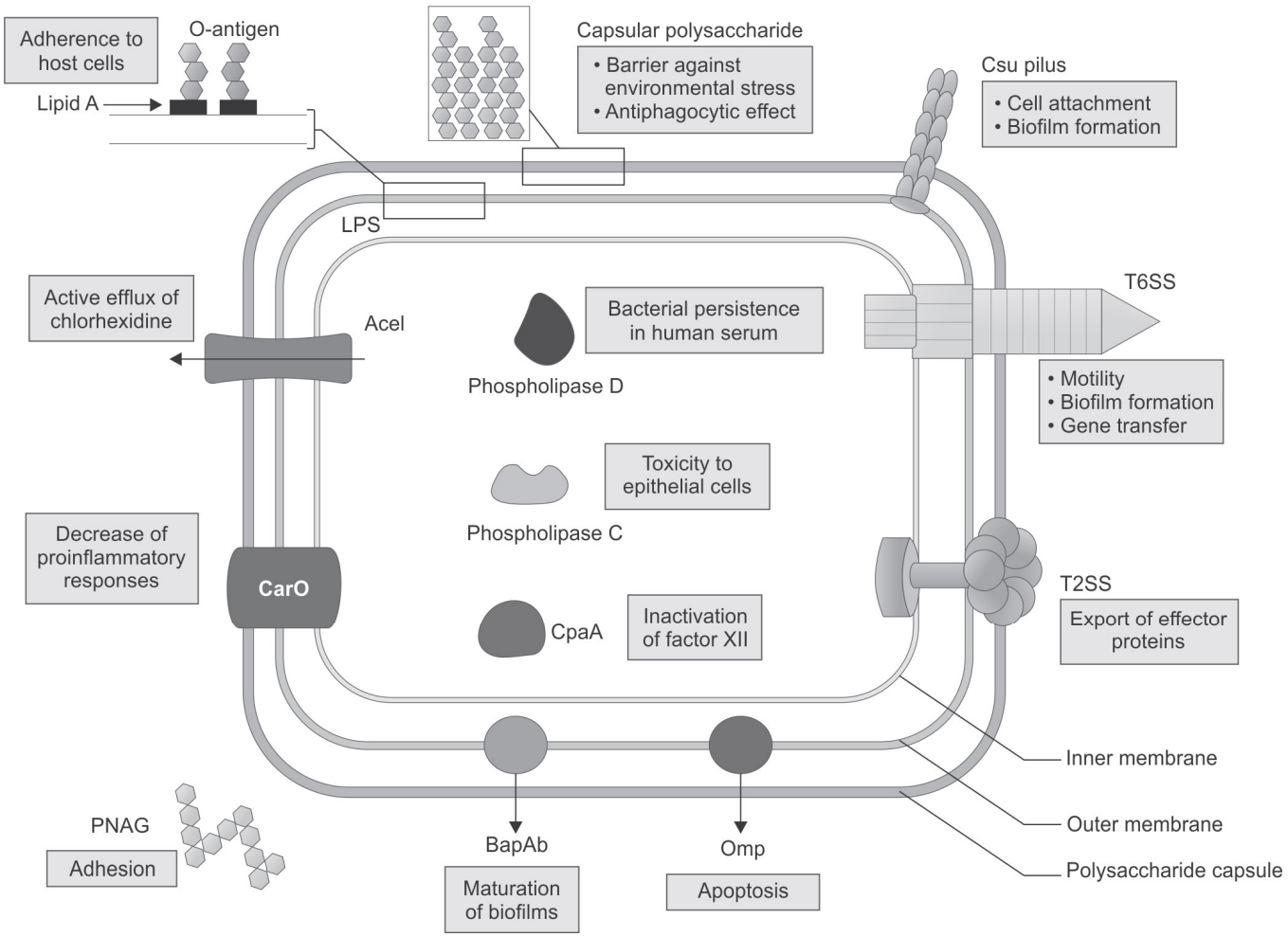


Fig. 4: Virulence determinants possessed by *Acinetobacter baumannii*. The function of each determinant is shown in the adjacent box. (AceI; *Acinetobacter* chlorhexidine efflux protein; CpaA: glycan-specific adamalysin-like protease; Csu: chaperon/usher pilus system; LPS: lipopolysaccharide; Omp: outer membrane protein; PNAG: poly-β-1,6-N-acetylglucosamine; T2SS: type II secretion system; T6SS = type VI secretion system.[6]

3. *KI capsule*: One-third of *Acinetobacter* strains produce a polysaccharide capsule that works with cell lipopolysaccharide (LPS) and prevents complement activation and also delays phagocytosis.
4. *Siderophore-mediated iron acquisition system*: AB can use multiple siderophores for iron acquisition, but only "Acinetobactin" is required for virulence. Thus, they survive long in iron-deficient conditions.
5. *Fimbriae*: Fimbriae helps attach the organism to surfaces and help colonizing biotic surfaces.

DIAGNOSIS

The diagnosis of *Acinetobacter* infection is made by the growth of *Acinetobacter* from the specimen (e.g., sputum, blood, and CSF) in the setting of other clinical findings that suggest an infection at that site. Since *Acinetobacter* colonization is common and treatment difficult and potentially associated with substantial toxicity, distinction between colonization and infection, with treatment reserved for true infections, is important. As an example, *Acinetobacter* isolated from sputum of a ventilated patient in the absence of fever, leukocytosis, increased respiratory secretions, need for additional respiratory support, or a new abnormality on chest imaging is more likely to represent colonization than infection.[7]

Rapid diagnostic tests (RDTs) provide a more rapid and accurate diagnosis for AB infections as compared to the conventional microbiological methods. RDTs along with active antimicrobial stewardship (AMS) intervention has shown to improve the patients clinical outcomes and decreases mortality primarily by improving the time to effective antimicrobial therapy.[8]

ACINETOBACTER BAUMANNII INFECTION SYNDROMES

The most common clinical manifestations of *Acinetobacter* infections are VAPs and bloodstream infections. Also AB can cause suppurative infections in any organ system including urinary tract, respiratory tract, gastrointestinal tract, skin wounds, and meninges as shown in **Table 1**.

TABLE 1: *Acinetobacter* infection syndromes.

Infection syndromes	*Route of entry*	*Risk factors*	*Symptoms*	*Treatment*
Pneumonia	Nose and mouth	ICU admission, mechanical ventilation	Fever, chills, and cough	Broad-spectrum cephalosporin, combination beta lactam/beta-lactamase inhibitor (including sulbactam), or a carbapenem. When resistance rates are high then an antipseudomonal fluoroquinolone, aminoglycoside, or colistin should be added
Blood infection	IV Catheters	Immunocompromised patients	Fever, chills, and vomiting	Monotherapy with carbapenems, polymyxins, OR combination of cefoperazone/sulbactam and tigecycline
Meningitis	Shunt or drain in the head	Recent brain surgery	Fever, altered sensorium headache	Carbapenem, Ceftazidime or cefepime can also be used at meningeal doses. Treatment of *Acinetobacter meningitis* is usually at least 3 weeks
Urinary tract infection	Urinary catheter	Diabetes, immunocompromised patients	Frequent urination, pain or burning during urination, blood in the urine, cloudy or foul-smelling urine, and altered mental status	Treatment should be started if patient has systemic signs with pyuria and a positive culture Tigecycline should be used only if no other options available as it has poor excretion in urinary tract
Skin or wound infection	Skin opening/ open wound		Fever and redness, increasing pain, and pus around the wound	In addition to appropriate antimicrobials, affected tissue should be debrided, especially in osteomyelitis. These patients should be treated for 4–6 weeks after surgical debridement

TREATMENT

Therapeutic options for susceptible organisms are as follows:

- Broad-spectrum cephalosporin (ceftazidime or cefepime)
- Combination beta-lactam/beta-lactamase inhibitor (including sulbactam as it is bactericidal against *Acinetobacter*)
- Carbapenem (e.g., imipenem, meropenem, or doripenem).

General Approach to Antimicrobial Selection

Empiric Therapy

Empiric antibiotic therapy for *Acinetobacter*, before results of antimicrobial susceptibility testing are available, should be selected based on local susceptibility patterns. It should consist of a broad-spectrum cephalosporin, a combination beta-lactam/beta-lactamase inhibitor (e.g., a combination including sulbactam), or a carbapenem. Carbapenems are highly bactericidal against susceptible strains of *Acinetobacter*.[9] The clinical cure rates with imipenem for VAP due to *Acinetobacter* range from 57 to 83%.[10] Because isolates that are susceptible to imipenem may be resistant to meropenem, and vice versa, susceptibility to the specific carbapenem should be confirmed prior to its use. Monotherapy should be initiated according to the antimicrobial susceptibility reports, favoring choosing the agent with the narrowest spectrum of activity. An additional agent may be warranted if local resistance rates to the chosen antibiotic class are high (e.g., >10–15%).[10] When ampicillin-sulbactam, cephalosporins, and carbapenems are used as single agents, there may be emergence of resistance so they are sometimes used in combination with an antipseudomonal fluoroquinolone or an aminoglycoside. While there are no clear clinical data to support this practice for *Acinetobacter* infections, some experts favor empiric combination therapy for serious infections with these and other potentially resistant gram-negative organisms due to high mortality associated with inappropriate empiric therapy.[11]

Directed Therapy

Once results of antimicrobial susceptibility testing are available, a regimen can be chosen from among the active agents. If results of antimicrobial susceptibility testing reveal susceptibility to beta-lactams or carbapenems, an agent from one of these classes should be chosen as monotherapy. The agent with the narrowest spectrum of activity should be chosen. With any of these agents, there is the risk of resistance emerging during therapy. However, there are no data to demonstrate that adding a second agent limits this risk. For cases of *Acinetobacter*

central nervous system infections, variable penetration of antibiotics into the CSF further limits the selection of antibiotics.

There are no clinical data that shows improved outcomes with combination versus monotherapy, and some randomized trials have suggested that certain combinations (colistin and rifampin or colistin and meropenem) resulted in comparable clinical outcomes as monotherapy with colistin.[12] Nevertheless, infections with multidrug-resistant *Acinetobacter* are associated with high mortality rates, and the concern is that the use of a single agent may not be adequate. Note that resistance can develop during therapy, leaving no therapeutic alternatives.

CARBAPENEM-RESISTANT *ACINETOBACTER* INFECTIONS[13]

Carbapenem-resistant *Acinetobacter* infections are posing significant challenges in hospital settings. They are mostly recovered from respiratory specimens and wounds. Production of OXA-24/40 carbapenemases, OXA-23 carbapenemases, metallo-β-lactamases, and additional serine carbapenemases are responsible for developing resistance to carbapenems.

TREATMENT

Mild Carbapenem-resistant *Acinetobacter* Infections

Mild CRAB infections include infection of urinary tract, skin and soft tissue, trachea with no evidence of hemodynamic instability. Preferred therapeutic approach is monotherapy with ampicillin and sulbactam. Alternative treatment options are minocycline, tigecycline, polymyxin B, cefiderocol, colistin for cystitis **(Table 2)**. However, if mild CRAB infection is not susceptible to ampicillin sulbactam then high dose of Ampicillin Sulbactam is an effective option or might need an additional second agent.

Moderate-to-severe Carbapenem-resistant *Acinetobacter* Infections

Combination therapy is recommended in moderate and severe CRAB infections. High-dose of ampicillin sulbactam is used as a component of combination therapy. Step down to single active agent is suggested only after clinical improvement.

Combination Therapy

Combination antimicrobial therapy has favorable outcomes on multidrug-resistant isolates. The combinations may be:

- Carbapenem with colistin
- Tigecycline with colistin
- Vancomycin with colistin
- Minocycline with colistin
- Meropenem and fosfomycin with colistin

It is known to decrease the risk of emergent resistance, and to improve outcomes in multidrug-resistant infections. The 30-day mortality rate associated with combination therapy is much lower than monotherapy.[14,15]

TABLE 2: Suggested dosing of antibiotics for the treatment of carbapenem-resistant *Acinetobacter* (CRAB).

Agents	*Adult dosage*
Ampicillin: Sulbactam	9 g IV q8hr over 4 hours OR 27 g IV q24hr as continuous infusion For mild infections susceptible to amp/sul administer 3 g IV q4hr
Cefiderocol	2g IV q8hr, infused over 3 hours
Colistin (for CRAB cystitis)/ polymyxin B	As per international consensus guidelines on polymyxin
Eravacycline	1 mg/kg/per dose IV q12hr
Imipenem-cilastatin	Cystitis (standard infusion); 500 mg IV q6hr infused over 30 minutes All other infections (extended infusion) 500 mg IV q6hr over 3 hours
Meropenem	Cystitis (standard infusion): 1 g IV q8hr All other CRAB infections: 2 g IV q8hrly infused over 3 hours
Minocycline	200 mg IV /PO q12hr
Tigecycline	200 mg IV first dose followed by 100 mg IV q12hr

(IV: intravenous)

PREVENTION AND CONTROL[16]

The goals for control of multidrug-resistant *Acinetobacter* are early recognition, aggressive control of spread, and preventing establishment of endemic strains.

Several infection controls are important and include the following:

- Strict protocols for such as hand hygiene, clothing, cleaning, and terminal disinfection of the environment and surfaces, disinfection and sterilization of reusable medical devices by healthcare workers from inside and outside the ICU.
- Single room isolation of patients or cohorting of colonized/infected patients in designated areas of the ICU, allocation of dedicated materials for patient care.
- Enhancement of contact precautions to interrupt transmission, including alcohol-based hand rub and use of disposable gloves and gowns.
- Provide training and information to all nursing and ancillary staff regarding the identified critical areas and operational and technical procedures.

- Compulsory placement of medical devices and personal protection devices (overalls, gloves, etc.) at the point where the patient is assisted for immediate access, in both structural and functional isolation.
- Evaluation of the process of environmental sanitation and adoption of specific disinfection procedures using.

CONCLUSION

Acinetobacter sepsis has become an alarming health hazard with upsurge of the multidrug resistant isolates due to irrational use of antibiotics. With the limited treatment options new strategies are needed to prevent and treat infections aggressively. Strict infection control policies and protocols, early recognition, aggressive control of spread, and appropriate antimicrobial therapy to prevent establishment of the endemic strains is the need of the hour.

REFERENCES

1. Wu JH, Chen CY, Tsao PN, Hsieh WS, Chou HC. Neonatal sepsis: a 6-year analysis in a neonatal care unit in Taiwan. Pediatr Neonatol. 2009;50(3):88-95.
2. Hsu JF, Chu SM, Lien R, Chiu CH, Ming-Chou Chiang MC, Fu RH, et al. Case-control analysis of endemic *Acinetobacter baumannii* bacteremia in the neonatal intensive care unit. Am J Infect Control. 2014;42(1)23-7.
3. Sheng WH, Liao CH, Lauderdale TL, Ko WC, Chen YS, Liu JW, et al. A multicenter study of risk factors and outcome of hospitalized patients with infections due to carbapenem-resistant *Acinetobacter baumannii*. Int J Infect Dis. 2010;14(9):e764-9.
4. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18(3):268-81.
5. Kim T, Lee EJ, Park SY, Yu SN, Lee YM, Park KH, et al. Natural prognosis of carbapenem-resistant *Acinetobacter baumannii* bacteremia in patients who did not receive appropriate antibiotic treatment: A retrospective multicenter study in Korea. 2018;97(43):e12984.
6. Moubareck CA, Halat DH. Insights into *Acinetobacter baumannii*: A review of microbiological, virulence, and resistance traits in a threatening nosocomial pathogen. Antibiotics. 2020;9(3):119.
7. Gozdas HT. Diagnosis of *Acinetobacter baumannii* infections. Int J Prev Med. 2012;3(11):817.
8. Wenzler E, Goff DA, Mangino JE, Reed EE, Wehr A, Bauer KA. Impact of rapid identification of *Acinetobacter baumannii* via matrix-assisted laser desorption ionization time-of-flight mass spectrometry combined with antimicrobial stewardship in patients with pneumonia and/or bacteremia. Diagn Microbiol Infect Dis. 2016;84(1):63-8.
9. Fishbain J, Peleg AY. Treatment of *Acinetobacter* infections. Clin Infect Dis. 2010;51(1):79-84.
10. Peleg AY, Adams J, Paterson DL. Tigecycline efflux as a mechanism for nonsusceptibility in *Acinetobacter baumannii*. Antimicrob Agents Chemother. 2007;51(6):2065-9.
11. Lesho E, Wortmann G, Moran K, Craft D. Fatal *Acinetobacter baumannii* infection with discordant carbapenem susceptibility. Clin Infect Dis. 2005; 41(5):758-9.
12. Durante-Mangoni E, Signoriello G, Andini R, Mattei A, De Cristoforo M, Murino P, et al. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant *Acinetobacter baumannii*: a multicenter, randomized clinical trial. Clin Infect Dis. 2013;57(3):349-58.
13. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*). Clin Infect Dis.2021;72(7):e169-83.
14. Rigatto MH, Vieira FJ, Antochevis LC, Behle TF, Lopes NT, Zavascki AP. Polymyxin B in combination with antimicrobials lacking in vitro activity versus polymyxin b in monotherapy in critically ill patients with *Acinetobacter baumannii* or *Pseudomonas aeruginosa* infections. Antimicrob Agents Chemother. 2015;59(10):6575-80.
15. Özvatan T, Akalın H, Sınırtaş M, Ocakoğlu G, Yılmaz E, Heper Y, et al. Nosocomial *Acinetobacter baumannii*: Treatment and prognostic factors in 356 cases. Respirology. 2016;21(2):363-9.
16. Bianco A, Quirino A, Giordano M, Marano V, Rizzo C, Liberto MC, et al. Control of carbapenem-resistant *Acinetobacter baumannii* outbreak in an intensive care unit of a teaching hospital in Southern Italy. BMC Infect Dis. 2016;16(1):747.

CHAPTER 11

Higher Dose of Antibiotics: When and Where?

Pratibha Dileep, Arundhati Dileep

INTRODUCTION

Infections are the major cause of mortality and morbidity in modern intensive care unit (ICU), high mortality has been seen in infections caused by multidrug resistant (MDR), extensive drug resistant (XDR), or pan drug resistant (PDR) organisms. These infections are usually severe, and are very difficult to treat. There is an associated increased risk of mortality and length of stay with such infections.[1] Rapid emergence of resistance, rampant use or misuse of antibiotics, and rising population of sicker and immunocompromised patient population has increased the incidence of hospital-acquired infections (HAIs) to a great extent. The key to successful treatment of this group of patients is early appropriate antibiotics along with other supportive care.[2] The most common MDR organisms seen in ICU are methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and carbapenem-resistant *Enterobacteriaceae* (CRE).

Studies have been performed regarding use of higher than usual dose of antibiotics in severe sepsis and septic shock caused by these MDR organisms and in certain special situations.[3] This chapter would focus on the various trials which were done for higher than usual dose of antibiotics in a very severe sepsis and septic shock is in patients admitted in the ICU, especially with nosocomial infections. A subset of these patients in ICU requires higher than usual antibiotics, like those who have life-threatening infections with MDR/XDR organisms, those who are undergoing continuous renal replacement therapy (CRRT) or are on extracorporeal membrane oxygenation (ECMO), pregnant patients with sepsis, or morbid obesity.

Pharmacokinetic–pharmacodynamic (PK/PD) optimization of antibiotics is essential for appropriate management of infections while treating this subset of patients. The optimization of antibiotics can be done more effectively by using therapeutic drug monitoring (TDM).

Clinical outcomes in patients with septic shock or severe sepsis is dependent on multitude of host factors. This is one of the reasons that sometimes-standard dosing in critically ill patients with MDR organisms may have unpredictable clinical outcome. Low concentration of antibiotics has resulted in poor outcomes in patients.[4] Best antimicrobial therapy was defined by Joseph and Redvold as 4D's "right drug, right dose, de-escalation and right duration."[5] In the initial phase of sepsis, there is increase in distribution volume, which limits therapeutic concentration of hydrophilic antibiotics in the target tissues. This necessitates loading dose of initial dose at least 1.5 times the normal dose. Defining antibiotic level in intensive care (DALI) study showed 500-fold difference in antibiotic concentration, about one-fifth of patients did not achieve PK/PD targets in severe sepsis. Higher than normal and extended infusions of antibiotics are recommended especially while treating MDR organisms.

CARBAPENEMS

Carbapenems are the highest used antibiotics in modern ICU, especially in MDR/XDR organism causing sepsis. But of late the incidence of resistance to carbapenems is rising because of high incidence of extended spectrum beta-lactamases (ESBL) and carbapenemases-induced resistance. Amongst carbapenems, the maximally used molecule is meropenem. It inhibits the bacterial cell wall synthesis by binding to penicillin-binding proteins, which inhibits the final transpeptidation pathway for peptidoglycan synthesis in turn inhibiting the cell wall biosynthesis.

A study was conducted comparing 2 g of meropenem IV Q8 over 1 g of standard dose of meropenem IV Q8 in severe sepsis and septic shock. The study randomized 76 patients. The results were showing no difference between Delta qSOFA of the standard dose group versus the high-dose meropenem group, but the high-dose group showed increased microbiological cure compared to standard dose group in the emergency department patients. Study had several limitations, like the sample was insufficient, 50% of the patients in the study had a negative culture. The study did not show that empirically higher dosage of meropenem

in critically ill patients led to any statistical difference in the clinical outcomes compare to the standard dosage of meropenem.[6]

TIGECYCLINE

Tigecycline is a glycylcycline antibiotic which binds to the 30S ribosomal subunit of susceptible bacteria and inhibits protein synthesis. It works against expanded-spectrum activity against gram-positive, gram-negative, aerobic, anaerobic, and atypical bacterial species, including antibiotic-resistant strains.

United States Food and Drug Administration (US FDA) approved dosing for tigecycline is 100 mg followed by 50 mg every 12 hours. 10 studies with 593 patients showed that higher than 200 mg/day along with other antibiotics when used concomitantly to treat *Enterobacteriaceae* and *Acinetobacter* spp. with minimum inhibitory concentration (MIC) values close to the clinical breakpoint, especially for severe infections decreased overall mortality, also improved clinical outcomes and microbiological cure rates.[7] It has especially shown good results in skin and soft tissue infections and intra-abdominal infections.

However, most of the studies were not properly powered and were done in single center, hence properly powered randomized controlled trials (RCTs) are needed to confirm the effectiveness and safety of the higher dose tigecycline compared to standard dose tigecycline.[8]

CIPROFLOXACIN

Ciprofloxacin belongs to the group of fluoroquinolones; they are bactericidal antibiotics which inhibit bacterial DNA synthesis. Intravenous ciprofloxacin dosage used usually is administered 400 mg twice daily. The study focusing on higher dosage of ciprofloxacin based on renal function and MIC to obtain target dose for susceptible pathogens.[9]

COLISTIN

Colistin (polymyxin E) are bactericidal agents which bind to lipopolysaccharides (LPS) and phospholipids in the outer cell membrane of gram-negative bacteria. Colistin is used as colistimethate a prodrug. One million IU is equal to 80 mg of colistimethate and 30 mg of colistin.

In one prospective study, 144 patients were treated with higher dose of colistin and 385 with lower-dose colistin regimens in both first and second study, the results found no significant difference in 28-day all-cause mortality.

It did show higher rates of nephrotoxicity and neurotoxicity in patients receiving higher dose of colistin.[10] However, when colistin was used as a loading dose of 9 million units or maximum 300 mg (10 million) followed by 3 million q8hrs or 4.5 million q12hr along with carbapenems it was associated with better outcome.[11]

POLYMYXIN B

Higher than usual dose loading dose of 25,000 units/kg instead of 15,000 IU and 30,000 IU/kg/day instead of 25,000 IU/kg/day maintenance dose is used in carbapenem-resistant GNB (CR-GNB). Though this dose is associated with higher renal impairment, but it has better bacterial eradication rates.[12]

MINOCYCLINE

Minocycline is a semi-synthetic derivative of tetracycline, again an old molecule introduced in 1960s. It is a broad-spectrum molecule active against Gram-positive and negative, aerobic, and anaerobic organisms. It can also be used orally. It has found a special role in use against MDR, XDR, or PDR *Acinetobacter baumannii* (*A. baumannii*). Minocycline is usually used 200 mg loading dose followed by 100 mg twice a day. Higher doses 200 mg four times a day was either used as monotherapy or in combination with either carbapenems or colistin. Clinical cure rates were found to be comparable in single or combination regimens. Though the current data shows minocycline a promising option for MDR *Acinetobacter* alone or in combination, the data is still small.[13]

SULBACTAM

High-dose sulbactam ≥6 g/day with an additional molecule such as colistin has been tried with MDR/XDR *Acinetobacter*. Sulbactam is also used in combination with levofloxacin and tigecycline. Lesser nephrotoxicity was observed in this combination.[14]

CEFIDEROCOL

Cefiderocol can be a good alternative to high-dose meropenem in Gram-negative nosocomial pneumonias. It is a novel siderophore cephalosporin with low MIC against CR-GNB. It has no role against gel permeation chromatography (GPC) or anaerobic organisms.

COMBINATION THERAPY

Combination therapy has been the mainstay of MDR infections such as combination of carbapenem with colistin or polymyxin, carbapenem with tigecycline or minocycline. There are limited data available about dosing schedule, but they have been used successfully in multiple small series of patients. Colistin with meropenem combination therapy has shown fewer side effects and better cure rates than meropenem alone or colistin alone. Triple drug combination has also been used as a desperate measure against PDR organisms.[15]

CONCLUSION

The higher dose of antibiotics in the above-mentioned studies so far have not shown any improved clinical outcomes

but there has been some improvement in microbiological eradication rates, but it comes with a price of higher toxicity. Combining two molecules can reduce the toxicity if used judiciously. Conflicting results have been there while using higher doses, the main reason seems to be smaller number of patients, hence there is a dire need of appropriately powered, well-designed RCTs to prove the efficacy of higher dose of antibiotics for severe infections.

SUMMARY OF THE RECOMMENDATION

Antibiotic	*Indication*	*Comment*
Carbapenems–meropenem	Septic shock and MDR infections	Better bacteriological clearance, higher rates adverse events
Tigecycline	MDR gram-negative intra-abdominal infections, skin, and soft tissue infections	Better outcome, under-powered studies
Ciprofloxacin	MDR gram-negative	Not much use
Colistin	MDR gram-negative	No advantage, higher nephron- and neurotoxicity
Polymyxin B	MDR gram-negative	Better bacteriological clearance but higher renal impairment
Minocycline	MDR *Acinetobacter*	Better bacteriological clearance
Sulbactam	MDR/XDR *Acinetobacter*	Works better in combination

REFERENCES

1. Arthur C, Awa Marie CS, Bent HI, Moeloek N, Motsoaledi A, Rajatanavin R, et al. Antimicrobial resistance: a priority for global health action. Bull World Health Organ. 2015;93(7):439.
2. Armstrong BA, Betzold RD, May AK. Sepsis and Septic Shock Strategies. Surg Clin North Am. 2017;97(6):1339-79.
3. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017;43(3):304-77.
4. Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, et al. DALI: defining antibiotic levels in intensive care unit patients: are current β-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis. 2014;58(8):1072-83.
5. Martínez ML, Plata-Menchaca EP, Ruiz-Rodríguez JC, Ferrer R. An approach to antibiotic treatment in patients with sepsis. J Thorac Dis. 2020;12(3):1007-21.
6. Ye X, Wang F, Zeng W, Ding Y, Lv B. Comparison of empirical high-dose and low-dose of meropenem in critically ill patients with sepsis and septic shock: A randomized controlled study protocol. Medicine (Baltimore). 2020;99(51):e22829.
7. De Pascale G, Lisi L, Ciotti GMP, Vallecoccia MS, Cutuli SL, Cascarano L, et al. Pharmacokinetics of high-dose tigecycline in critically ill patients with severe infections. Ann Intensive Care. 2020;10:94.
8. Zha L, Pan L, Guo J, French N, Villanueva EV, Tefsen B. Effectiveness and safety of high dose tigecycline for the treatment of severe infections: A systematic review and meta-analysis. Adv Ther. 2020;37(3):1049-64.
9. Gieling EM, Wallenburg E, Frenzel T, de Lange DW, Schouten JA, Ten Oever J, et al. Higher dosage of ciprofloxacin necessary in critically ill patients: a new dosing algorithm based on renal function and pathogen susceptibility. Clin Pharmacol Ther. 2020;108(4):770-4.
10. Benattar YD, Omar M, Zusman O, Yahav D, Zak-Doron Y, Altunin S, et al. The effectiveness and safety of high-dose colistin: Prospective cohort study. Clin Infect Dis. 2016;63(12):1605-12.
11. Moni M, Sangita Sudhir A, Dipu TS, Mohamed Z, Prabhu BP, Edathadathil F, et al. Clinical efficacy and pharmacokinetics of colistimethate sodium and colistin in critically ill patients in an Indian hospital with high endemic rates of multidrug Gram-negative bacterial infections: a prospective study. Int J Infect Dis. 2020;100:497-506.
12. Cai Y, Leck H, Tan RW, Teo JQ, Lim TP, Lee W, et al. Clinical experience with high dose polymyxin B against Carbapenem resistant Gram Negative bacterial infections- A cohort study. Antibiotics (Basel). 2020;9(8):451.
13. Fragkou PC, Polakou G, Blizou A, Blizou M. The role of Minocycline in the treatment of Nosocomial infections caused by Multidrug, extensively drug and pan drug resistant Acinetobacter Baumanni. A systemic review of clinical evidence. Microorganisms. 2019;7(6):159.
14. Liu J, Shu Y, Zhu F, Feng B, Zhang Z, Liu L, et al. Comparative efficacy and safety of combination therapy with high dose sulbactam or Colistin with additional antibacterial agents for multiple drug-resistant and extensive drug-resistant *Acinetobacter Baummani* infections: a systematic review and network meta-analysis. J Glob Antimicrob Res. 2021;24:136-47.
15. Assimakopoulos SF, Karamouzos V, Lefkaditi A, Sklavou C, Kolonitsiou F, Christofidou M, et al. Triple combination therapy with high dose ampicillin/sulbactam, high dose Tigecycline and Colistin in the treatment of ventilator associated pneumonia caused by pan drug resistant Acinetobacter baumannii a case series study. Infez Med. 2019;27(1):11-6.

CHAPTER 12

Immunoglobulins in Sepsis: Where to Use?

Payel Bose, Saurabh Debnath

INTRODUCTION

Sepsis associated with multiorgan dysfunction syndrome and septic shock imposes an overwhelming burden on worldwide healthcare and is associated with mortality rate of 22 and 76%,[1] respectively. Sepsis occurs due to a complicate interplay among the microorganism and the defense mechanism of the host. It is the deleterious outcome of dysregulation of the immune response and alteration of homeostasis. The inflammatory pathway is activated, proinflammatory mediators are released, coagulation system is enhanced, fibrinolysis is impaired, and complement-mediated lymphopenia occurs. All of these events results in impairment of tissue perfusion and resultant organ failure. The fine tuning between the proinflammatory and the anti-inflammatory response is disrupted during sepsis development. The attributes of the patient, such as age, genotype, comorbidities, immune status, and level of nourishment determine the balance between these opposing phases.

There has been a paradigm shift in the pathogenesis of sepsis. Attention has been diverted from systemic inflammatory response syndrome (SIRS) to compensative anti-inflammatory response syndrome (CARS), which is also capable to bring about organ dysfunction. The fine tuning between the proinflammatory and the anti-inflammatory response is disrupted during sepsis development. Cytokine storm is induced with excessive production of inflammatory chemokines such as interleukins (IL-1 and IL-6), tumor necrosis factor (TNF) α.[2] Then anti-inflammatory mechanisms come into play, apoptotic mediators induce with an attrition of CD4 and CD8 T lymphocytes, dendritic cells, and B cells.[3] Activating cell-surface molecules, such as human leukocyte antigen (HLA)-DR, are also down-regulated, T cells are exhausted, suppressor cells such as T regulatory cells and myeloid-derived s cells are increased **(Fig. 1)**.[4-6]

Though there have been path-breaking researches in the arena of diagnostic tests, the mortality rate for sepsis is still very high and new therapeutic armamentarium is the need of the day. A parameter is needed to monitor the immunologic responses and select personalized therapeutic immune-modulating strategies.

Intravenous immunoglobulin (IVIg) is obtained from a pool of healthy human volunteers. Therapeutic uses include patients with antibody deficiencies (primary or acquired), hematological, neurological, and systemic inflammatory disorders. IVIg administration maintains normal trough IgG level and reduces the number and severity of acute septic complications.

Immunoglobulins G, A, and M (IgGAM) preparations (which contains all three immunoglobulin classes such as human plasma) are physiological compositions.[7] Pentaglobin contains about 12% each of IgM and IgA with 76% IgG. Pentaglobin consists of antibodies which are effective against both gram-positive and gram-negative bacteria by binding toxins and neutralizing their effects by bacterial agglutination.[8,9] Trimodulin is the other compound, containing a greater concentration of IgM (23%) and IgA (21%), which is under clinical research.[10] IgA exerts strong anti-inflammatory effect on mononuclear cells and monocytes. IgM has increased opsonin titers. IgGAM leads to downregulation of IL-2, B-lymphocytes are not that activated. The production of proinflammatory TNF, IL-4, and IL-5 therefore decreases. Hence, better results have been observed when IgM and IgA containing preparations are used.

The clinical rationale for IVIg therapy in sepsis lies in (1) identification and neutralization of microbes and toxins, (2) counterpoising the action of the inflammatory mediators, and (3) prevention of apoptosis of immune cells. Previous studies revealed that a specific macrophage receptor existed with the ability to identify sialic acid-rich residue, reiterating the contribution of sialic acid residues and IgG Fc fragment in immunomodulation.[11] Polyvalent IVIg improves opsonization, prevents complement mediated damage, counteracts endotoxin and superantigens **(Fig. 2)**.[12]

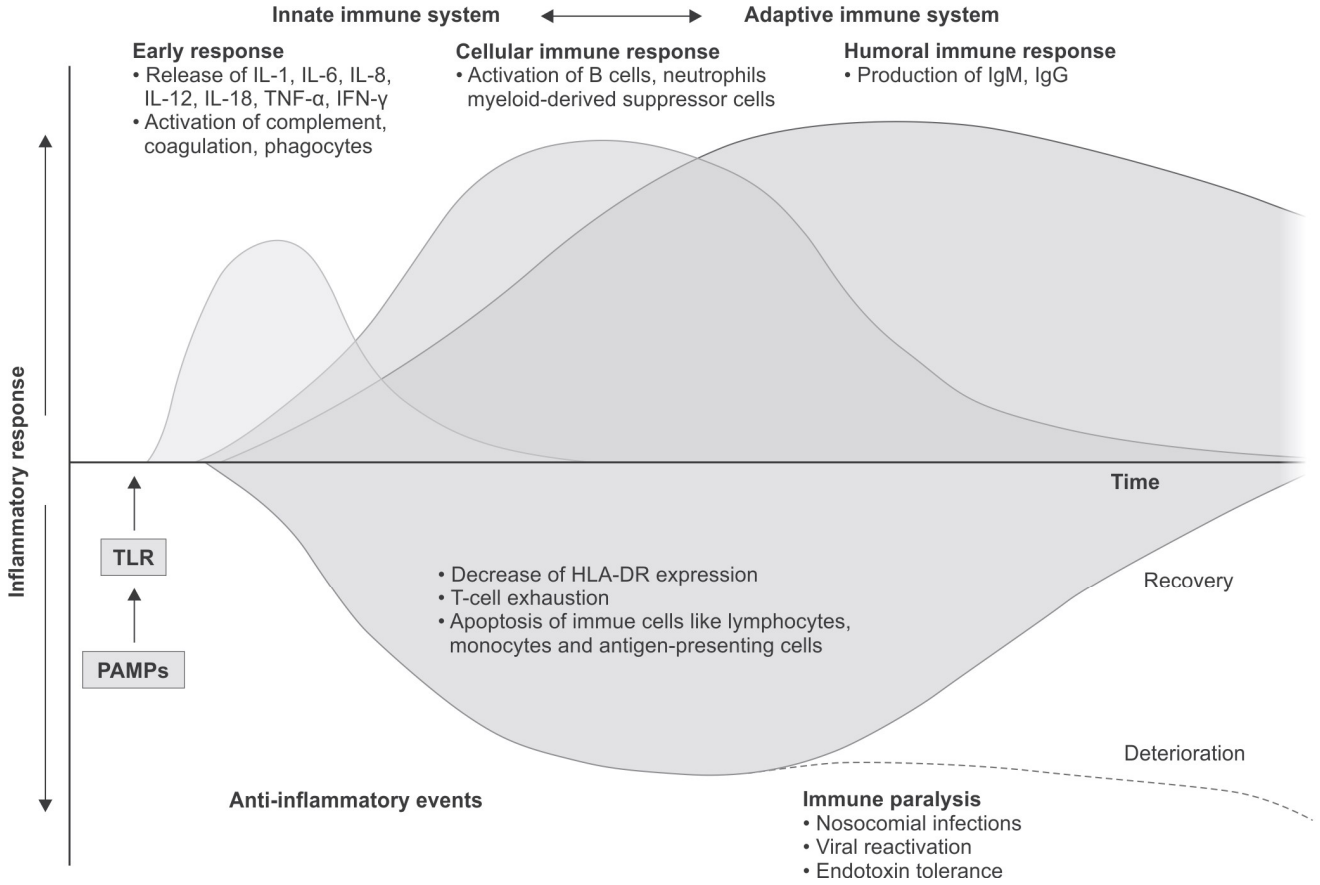


Fig. 1: Pro- and anti-inflammatory changes of the immune system during the course of sepsis and septic shock.
(HLA-DR: human leukocyte antigen-D related; IgM/G: immunoglobulin M/G; IL: interleukin; IFN-g: interferon gamma; PAMPs: pathogen-associated molecular patterns; TNF-a: tumor necrosis factor alpha; TLR: toll-like receptor.)

INTRAVENOUS IMMUNOGLOBULIN AND SEPSIS—LITERATURE REVIEW

Asakura et al.[13] showed that lipopolysaccharide infusion in animal models led to multiorgan dysfunction and disseminated intravascular coagulation. IVIg leads to modulation of T cell subgroups such as Th-17 and regulatory T cells (T_{reg}). Hence, inflammatory mediators such as IL-17A, IL-17F, IL-21, and CCL20 are produced in lesser quantity. Therefore, IVIg renders protective anti-inflammatory effects during sepsis.

Kessel et al.[14] demonstrated that CD4+, CD25+ T cells suppresses TNF-α production. Polyclonal IVIg and those solutions which are enriched with IgA and IgM, improve the integrity of the blood-brain barrier. Catalytic antibodies of the IgG and IgM isotypes remove metabolic wastes and protect from bacterial infections by conversion of molecular oxygen into hydrogen peroxide and ozone. Lacroix-Desmazes et al.[15] showed that septic patients with high catalytic rates of IgG survived better.

The Cochrane Library meta-analysis (Alejandria et al. in 2000),[16] and its further updated version in 2002[17] revealed that mortality rate was reduced in the patients who received IgM-enriched preparations. However, uniform definition of sepsis severity was lacking and patient population was also small in maximum studies.

Ohlsson et al. in 2001[18] studied the effect of using IVIg prophylactically in neonatal sepsis. The meta-analysis revealed that nonspecific IVIg resulted in reduction of incidence of sepsis. But definite reduction in mortality was not observed. However, further meta-analyses (2004 and 2010)[19,20] revealed that there was statistically significant reduction of mortality when IVIg was used in the treatment of proven infection in newborn infants.

Neonatal sepsis differs from sepsis in adults or older children. The transplacental transfer of Igs takes place after 32 weeks of gestational age and Igs are endogenously synthesized after 24 weeks of birth. Hence, it would be prudent to consider that immunoglobulin serves a dual purpose, as replacement and as well as immune-modulation therapy in neonatal sepsis.

Cochrane meta-analyses by Alejandria et al. in 2010[21] and subsequent studies[22-25] showed that mortality was significantly reduced in adults treated with polyclonal IVIg as well as with IgM- and IgA-enriched preparations. However, there was no significant reduction in mortality

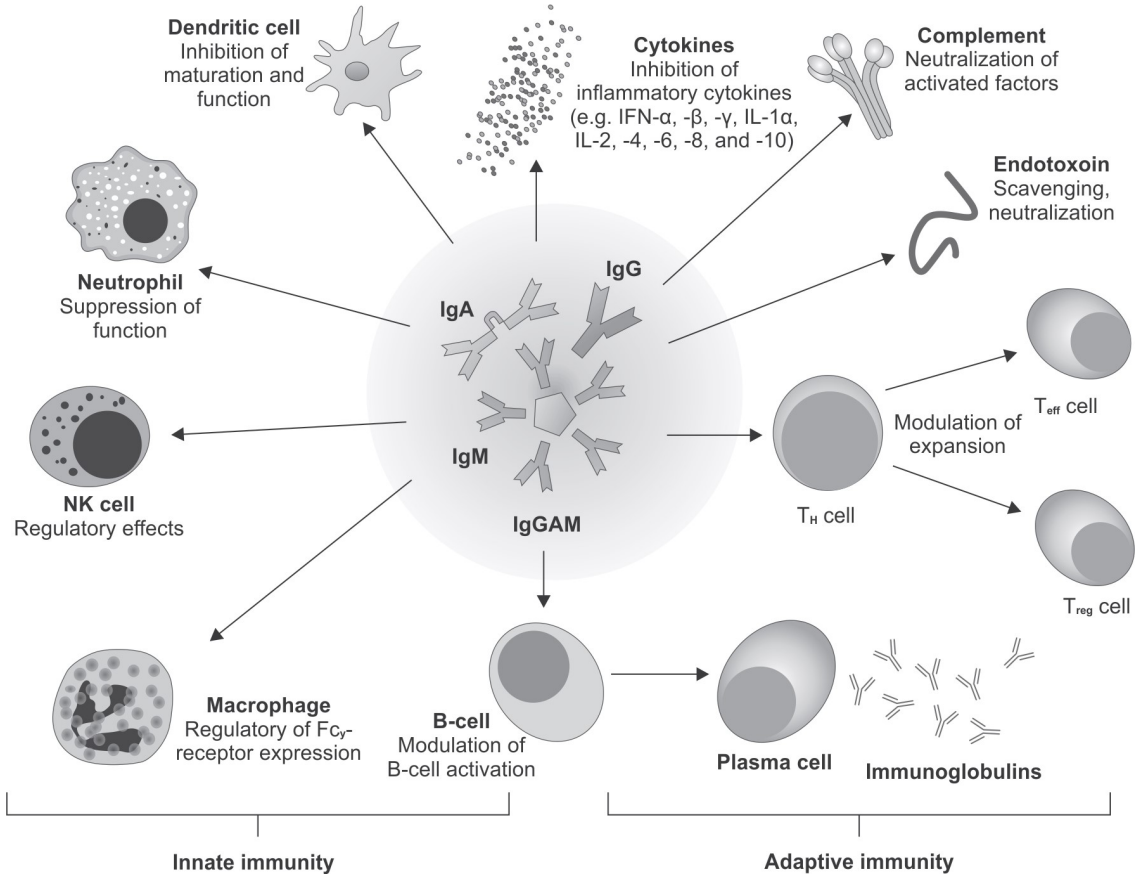


Fig. 2: The central role of intravenous immunoglobulins IgGAM on the innate and adaptive immune response, using different regulatory pathways to interact with the cellular and humoral components.
(IFN: interferon; Ig: immunoglobulin; IgGAM: immunoglobulin G/A/M; IL: interleukin; NK cell: natural killer cell; T_{eff} cell: effector T cell; T_H cell: helper T cell; T_{reg} cell: regulatory T cell.)

for neonates receiving standard polyclonal IVIg versus IgM-enriched polyclonal IVIg. On the other hand, a trend toward increased mortality was noticed in the patients having normal IgM levels who were treated with IgM- and IgA-enriched preparations. This suggests that target population needs to be identified precisely.

International Neonatal Immunotherapy Study (INIS Study)[26] was conducted for the assessment of the role of immunoglobulins in the modulation of neurodevelopmental outcome following neonatal sepsis. However, no significant difference was observed. Hence, the international guidelines[27] followed which refuted the role of immunoglobulins for the management of sepsis in newborn infants.

INTRAVENOUS IMMUNOGLOBULIN AND SEPSIS-SPECIFIC CLINICAL BACKGROUND

Multiple researches have revealed that the patients with gram-negative sepsis have better outcome when treated with IgM-enriched IVIg preparations.[28] However, immunoglobulins is reported to be highly effective for severe invasive gram-positive sepsis such as group A streptococcal (GAS) infections, in particular streptococcal toxic shock syndrome (STSS) associated with necrotizing fasciitis or myositis (approved by the US Food and Drug Administration).[29] This can be attributed to the ability of IVIg (particularly IgM-enriched preparation) to opsonize *Streptococci* and bring about neutralization of superantigens.

Again, in a retrospective study, the benefit of mortality reduction was observed in the septic postcardiac surgery patients to whom IVIg was used as an adjunct therapy.[30]

But, nonconcurring experiences were noted in neutropenic patients with septic shock who did not have any benefit from use of IgM-enriched IVIg compounds.[31]

Transient hypogammaglobulinemia, especially with low IgG level, occurs in the initial phase of septic shock. Berlot et al.[25] noted that the IVIg had been administered earlier in survivors in comparison to nonsurvivors. Therefore, the timing of administration might be a critical determining factor of therapeutic efficacy of IVIg in septic shock.

ADVERSE EFFECTS

Intravenous immunoglobulin therapy may be associated with serious adverse reactions—hyperviscosity syndrome, thromboembolic events, and acute renal failure (due to

the stabilizers in the IVIg preparations). The risk factors for ARF include renal impairment, diabetes mellitus, advanced age, volume depletion, or concomitant use of other nephrotoxic substances. However, these adverse effects can be mostly avoided by adopting proper measures. Renal failure as well as thromboembolic events may be prevented by adequately hydrating the patient and slowing down the rate of infusion.

INTRAVENOUS IMMUNOGLOBULIN AND COVID-19

In 2019, "Severe Acute Respiratory Syndrome CoronaVirus-2" (SARS-CoV-2) caused a pandemic with a global crisis, severely affecting healthcare sector.

Research data so far suggests that probably the severity of infection and the dysregulated immune reaction ("cytokine storm") are linked. However, excessive inflammatory surge might lead to chronic hyperinflammation. Hence, the functionality of the adaptive immune response might be jeopardized, which then fails to produce functional immunoglobulin. This, along with virus associated lymphopenia, result in progressive organ dysfunction. Therefore, IgGAM therapy might be beneficial in this category of patients.

CONCLUSION

The monitoring of circulating immunoglobulins as sepsis biomarker has become an interesting aspect of research work in the previous decade. Various immune scores have been developed for outcome prediction. Chronic immunoparesis leads to higher mortality rate later. Patients might suffer from secondary nosocomial infections with multidrug-resistant bacteria (MDR), viruses, or fungi. Probably, ongoing immune dysfunction can be indicated by low HLA-DR expression on monocytes.

The use of immunoglobulins in sepsis is still highly controversial. Gray areas include dosage protocols, patient selection, laboratory parameters to be analyzed.[32] There is no definitive guideline regarding initial dose, frequency (continuous versus intermittent), total amount, but also therapeutic target ("normal" or "supra-normal").

Presently, the mainstay of sepsis therapy consists of early, appropriate, and adequate source control, the initiation of antimicrobial therapy and achievement of hemodynamic stabilization through judicious and optimum fluid and vasopressors. Despite of the advancement in the development of novel therapeutic strategies, such as techniques for extracorporeal blood purification, the use of newer antimicrobials or focused immunomodulation, yet there is no definitive intervention that translates to a reduced mortality.

Surviving Sepsis Campaign (SSC) guidelines have recommended against the use of IVIg in sepsis.[33] This therapy is limited by comparatively high cost and variable availability.

However, further clinical research is the need of the hour to justify the use of immunoglobulins and to establish efficacy of the interventions in the proper patient population, at the precise time, at an optimum dose, and for an adequate duration.

REFERENCES

1. Levy MM, Artigas A, Phillips GS, Rhodes A, Beale R, Osborn T, et al. Outcomes of the Surviving Sepsis Campaign in intensive care units in the USA and Europe: a prospective cohort study. Lancet Infect Dis. 2012;12(12):919-24.
2. Hotchkiss RS, Monneret G, Payen D. Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach. Lancet Infect Dis. 2013;13(3):260-8.
3. Hotchkiss RS, Tinsley KW, Swanson PE, Grayson MH, Osborne DF, Wagner TH, et al. Depletion of dendritic cells, but not macrophages, in patients with sepsis. J Immunol. 2002;168(5):2493-500.
4. Landelle C, Lepape A, Voirin N, Tognet E, Venet F, Bohé J. Low monocyte human leukocyte antigen-DR is independently associatedwith nosocomial infections after septic shock. Intensive Care Med. 2010;36(11):1859-66.
5. Brahmamdam P, Inoue S, Unsinger J, Chang KC, McDunn JE, Hotchkiss RS. Delayed administration of anti-PD-1 antibody reverses immune dysfunction and improves survival during sepsis. J Leukoc Biol. 2010;88(2):233-40.
6. Inoue S, Bo L, Bian J, Unsinger J, Chang K, Hotchkiss RS. Dose-dependent effect of anti-CTLA-4 on survival in sepsis. Shock. 2011;36(1):38-44.
7. Azevedo LC, Park M, Schettino GP. Novel potential therapies for septic shock. Shock. 2008;30(Suppl. 1):60-6.
8. Vaschetto R, Clemente N, Pagni A, Esposito T, Longhini F, Mercalli F, et al. A double blind randomized experimental study on the use of IgM-enriched polyclonal immunoglobulins in an animal model of pneumonia developing shock. Immunobiology. 2017;222(12):1074-80.
9. Barratt-Due A, Sokolov A, Gustavsen A, Hellerud BC, Egge K, Pischke SE, et al. Polyvalent immunoglobulin significantly attenuated the formation of IL-1beta in *Escherichia coli*-induced sepsis in pigs. Immunobiology. 2013;218(5):683-9.
10. Welte T, Dellinger RP, Ebelt H, Ferrer M, Opal SM, Singer M, et al. Efficacy and safety of trimodulin, a novel polyclonal antibody preparation, in patients with severe community-acquired pneumonia: A randomized, placebo-controlled, double-blind, multicenter, phase II trial (CIGMA study). Intensive Care Med. 2018;44(4):438-48.
11. Kaneko Y, Nimmerjahn F, Ravetch JV. Anti-inflammatory activity of immunoglobulin G resulting from Fc sialylation. Science. 2006;313(5787):670-3.
12. Negi VS, Elluru S, Sibéril S, Graff-Dubois S, Mouthon L, Kazatchkine MD, et al. Intravenous immunoglobulin: an update on the clinical use and mechanisms of action. J Clin Immunol. 2007;27(3):233-45.
13. Samuelsson A, Towers TL, Ravetch JV. Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. Science. 2001;291(5503):484-6.
14. Kessel A, Ammuri H, Peri R, Pavlotzky ER, Blank M, Shoenfeld Y, et al. Intravenous immunoglobulin therapy affects T regulatory cells by increasing their suppressive function. J Immunol. 2007;179(8):5571-5.

15. Lacroix-Desmazes S, Bayry J, Kaveri SV, Hayon-Sonsino D, Thorenoor N, Charpentier J, et al. High levels of catalytic antibodies correlate with favorable outcome in sepsis. Proc Natl Acad Sci U S A. 2005;102(11):4109-13.
16. Alejandria MM, Lansang MA, Dans LF, Mantaring JB. Intravenous immunoglobulin for treating sepsis and septic shock. Cochrane Database Syst Rev. 2000;2:CD001090.
17. Alejandria MM, Lansang MA, Dans LF, Mantaring JB. Intravenous immunoglobulin for treating sepsis and septic shock. Cochrane Database Syst Rev. 2002;1:CD001090.
18. Ohlsson A, Lacy JB. Intravenous immunoglobulin for preventing infection in preterm and/or low-birth-weight infants. Cochrane Database Syst Rev. 2001;2:CD000361.
19. Ohlsson A, Lacy J. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. Cochrane Database Syst Rev. 2004;1:CD001239.
20. Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. Cochrane Database Syst Rev. 2010;3:CD001239.
21. Alejandria MM, Lansang MA, Dans LF, Mantaring III JB. Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock. Cochrane Database Syst Rev. 2010;9:CD001090.
22. Alejandria MM, Lansang MA, Dans LF, Mantaring III JB. Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock. Cochrane Database Syst Rev. 2013;2:CD001090.
23. Kress HG, Scheidwig C, Schmidt H, Silber R. Reduced incidence of postoperative infection after intravenous administration of an immunoglobulin A and immunoglobulin M-enriched preparation in anergic patients undergoing cardiac surgery. Crit Care Med. 1999;27(7):1281-7.
24. Venet F, Gebeille R, Bancel J, Guignant C, Poitevin-Later F, Malcus C, et al. Assessment of plasmatic immunoglobulin G, A and M levels in septic shock patients. Int Immunopharmacol. 2011;11(12):2086-90.
25. Berlot G, Vassallo MC, Busetto N, Bianchi M, Zornada F, Rosato I, et al. Relationship between the timing of administration of IgM and IgA enriched immunoglobulins in patients with severe sepsis and septic shock and the outcome: a retrospective analysis. J Crit Care. 2012;27(2):167-71.
26. INIS Collaborative Group; Brocklehurst P, Farrell B, King A, Juszczak E, Darlow B, et al. Treatment of neonatal sepsis with intravenous immune globulin. N Engl J Med. 2011; 365(13):1201-11.
27. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. Crit Care Med. 2012;41(2):580-637.
28. El-Nawawy A, El-Kinany H, Hamdy El-Sayed M, Boshra N. Intravenous polyclonal immunoglobulin administration to sepsis syndrome patients: a prospective study in a pediatric intensive care unit. J Trop Pediatr. 2005;51(5):271-8.
29. Lappin E, Ferguson AJ. Gram-positive toxic shock syndromes. Lancet Infect Dis. 2009;9(5):281-90.
30. Buda S, Riefolo A, Biscione R, Goretti E, Cattabriga I, Grillone G, et al. Clinical experience with polyclonal IgM-enriched immunoglobulins in a group of patients affected by sepsis after cardiac surgery. J Cardiothorac Vasc Anesth. 2005;19(4):440-5.
31. Hentrich M, Fehnle K, Ostermann H, Kienast J, Cornely, Salat C. IgMA-enriched immunoglobulin in neutropenic patients with sepsis syndrome and septic shock: A randomized, controlled, multiple-center trial. Crit Care Med. 2006;34(5):1319-25.
32. Kakoullis L, Pantzaris ND, Platanaki C, Lagadinou M, Papachristodoulou E, Velissaris D. The use of IgM-enriched immunoglobulin in adult patients with sepsis. J Crit Care. 2018;47:30-5.
33. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017;43(3):304-77.

CHAPTER 13

Therapeutic Drug Monitoring

Chandrashish Chakravarty

INTRODUCTION

Therapeutic drug monitoring (TDM) is defined as the measurement of a drug concentration (usually in blood) at a predicted interval to optimize individual doses and monitor drug toxicity. It is believed that TDM will directly influence the drug prescription by individualizing the drug dose so as to maintain the drug concentration in the desired range. This will help to maximize the drug efficacy and improve patient safety.[1,2]

WHY DO IT?

As TDM is an expensive tool, its indications should be clearly crafted and the results carefully documented and interpreted. The most common indications of TDM are:

- To diagnose drug toxicity when the clinical symptoms are nonspecific
- To predict adequate loading dose of drugs
- To monitor plasma levels after dose adjustment and predict changes in individual doses from patient to patient
- To monitor drug compliance and underdosing
- To diagnose failed therapy.[3]

THERAPEUTIC DRUG MONITORING IN INTENSIVE CARE UNIT

Therapeutic drug monitoring has specific relevance in patients who are critically ill. This is because of the altered pharmacokinetics (PK) of drugs in severely altered pathophysiological state. The various factors responsible for the altered PK of drugs in critically ill patients are as follows:

- Hyperdynamic circulation leading to very high clearance (Cl) of the drug
- Altered fluid balance, altered plasma protein binding, altered protein concentration leading to changes in volume of distribution (Vd) and free drug levels.
- Multiple organ dysfunction affecting drug metabolism
- Pre-existing co-morbidities.

In critical illness, the pharmacokinetics of a drug show large inter- and intraindividual variability. Since most of the drug dosages are formulated from their efficacy in healthy volunteers or noncritical patients, extrapolation of these dosing regimens are fraught with the risk of underdosing. Underdosing subsequently leads to treatment failure and emergence of multidrug resistance among microbes.[4]

Some intensive care unit patients also show the phenomenon of "augmented renal clearance"[5] where the creatinine clearance is >130 mL/min/1.73 m^2 leading to increased clearance of drugs from the system and subtherapeutic drug levels. This is particularly common in young healthy trauma or septic patients. Augmented clearance is difficult to predict and not picked up by standard Cockcroft Gault or MDRD (Modification of Diet in Renal Disease) equations but present in 14–80% of patients. Hence, urinary creatinine clearance must be measured to pick this up from 8 to 24 hours urine collection.

On the opposite side, renal dysfunction is very common in ICU and so is toxicity of accumulated drugs from over exposure.

The Vd in critical illness can go up from intravenous (IV) fluid bolus and capillary leakage (endothelial dysfunction and loss of glycocalyx). Hydrophilic drugs such as aminoglycosides, beta-lactams, teicoplanin, etc., can change drug concentration from these altered Vd. Similarly very protein bound drugs such as teicoplanin can produce higher free or unbound drug fraction.

Obesity is another factor that determines distribution of lipid soluble drugs such as linezolid.

INTERPRETATION OF THERAPEUTIC DRUG MONITORING

For accurate analysis of any TDM data, patient's clinical status has to be taken into account. To do an accurate TDM, the team must be informed in detail about the time of sample, the time of initiation of therapy, and the time of last dose because if a sample is obtained before the drug distribution is complete, the levels will be falsely high.

The time of administration and the mode of administration like bolus versus infusion should be taken into account.

Any factor which leads to changes in drug absorption should also be kept in mind. Except in few situations, the samples are drawn at the trough or just before the next dose.

Peak plasma concentration, C_{max}, is helpful for certain antibiotics such as aminoglycosides. For antibiotics whose peak plasma concentration is to be measured, the TDM should be done 30 minutes after the end of infusion and if given by bolus, TDM should be done 60 minutes after the bolus dose.

In cases of repeated drug administration, a steady state concentration is reached after about 5 plasma half-lives, so plasma concentration should be measured at this point. However, steady state concentration is reached earlier if a loading dose has been given.

For drugs such as amiodarone with long half-lives, the TDM should be done earlier than steady state concentration because there is a risk of toxicity at the initial dose regimen.[6,7]

In case the drug produces any active metabolite, TDM should encompass both the drug and the metabolite.[8]

THERAPEUTIC DRUG MONITORING FOR INDIVIDUAL DRUG GROUPS

Antimicrobials

Antimicrobials generally have different PK/PD indices. These are as follows:

- The ratio of [C_{max}/minimal inhibitory concentration (MIC)]
- The fraction of time (T) that the unbound drug concentration remains over the MIC during a dosing interval (fT>MIC)
- The "area under the concentration–time curve during a 24-hour period" to MIC (AUC/MIC) ratio.

Now in most laboratories they use limited sampling studies to predict AUC instead of sampling blood every 15 minutes. Use of dosing software have replaced complex nomograms for drugs such as vancomycin.

Therapeutic drug monitoring is important for this group of drugs to find out if drug concentrations are reaching above the MIC for the desired period of time. MIC of the drug determines the minimum concentration in blood necessary to kill the microbe growing in culture. It is an important component of PK/PD of the antimicrobial and hence monitoring the drug level is of great significance.

Therapeutic drug monitoring is also relevant when we want to ensure minimum drug toxicity like for nephrotoxic drugs. TDM allows dose reduction when unnecessary high concentration is measured. The recent surge of multidrug-resistant (MDR) organism along with a lack of upcoming antibiotics has made TDM all the more essential besides antimicrobial stewardship.

Measuring therapeutic drug levels are important and cost-effective for antimicrobials which satisfy the following criteria:

- Significant intra/interindividual PK variability
- Defined exposure range is associated with drug response.
- Has defined sampling end points
- Accurate and timely bioanalytical assays are available.

The A-TEAMICU survey[9] was done to understand the use and feasibility of anti-microbial stewardship programs and TDM policies in critical care units from across the globe including USA, Europe, and India. TDM of antimicrobials was practised in 61% of ICUs. Most commonly done are glycopeptides (89%), aminoglycosides (77%), carbapenems (32%), penicillins (30%), azole antifungals (27%), cephalosporins (17%), and linezolid (16%). Continuous infusion of antimicrobials was found in more than 3/4th ICUs. Wherever there was a structured AMS programme, TDM policies also found to be co-existing.

In its position paper on TDM for antimicrobials,[8] ESICM has given the following guidelines for TDM. It recommends TDM for the following antibiotics:

- *Aminoglycosides*: AUC/ MIC has replaced C_{max} as the PK/PD index which determines the efficacy of the drug. C_{min} (minimum blood concentration) is measured to determine the threshold for oto- and nephrotoxicity.
  Here, two samples are to be taken. First one should be drawn 30 minutes after infusion is over and the second one should be drawn between 6 and 22 hours postinfusion.
  To determine C_{max}/MIC, another less reliable target, only one sample 30 minutes after infusion needs to be collected. C_{max} refers to peak plasma concentration of the drug. C_{min} refers to minimum plasma concentration.
- *Beta-lactams, carbapenems*: These antimicrobials have concentration-dependent PK and hence fraction of time when blood concentration remains above MIC needs to be measured. Usual target is >50% fT>MIC. C_{min} needs to be measured to determine toxicity. Based on this fact, the TDM sample needs to be collected just before or 30 minutes before the next dose.
- *Vancomycin*: The AUC/MIC of vancomycin determines its efficacy against the bacteria. Two blood samples need to be collected. First sample should be drawn 60 minutes after end of infusion and the second sample should be drawn 1–2 hours after starting of next infusion.
  C_{min} is measured by collecting blood 30 minutes or just before the next dose. C_{min} is used to determine toxic range. AUC/MIC >400 is the target which becomes difficult to achieve for MIC >1.
  For teicoplanin and linezolid also, it is recommended to measure AUC/MIC for efficacy.
  Linezolid dosing may need to be increased or dosing intervals changed in critical illness, ARDS, or against microbes with high MIC. Linezolid is lipophilic and dose needs to be changed for obesity. The AUC and C_{min} values can predict hematological toxicity of linezolid.

On the other hand, teicoplanin is largely protein bound and has very variable unbound drug fractions in patients with low plasma proteins.

- *Voriconazole*: It is an anti-fungal drug with concentration-dependent PK and hence C_{min} needs to be measured. Based on this fact, the TDM sample needs to be collected just before or 30 minutes before the next dose. The blood sampling should be done between day 2 and day 5 of therapy.

  For certain other toxic antifungals such as flucytosine, Cmax determines toxicity.
- Antivirals do not fall under society guidelines for measuring TDM. However, there is provision for TDM of ganciclovir/valganciclovir and ribavirin. AUC is the clinical target here.
- *Others*: For other antimicrobials, there is no recommendation in favor or against TDM. But for certain drugs such as polymyxins and daptomycin, TDM is useful to determine efficacy and toxicity in special situations and the AUC/MIC should be measured.

In the Indian subcontinent, a short mention of polymyxins in regard to TDM seems reasonable. The therapeutic index for colistin is very narrow and hence TDM samples should be collected for C_{min} just before the next dose. These samples should also be quickly processed.

The data on polymyxin B is scarce. Current evidence suggests that normal dose for loading is 2.5 mg/kg followed by 2.5 mg/kg in divided doses. For MIC >1, the daily dose should be up to 3 mg/kg. These doses are based on total body weight.

EXTRACORPOREAL MEMBRANE OXYGENATION AND THERAPEUTIC DRUG MONITORING FOR ANTIMICROBIALS

Increase in the use of extracorporeal membrane oxygenation (ECMO) in the ICU for the treatment of respiratory and/or cardiac failure has made TDM in ICU more relevant. Particularly, drug dosing may seem impossible in situations where these patients are on both ECMO and continuous renal replacement therapy (CRRT). However, it is still an uncharted territory whether dose modifications are necessary to improve efficacy of an antimicrobial in septic ECMO patients. In a single centre observational study,[10] it was seen that:

- Serum concentrations of piperacillin and standard-dose meropenem (1 g IV 8 hourly) were significantly lower in ECMO patients than in control population.
- A large chunk of ECMO patients treated with piperacillin (48%) and linezolid (35%) did not attain the prespecified MIC targets.
- It is interesting to note that 13–15% patients receiving piperacillin or linezolid also did not achieve adequate drug concentration in the non-ECMO group making a point for monitoring TDM in case of these drug therapies.
- The ECMO blood flow does not influence the drug levels.

Therapeutic drug monitoring for antimicrobials in patients on renal replacement therapy (RRT) are as follows:

Various renal replacement therapies (RRTs) affect drug clearance in different ways. In general, the following conditions lead to higher drug clearance:

- Higher dialysate and ultrafiltrate rates
- Longer durations of dialysis
- Higher permeability hemofilters.

If we put together the methods of drug clearance by dialysis along with duration of RRT, as a general rule, we arrive at the following efficiency of drug removal: Continuous venovenous hemodiafiltration (CVVHDF) > continuous venovenous hemodialysis (CVVHD) > continuous venovenous hemofiltration (CVVH) > prolonged intermittent renal replacement therapy (PIRRT) ≥ ischemic heart disease (IHD).[11]

In patients receiving CRRT, although the standard dose of meropenem is 500 mg IV 8 hourly, the dosing of 1 g every 8 hours infused over 3 hours should be considered for pathogens with higher MICs (2–4 mg/L).[12]

Piperacillin-tazobactam 4.5 g every 8 hours in ICU patients receiving CVVHDF has been shown to attain target drug levels for organisms with an MIC ≤32 mg/L.[13]

A prospective study of intensive care unit patients receiving CVVH and vancomycin therapy concluded that 500–750 mg every 12 hours would be adequate to achieve the target trough goals, and serum vancomycin concentrations should be closely monitored.[14]

THERAPEUTIC DRUG MONITORING FOR ANTICONVULSANT MEDICATIONS (ANTIEPILEPTIC DRUGS)

Antiepileptic drugs (AEDs) are one of the most frequently used drug in the ICU and here lies the relevance of TDM for AEDs in ICU.[15]

Therapeutic drug monitoring helps to improve the quality of care, helps to check adherence, and increase safety especially in ICU patients and patients who are on polypharmacy. It has been noted that there is a significant PK variability for individual AED drugs and lot of enzyme inductions in view of multiple drugs patients are on, hence TDM is a safe bet for optimal therapy.

There have been various studies on TDM for AED but there is a lack of such studies for critically ill patients. Still we will discuss some of the large studies in order to see what are the observations of TDM for AED.

In a tertiary center study in India, we see that a significant percentage (51%) of patients had a plasma concentration of the AEDs below the therapeutic levels. This percentage was even higher, (54%) when two or more AEDs were being used.[16]

In patients who were referred for TDM, because of suspected toxicity, 59% had a drug concentration above the desired range.

In another study on TDM for valproate levels, they chose to study the unbound fraction of valproate. The unbound valproate levels in patients with glomerular filtration rate (GFR) <30 g/L, age >70 years, and those who were suspected to have toxicity were studied. The study concluded that it was clinically more useful to monitor the free fraction of valproate as compared to total valproate levels. In patients with signs of toxicity, only 5% had a total VAL level above the desired range whereas 37% had an unbound valproate level in the toxic range.[17]

In a systemic review by Zanab et al., it was concluded that TDM of AEDs had no effect on final seizure outcome. It only led to a better control of seizure frequency.[18]

CONCLUSION

The complex pathophysiology and polypharmacy in ICU makes it difficult to predict drug dosages which shall reach effective drug concentrations at the site of action. The two most common classes of drugs in this category are antimicrobials and anticonvulsants. There is increasing evidence and recommendation that TDM is necessary in ICU population. Also with increasing antimicrobial resistance, TDM will become an important equipment to fight emergence of super bugs in near future.

REFERENCES

1. Touw DJ, Neef C, Thomson AH, Vinks AA. Cost effectiveness of therapeutic drug monitoring: a systemic review. Ther Drug Monit. 2005;27(1):10-7.
2. Birkett DJ. Pharmacokinetics made easy: Therapeutic Drug Monitoring. Aust Prescr. 1997;20:9-11.
3. Ghiculescu RA. Therapeutic drug monitoring: which drugs, why, when and how to do it. Aust Prescr. 2008;31:42-4.
4. Bodenham A, Shelly MP, Park GR. The altered pharmacokinetics and pharmacodynamics of drugs commonly used in critically ill patients. Clin Pharmcokinet. 1998;14(6):347-73.
5. Mahmoud SH, Shen C. Augmented renal clearance in critical ill- ness: an important consideration in drug dosing. Pharmaceutics. 2017;9(3):36.
6. Kang JS, Lee MH. Overview of therapeutic drug monitoring. Korean J Intern Med. 2009;24(10):1-10.
7. Tabah A, De Waele J, Lipman J, Zahar JR, Cotta MO, Barton G, et al. The ADMIN-ICU survey: a survey on antimicrobials dosing and monitoring in ICU. J Antimicrob Chemother. 2015;70(9):2671-7.
8. Abdul-Aziz MH, Alffenaar JC, Bassetti M, Bracht H, Dimopoulos G, Marriott D, et al. Antimicrobial therapeutic drug monitoring in critically ill adult patients: A position paper. Intensive Care Med. 2020;46(6):1127-53.
9. Lanckohr C, Boeing C, De Waele JJ, de Lange DW, Schouten J, Prins M, et al. Antimicrobial stewardship, therapeutic drug monitoring and infection management in the ICU: results from the international A- TEAMICU survey. Ann Intensive Care. 2021;11(1):131.
10. Kühn D, Metz C, Seiler F, Wehrfritz H, Roth S, Alqudrah M, et al. Antibiotic therapeutic drug monitoring in intensive care patients treated with different modalities of extracorporeal membrane oxygenation (ECMO) and renal replacement therapy: a prospective, observational single-center study. Crit Care. 2020;24:664.
11. Hoff BM, Maker JH, Dager WE, Heintz BH. Antibiotic dosing for critically ill adult patients receiving intermittent hemodialysis, prolonged intermittent renal replacement therapy, and continuous renal replacement therapy: An Update. Ann Pharmacother. 2020;54(1):43-55.
12. Ulldemolins M, Soy D, Llaurado-Serra M, Vaquer S, Castro P, Rodríguez AH, et al. Meropenem population pharmacokinetics in critically ill patients with septic shock and continuous renal replacement therapy: influence of residual diuresis on dose requirements. Antimicrob Agents Chemother. 2015;59(9):5520-8.
13. Varghese JM, Jarrett P, Boots RJ, Kirkpatrick CM, Lipman J, Roberts JA. Pharmacokinetics of piperacillin and tazobactam in plasma and subcutaneous interstitial fluid in critically ill patients receiving continuous venovenous haemodiafiltration. Int J Antimicrob Agents. 2014;43(3):343-8.
14. Sin JH, Newman K, Elshaboury RH, Yeh DD, de Moya MA, Lin H. Prospective evaluation of a continuous infusion vancomycin dosing nomogram in critically ill patients undergoing continuous venovenous haemofiltration. J Antimicrob Chemother. 2018;73:199-203.
15. Landmrak CJ, Johannessen SI, Patsalos PN. Therapeutic drug monitoring of antiepileptic drugs: Current status and future prospects. Expert Opin Drug Metab Toxicol. 2020;16(3): 227-38.
16. Taur SR, Kulkarni NB, Gogtay NJ, Thatte UM. An audit of therapeutic drug monitoring services of anticonvulsants at a tertiary care hospital in India. Ther Drug Monit. 2013;35(2):183-7.
17. Wallenburg E, Klok B, de Jong K, de Maat M, van Erp N, Stalpers-Konijnenburg S, et al. Monitoring protein-unbound valproic acid serum concentrations in clinical practice. Ther Drug Monit. 2017;39(3):269-72.
18. Al-Roubaie Z, Guadagno E, Ramanakumar AV, Khan AQ, Myers KA. Clinical utility of therapeutic drug monitoring of antiepileptic drugs: Systematic review. Neurol Clin Pract. 2020;10(4):344-55.

CHAPTER 14

Syndromic Polymerase Chain Reaction-based Diagnostics in Sepsis

Bhavini Shah

INTRODUCTION

Sepsis is a life-threatening organ failure induced by a dysregulated host response to infection, and it is the leading cause of mortality in intensive care units (ICUs).[1] When the body's immunological reaction to a viral, fungal, or (more typically) bacterial infection produces damage, malfunction, or even failure of the host's own tissues and organs, sepsis develops. The cornerstone of sepsis therapy is the prompt use of antimicrobial medicines that are active against the causing bacteria.[2] Represents a prime public fitness hassle and is most of the maximum not unusual place motives for admission to the in depth care unit (ICU). Mortality associated with sepsis stays high, regardless of enhancing effects in healthcare, being the second one main motive of loss of life withinside the noncoronary.[3] Patients who remain in the critical care unit for >24 hours were examined daily for signs and symptoms of systemic inflammatory response syndrome (SIRS), sepsis, and severe sepsis using American College of Chest Physicians (ACCP)/Society of Critical Care Medicine (SCCM) criteria. If the patient presented two almost all of the following clinical symptoms, SIRS was considered to be present; (1) body temperature >38°C or <36°C; (2) heart rate >90 bpm; (3) hyperventilation indicated by a respiratory rate >20 beats per minute (bpm) or a $PaCO_2$ (partial pressure of carbon dioxide) <32 mm Hg; (4) white blood cell count larger than 12,000 cells/L or fewer than 4,000 cells/L. The presence of infection and a SIRS was classified as sepsis, while severe sepsis was defined as sepsis with at least one criteria of organ dysfunction. The respiratory tract was the most prevalent location of infection in patients with severe sepsis (53.3%), followed by the abdomen (14.9%), circulatory system (14.3%), and urinary tract infections (14.3%). (12.9%). There was no significant difference in mortality between men and women.[4] Although blood cultures processed using normal microbiological procedures are a typical diagnostic step, the chance that they would return with the pathogen of interest is dependent on a range of conditions, including past antibiotic medication.[5] Inadequate antibiotic therapy is a key issue that has been linked to higher fatality rates.[3] In nosocomial infections and infections caused by developing multidrug-resistant gram-negative bacteria, unsatisfactory therapy is due to insufficient coverage of the underlying pathogen and antibiotic resistance of the causative pathogen. Because empirical antifungal coverage is only indicated in high-risk patients, increased mortality can also be found following incorrect fungal medication (e.g., neutropenia and intra-abdominal infections). Many people still believe that blood culture is the gold standard for detecting and identifying bloodstream infections (BSIs). This traditional laboratory approach, on the other hand, lacks sensitivity, has a poor pretest probability in some clinical scenarios, and is hampered by delayed results. New technologies have been developed to improve the speed of diagnosis, sensitivity, and clinical value of identifying infections in the blood. Molecular detection methods for bacterial and fungal DNA have been developed, however they are not frequently employed in clinical applications.[3] Multiplex polymerase chain reaction (PCR) offers the ability to detect circulatory infections quickly and compensate for blood culture sensitivity decrease.[6] The quick multiplex pathogen detection technique supplemented established culture-based approaches and provided extra diagnostic value for pathogen identification, particularly in patients who had recently received antibiotic treatment.[7]

EPIDEMIOLOGY OF SEPSIS

The leading causes of sepsis and accompanying death in 2017 were diarrheal illnesses (9.2–15 million cases per year) and lower respiratory tract infections (1.82.8 million cases per year) sepsis in all age groups. Noncommunicable illnesses, on the other hand, are on the rise; in 2017, a third of sepsis cases and almost half of all sepsis-related fatalities were caused by an underlying injury or chronic illness (WHO 2020). Hospitalization for sepsis is substantially more common among 65-year-olds (122.2 per 10,000 population) than among 65-year-olds (9.5 per 10,000 population).

According to recent data, the incidence rate rises every year as the population ages, invasive methods and surgical operations become more common, chronic illnesses, immunosuppressants, chemotherapy, transplants, and the number of germs resistant to numerous treatments rise (Marcello Guido et al 2016). Group B *Streptococci* are the leading cause of sepsis in newborns and mothers, although *Escherichia coli* is a new threat. Both pathogens have shown considerable resistance to treatment and are recognized as the main pathogens for research and development (R&D) of new antibiotics (WHO 2020). Sepsis is the third largest cause of mortality, and regardless of the criteria employed, the incidence of this main cause of death is growing. Infections, microbiological profiles, resistance patterns, and no sepsis, which is an unregulated host response, are among the few data points available from India.[18]

Sepsis is an immune-mediated illness that is one of the primary causes of mortality. However, the pathophysiology of sepsis is unknown, especially in terms of immune system malfunction. In the early stages of sepsis, the immune system responds excessively hyperinflammatorily, followed by the production of anti-inflammatory effectors [interleukin (IL)-4, IL-10, IL-13, cortisol, etc.] and shifts in T cells from Th1 to Th2 that might cause a compensatory anti-inflammatory syndrome. The body becomes more prone to secondary infections and viral reactivation when the immune system is compromised (Marcello Guido 2016). In sepsis, both anti-inflammatory and inflammatory mediators play a role, and too much of either can contribute to poor treatment results.[21] A growing number of critical mediators and signaling pathways have been identified, which might lead to the development of novel medicines to address immunological dysregulation. While most pharmacists are familiar with the coagulation cascade and how anticoagulants might be utilized, sepsis-related coagulopathy and the impact of mediators such as cytokines and complement, as well as the significance of activated platelets and neutrophils, necessitate a distinct viewpoint.[21]

MARKERS OF SEPSIS

The discovery of sepsis-specific biomarkers for host response and pathogen detection might lead to medication development and improved sepsis clinical treatment. A recent comprehensive analysis found about 180–200 distinct molecules as possible biomarkers of sepsis, owing to the complicated pathophysiology of sepsis, which spans cell types, tissues, and organ systems. None of them, however, have enough specificity or sensitivity to be employed in clinical practice. Acute phase protein indicators [C-reactive protein (CRP), procalcitonin (PCT), and lipopolysaccharide-binding protein], cytokine/chemokine biomarkers (IL-6 and IL-8), and markers of other pathophysiological processes (clotting factors and soluble cells) may all be transformed into sepsis biomarkers. Complement factors (C3a, C5a, and the soluble version of the C5a receptor, cC5aR) are currently used to diagnose sepsis and determine its severity. The most common tests for BSI are CRP and PCT.

- *CRP*: Infection (reaches values of 0.200 mg/L). When compared to PCT, this biomarker has been demonstrated to be more sensitive to temperature and white blood cell count. However, it is less specific.
- *PCT*: Patients with plasma PCT levels of <0.5 ng/mL are unlikely to develop severe sepsis or septic shock. 2 ng/mL is used to identify people who are at high risk (Marcello Guido et al, 2016).

More than 100 distinct molecules have been demonstrated to be potentially effective biomarkers for sepsis, in addition to PCT and CRP. Among these, CD64, a leukocyte surface antigen, has been described as a good biomarker of sepsis. Without infection, CD64 is expressed constitutively on neutrophils, albeit in modest levels. The innate immune response to bacterial infections is thought to begin with the upregulation of CD64 on the cell surface of polymorphic mononuclear neutrophils. The capacity of CD64 neutrophil expression to distinguish between sepsis and nonsepsis has been documented in several investigations.[27]

SIGNIFICANCE OF DETECTION OF SEPSIS AT EARLY STAGE

Early and focused antimicrobial treatment improves mortality in patients with bacterial sepsis, according to studies and systematic reviews. However, the precise timing of such therapy is debatable. A recent study found that each hour of late antibiotic medication within the first 6 hours after admission to the hospital was linked to a 7.6% increase in death. These findings are supported by a recent study that found that hourly delays in antibiotic administration increase mortality, even when given within 6 hours, and a meta-analysis that found a significant reduction in the likelihood of death (33%) when immediate (within 1 hour) antibiotic administration was compared to subsequent (>1 hour) antibiotic administration.

Recent research has helped to clarify the main signals about what should be included in early childhood care. It showed that early resuscitation in the first 6 hours after an aggressive search for sepsis/septic shock using bedside information and serial lactate measurements (to aid in resuscitation assessment) was not inferior to the more regulated and resource-intensive early goal-directed therapy (EGDT) approach, which had hospital mortality rates of 17–23% (Ginn, A. N et al., 2015). Adding quick molecular detection of bacterial/fungal infections that cause sepsis to the sepsis criteria will improve the specificity of diagnosis and guarantee that patients are treated promptly and appropriately. Although relatively quick detection is now possible in clinical samples, the technique and quality

of template preparation can have a major impact on the test's sensitivity and specificity. A multicenter study in nine European intensive care units discovered that the detection of bacterial and fungal DNA independent of blood culture results is linked to poorer clinical outcomes and higher mortality, and that molecular testing can be used to identify groups of patients at higher risk of sepsis death.[29]

DIAGNOSIS

Infections such as pneumonia, urinary tract infection, contaminated invasive devices, intra-abdominal, and surgical infections can all cause sepsis and septic shock. To detect sepsis, active screening of emergency room and hospitalized patients is required. Temperature, heart rate, respiratory rate, blood pressure, level of consciousness, oxygen saturation, blood cultures, lactate, urea, electrolytes, reactive protein, blood count, kidney function tests, and liver, urine tests and cultures, cerebrospinal fluid, wounds, respiratory secretions, or other bodily fluids that may be a source of infection, and imaging tests such as chest X-rays and computed tomography (CT) scans are all warranted based on medical history.[18]

The optimal technology should have the following features, given current clinical problems and the necessity to impact clinical care through particular treatment modalities (Mridu Sinha et al., 2021):

- Rapid detection (pathogens must be identified in less hour)
- Screening including bacteria, viruses, and fungi
- Invasive to the bare minimum, the use of tiny sample sizes in clinical samples (1 mL of blood for pediatric patients, including newborns and 5–10 mL of blood for adults).
- High sensitivity and specificity for initiating targeted antibiotic treatment as soon as indications and symptoms of systemic inflammation appear (diagnostic tests should not affect sensitivity to low concentrations of pathogens in the sample)
- Pathogen identification in the presence of pollutants in a wide spectrum of pathogens [1–100,000 CFU (colony forming unit)/mL of blood] polymicrobial detection is used. Clinical workflow integration (the process should be easy to use and require minimal technical expertise to process samples and interpret test results; to be most effective, the technology should be usable in noncentralized and resource-limited settings). The capacity to identify new and undiscovered diseases (detection functions should be easily expanded without affecting the robustness of detection and required sample volume).
- The capacity to tell whether the inflammatory response is being triggered by the host or by the infection.

BIOCHEMICAL PATHOGEN AND BLOOD CULTURE IDENTIFICATION FOR SEPSIS

Traditional methods include cultivating a blood sample in enriched broth, then utilizing established biochemical procedures to identify and assess the pathogen's susceptibility. Because incorrect antimicrobial medication is a major risk factor for mortality in critically ill patients with life-threatening illnesses, blood cultures are required for optimizing antibiotic therapy.[3] Standard blood culture techniques take time, and results are not usually available for at least 24 hours, highlighting the need for early diagnosis and risk stratification, where biomarkers may be useful.[5] Despite the Surviving Sepsis Campaign's suggestion that blood samples be archived for culture before being treated with broad-spectrum antibiotics, roughly 50–70% of septic patients are treated with antibiotics before receiving blood samples for culture. Some bacteria find it difficult to colonize while they are under antibiotic treatment, which lowers the efficacy of blood cultures, which generally provide a diagnosis within 48 hours. If solely the blood culture approach was used in clinical practice, no results would be available for 4 hours following patient recruitment.[20]

Routinely used blood culture methods are not an ideal gold standard because results are often too late, incomplete or not sensitive enough, can be misleading, and relatively time-consuming. There is a critical unmet need to shorten and improve current laboratory procedures for the detection and identification of microorganisms. Over the past decade, several technical innovations have led to promising approaches to pathogen detection including sample preparation, molecular detection, automation, miniaturization, multiplexing, and high-throughput testing to develop effective diagnostic technology. The following sections provide an overview of current and new detection systems that have been developed for the rapid, sensitive, and inexpensive diagnosis of circulatory infections.

Matrix-assisted Laser Desorption/Ionization-Time-of-flight Mass Spectrometry

Matrix-assisted laser desorption/ionization (MALDI) time-of-flight mass spectrometry (TOF MS) (Bruker Daltonics, Billerica, MA, USA; OR BioMèrieux, Marcy l`Etoile, France) offers a method for the rapid identification of bacteria and fungi (in 90% von BC) determining their proteomic profiles. This platform works by ionizing biomolecules (e.g., nucleic acids, proteins, and saccharides), which are separated by an electric field according to their mass-to-charge ratio (m/z). Some of the advantages of MALDI-TOF-MS compared to conventional methods are the rapid obtaining of results (waiting time of 1–2 hours), the simple protocol for sample preparation (reduced workload), the low cost, and the possibility to directly identify a large

number of microorganisms. It has a specificity of 96% and a sensitivity that varies between 76 and 98% depending on the pathogen. MALDI-TOF-MS as well as PCR amplification in combination with electrospray ionization mass spectrometry (PCR/ESIMS) (explained in the next paragraph) results in a promising instrument in clinical and epidemiological management.

Although the fast response time (in minutes or seconds) of single-cell MALDI-TOF-MS is a significant improvement over conventional MALDI-TOF-MS, it raises additional problems in relation to changes in the mass spectrum. As a result, they used a single-cell MALDI-TOF-MS with a machine learning (ML) algorithm to show that the generated spectra could be used to distinguish between various bacterial species in the laboratory.

Nonamplified Nucleic Acid-based Assays

One of these novelties is fluorescent in situ hybridization (FISH) technology, which uses oligonucleotide probes to target bacterial or fungal genes (typically rRNA genes from *Staphylococcus aureus* or coagulase-negative *Staphylococci* (CoNS), *Enterococcus faecalis*, or other selected *Enterococci*, *E. coli*, *Pseudomonas aeruginosa*, and *Candida* spp.). With the introduction of peptide nucleic acid (PNA) probes, this problem has been partially solved. PNA probes are oligomers that are synthesized to look like DNA or RNA. The negatively charged (deoxy)ribose phosphate nucleic acid backbone is substituted in PNA probes by an uncharged N (2 aminoethyl) glycine backbone, to which the nucleotide bases are linked through a methylenecarbonyl linker. PNA probes offer better hybridization properties than DNA probes because of their neutral charge. A medical intervention using PNA-FISH was designed to detect enterococcal bacteremia. More specifically, the time to initiate appropriate therapy was determined before and after the initiation of PNA-FISH. In the pre-PNA-FISH era, the decision on antimicrobial coverage was based on clinical data and changed when blood culture results were available. After the introduction of PNA-FISH for enterococcal species, the median time until bacteremia caused by *E. faecalis* was detected at 3 days and bacteremia caused by *Enterococcus faecium* in 2.3 days. Since the study protocol allowed treating physicians to use PNA-FISH information for the intervention, this significantly shortened the time to use appropriate antibiotics (Antigone Kotsaki et al., 2016).

Polymerase Chain Reaction-based Diagnostics

Polymerase chain reaction is a simple that allows the amplification of a specific DNA fragment from a complex DNA pool.[9] Pathogen-specific tests, broad-range assays, and multiplex assays are the three types of PCR-based procedures. Because the range of probable pathogens causing sepsis is substantially greater than their over-specific nature, pathogen-specific diagnostics are of poor use. Broad-range assays may be more clinically beneficial than pathogen-specific testing. Following PCR amplification of a target sequence, additional identification methods such as polymorphism analysis,[22] sequencing,[23] or subsequent genus- or species-specific real-time PCR are performed in these assays.

Multiplex PCR includes employing a variety of primers to amplify several DNA targets in the same sample at the same time. This method is frequently based on amplification of the microorganisms' internally transcribed spacer region.[3] The TaqMan-based multiplex real-time PCR assay, which has a high sensitivity, specificity, and detection range, is a quick and accurate approach for detecting bacterial infections that cause sepsis, and it could be useful in sepsis diagnosis (Chang-Feng Liu 2017). In comparison to traditional blood cultures, PCR-based approaches enable for faster and more sensitive identification of pathogens; the consensus is that PCR can currently supplement, but not replace, blood cultures. The combined detection rate of both approaches was much higher in multiple investigations than CRP or blood culture alone.[3] Multiplex PCR was added to traditional blood cultures and had a significant influence on the clinical care of a subset of patients with suspected sepsis. They found positive results in 21% of all samples using only the blood culture results, compared to 27.4% using only the SeptiFast (SF) test. In comparison to blood culture, SF discovered more fungal pathogens and *E. faecium*. SF found fewer central nervous system (CNS) samples than traditional blood cultures.[19]

Blood culture findings were examined blindly using PCR results. When a sample was not inhibited and all pathogen PCRs were negative, it was considered negative. When the extraction and amplification control (EAC) signal's quantification cycle (Cq) value was within 2 SD (standard deviation) of the EAC signal in the negative control samples, the sample was termed noninhibited. Cq of *Staphylococcus* spp. *S. aureus*, when the Cq of *Staphylococcus* spp. The 3 Cq values were lower in this assay than in the *S. aureus*-specific assay. Weak amplification findings in the *S. aureus*-specific assay were verified by a second PCR assay.[28]

There are various commercially available molecular assays for the detection of sepsis which are mentioned below.

Prove-it™ Sepsis

The Prove-it assay (Mobidiag, Espoo, Finland) is one of the first commercially accessible microarray-based assays that may identify positive blood culture-sepsis-causing bacteria and fungi in as little as 3 hours.[11] The Prove-it StripArray, for example, uses a wideband PCR to target conserved areas of the gyrB, ParE, and mecA genes, followed by a microarray that can process 1–96 samples simultaneously.

Direct detection of microbial DNA in the blood has a significant benefit in detecting sepsis: Results are available within a few hours and are presumably unaffected by treatments. Furthermore, the amount of microbial DNA can be measured. Low sensitivity and a lack of a sufficient gold standard are now the main barriers to widespread adoption of such direct approaches, although there are encouraging advancements on the horizon.[31]

A limitation of this approach is that it can target several clinically relevant pathogens, including *Streptococcus viridans*, *Candida* spp., and CoNS, which cannot be detected. Currently, the clinical utility of the test is limited only for blood culture due to its use.

Verigene®

The Verigene—gram-positive blood culture (BCGP) and gram-negative blood culture (BCGN) assays (Nanosphere, Chicago, IL, USA) are automated direct access tests that extract nucleic acid directly from blood culture-positive media by hybridization with nanospheres of gold labeled with specific oligonucleotides on a microarray.[12] BCGN and BCGP are reliable, accurate, and rapid assays that can be incorporated into the routine workflow of a microbiology laboratory, even if their clinical utility needs to be further evaluated.

The gram-positive Verigene® blood culture nucleic acid test (BCGP), which detects many of the potentially pathogenic gram-positive bacteria associated with BSI, including *Staphylococcus* spp., *Streptococcus* spp., *Listeria* spp., and *Enterococcus* spp. as well as specific resistance markers (mecA, vanA, and vanB). Based on >1,600 samples, there was a high degree of agreement between the BCGP test results and those obtained with conventional blood culture and analysis methods, regardless of whether the samples were fresh or frozen, and a high degree of concordance in the identification of a mecA-methicillin resistance mediated by *S. aureus* and *S. epidermidis* and vancomycin resistance mediated by vanA or vanB in *E. faecalis*, and *E. faecium* organisms.[32]

FilmArray®

FilmArray® (Biofire Diagnostics, Salt Lake City, UT, USA) is a multiplex PCR tool that analyzes 24 sepsis-causing organisms and four antibiotic resistance genes. The assay is based on the extraction and purification of blood culture-positive nucleic acids and the amplification of target genes by first-stage reverse transcriptase PCR. It is a low complexity system for the clinician that only requires injecting the blood culture sample into a bag and starting the instrument; therefore, laboratory procedures can be performed by personnel without training in molecular techniques.

The BioFire FilmArray BCID panel is a two-step nested multiplex PCR assay with the ability to detect 24 target organisms and 3 antimicrobial resistance genes from positive blood cultures in approximately 1 hour (bioMérieux Diagnostics, 2021). Bacterial targets detected by the BioFire FilmArray BCID panel include *Staphylococcus* species, *S. aureus*, *Streptococcus* species, *S. pneumoniae*, *S. pyogenes*, *S. agalactiae*, *Enterococcus* arten, *Listeria monocytogenes*, *Enterobacterales*, *Acinetobacter baumannii*, *Enterobacter cloacae*-complex, *E. coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Proteus* arten, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Haemophilus influenzae*, and *Neisseria meningitidis*.[3] The panel can also detect five common yeasts, including *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *C. krusei*, and *Candida tropicalis*. In terms of antimicrobial resistance, the BioFire (RoxanneRule et al., 2021).

Magicplex

Magicplex (Seegene, Seoul, South Korea) is a multiplex PCR performed on whole blood that identifies 73 gram-positive and 12 gram-negative bacteria, six fungi (five *Candida* spp. and *Aspergillus fumigatus*), and three antibiotic resistance markers can be detected (vanA, vanB, and mecA) with a turnaround time (TAT) of 4–5 hours. Assay evaluations have shown low-to-moderate sensitivity and specificity (0.47 and 0.66, respectively),[14] which limits its usefulness as a surrogate for blood cultures, but has the advantage of being able to detect pathogens clinically relevant from negative culture material.[15]

MagicPlex Sepsis Test is a real-time PCR test that simultaneously analyzes the presence of pathogens and resistance to methicillin (mecA) and vancomycin (vanA and vanB). After creating an amplicon bank using normal PCR, over 90 genus-level pathogens and resistance markers are screened. Results are available in 5 hours (including isolation of pathogen DNA). A subsequent selective identification of pathogens is possible (only 27 pathogens can be detected at the species level) in an additional 30 minutes. *P. aeruginosa*, *A. baumannii*, *Stenotrophomonas maltophilia*, *S. marcescens*, *Bacillus fragilis*, *Salmonella typhi*, Stacolaebsiella, *K. pneumoniae*, *Streptococcus haemolyticus*, *S. agalactiae*, *Streptococcus E. faecalis*, *E. faecium*, and *Enterococcus gallinarum* are among the bacteria that cause food poisoning.

Lightcycler SeptiFast

The SF MGrade Test (Roche Diagnostics, Mannheim, Germany) is a CE-IVD (CE-in vitro diagnostic)-approved MultiPlex Realtime PCR that can detect 25 sepsis pathogens directly from whole blood (19 bacteria and 6 fungi). With an analytical sensitivity of 3–30 CFU/mL, the TAT is between 5 and 8 hours.[16] SeptiFast's utility in the microbiology laboratory is most likely to enhance blood culture, as SF TAT may result in faster pathogen detection (positive results can

apply to both fungi and bacteremia), therefore combining blood culture and SF improves pathogen detection.[17]

The detection limit is 100 CFU/mL for *Candida glabrata*, *Streptococcus* spp., and coagulase-negative *Staphylococcus* and ranges from 3 to 30 for the others, depending on the infectious agent. Limitations are the high costs (€ 150–200 per test), the need for trained personnel, and the lack of information on antibiotic sensitivity. This assay is an important alternative to blood culture, primarily due to its short time to result and high specificity, although further advances in laboratory personnel and workflow are required to improve its suboptimal sensitivity.

Sequencing

In comparison to the traditional Sanger identification method, the MicroSEQ 500 kit (PerkinElmer Applied Biosystems, Waltham, MA, USA) and pyrosequencing (Biotage, Uppsala, Sweden) are sequencing technologies that attack microorganisms in CM positive and whole blood in a short time and at a lower cost. The first involves amplification and sequencing of the first 527 bp fragment of bacterial 16S rRNA genes, while the second was used to classify and identify a range of bacterial 16S rDNA fragments. Currently, next generation sequencing (NGS) technology (e.g., Illumina MiSeq) is posing a new challenge in identifying and genotyping viable, dead, and viable but nonculturable pathogens as well as antibiotic resistance markers in a cost-effective and timely manner. The most difficult aspect of using NGS to detect pathogenic nucleic acid in the vast amount of human genomic DNA is detecting very minute levels of pathogenic nucleic acid (Marcello Guido et al, 2016).

PLEX-ID

PLEX-ID (Abbott Molecular, Carlsbad, CA, USA) is a revolutionary and universal approach for diagnosing a wide range of infections and four resistance markers (mecA, vanA/B, and blaKPC) straight from a patient's blood. Automated DNA extraction, PCR setup, PCR amplification, amplicon purification, and PCR/ESIMS are all part of this procedure. It includes a PCR with nine pairs of primers that target 16S rDNA, 23S rDNA, and four internal genes, as well as ESIMS for amplicon analysis.

CONCLUSION

The most common causes of sepsis-related mortality appear to be incorrect diagnosis and inadequate antibiotic use. As a result, the necessity to find innovative approaches to improve diagnostic sensitivity and speed has become increasingly pressing. Blood culture has a response period of 2 days or more; additionally, for certain illnesses, this period of time is far too long for doctors to administer a targeted antibiotic treatment. Despite recent advances in technology, the sensitivity for detecting specific illnesses remains limited, and blood culture contamination is still a major concern. New approaches have recently been developed to minimize the time it takes to diagnose a disease, as well as to improve the sensitivity and clinical benefits of pathogen identification. In comparison to conventional blood culture, more infections and critical resistance genes have been discovered earlier thanks to molecular detection methods. The short TATs of molecular assays could be critical in the management and outcome of sepsis patients, as delayed antibiotic administration drastically raises fatality rates. The inability to provide information on antibiotic susceptibility of the discovered pathogen is a limitation of PCR-based tests. Another disadvantage of these tools is their high cost, which includes the requirement for specialized equipment, reagents, and long-term qualified people.

One of the drawbacks of PCR-based assays is their inability to offer information on the pathogen's antibiotic susceptibility. Another downside of these tools is their high cost, which necessitates the long-term purchase of equipment, reagents, and qualified employees.

All episodes of polymicrobial infection showed contradictory results between blood culture and PCR. This finding shows the difficulty in diagnosing polymicrobial sepsis, for example, the fact that blood cultures regularly detect only the fastest growing organism. In two episodes in which PCR detected both *S. aureus* and CoNS, only CoNS was detected in blood cultures. The BDL of CoNS was >25 times higher than that of *S. aureus*.[28]

As a result, despite the benefits of molecular approaches in terms of sensitivity and speed, only blood culture can accomplish the antibiotic resistance spectrum. As a result, none of the molecular tests can completely replace blood culture; rather, they are complementing and must be used in tandem to ensure a correct and timely diagnosis. In order to address the drawbacks of blood culture- and PCR-based tests, more progress will be required in the near future. The new methodologies should help to increase the restricted analytical sensitivity for detecting difficult-to-detect diseases and distinguishing between alive and dead bacteria. NGS technologies might provide rapid pathogen identification and have the potential to disclose pathogen specimens and antimicrobial susceptibility at the same time.

REFERENCES

1. Hollenberg SM, Singer M. Pathophysiology of sepsis-induced cardiomyopathy. Nat Rev Cardiol. 2021;18(6):424-34.
2. Eubank TA, Long SW, Perez KK. Role of rapid diagnostics in diagnosis and management of patients with sepsis. J Infect Dis. 2020;222(Suppl 2):S103-9.
3. Liesenfeld O, Lehman L, Hunfeld KP, Kost G. Molecular diagnosis of sepsis: New aspects and recent developments. Eur J Microbiol Immunol. 2014;4(1):1-25.

4. Chatterjee S, Bhattacharya M, Todi SK. Epidemiology of adult-population sepsis in India: a single center 5 year experience. Indian Soc Crit Care Med. 2017;21(9):573.
5. Nelson GE, Mave V, Gupta A. Biomarkers for sepsis: A review with special attention to India. BioMed Res Int. 2014;2014:264351.
6. Lucignano B, Ranno S, Liesenfeld O, Pizzorno B, Putignani L, Bernaschi P, et al. Multiplex PCR allows rapid and accurate diagnosis of bloodstream infections in newborns and children with suspected sepsis. J Clin Microbiol. 2011;49(6):2252-8.
7. Yanagihara K, Kitagawa Y, Tomonaga M, Tsukasaki K, Kohno S, Seki M, et al. Evaluation of pathogen detection from clinical samples by real-time polymerase chain reaction using a sepsis pathogen DNA detection kit. Crit Care. 2010;14(4):1-9.
8. Septimus EJ. Sepsis perspective 2020. J Infect Dis. 2020; 222(Suppl 2):S71-3.
9. Garibyan L, Avashia N. Research techniques made simple: polymerase chain reaction (PCR). J Invest Dermatol. 2013;133(3):e6.
10. Liu CF, Shi XP, Chen Y, Jin Y, Zhang B. Rapid diagnosis of sepsis with TaqMan-Based multiplex real-time PCR. J Clin Lab Anal. 2018;32(2):e22256.
11. Tissari P, Zumla A, Tarkka E, Mero S, Savolainen L, Vaara M, et al. Accurate and rapid identification of bacterial species from positive blood cultures with a DNA-based microarray platform: an observational study. Lancet. 2010;375(9710): 224-30.
12. Buchan BW, Ginocchio CC, Manii R, Cavagnolo R, Pancholi P, Swyers L, et al. Multiplex identification of gram-positive bacteria and resistance determinants directly from positive blood culture broths: evaluation of an automated microarray-based nucleic acid test. PLoS Med. 2013;10(7):e1001478.
13. Poritz MA, Blaschke AJ, Byington CL, Meyers L, Nilsson K, Jones DE, et al. FilmArray, an automated nested multiplex PCR system for multi-pathogen detection: development and application to respiratory tract infection. PLoS One. 2011;6(10):e26047.
14. Ziegler I, Fagerstrom A, Stralin K, Molling P. Evaluation of a commercial multiplex PCR assay for detection of pathogen DNA in blood from patients with suspected sepsis. PLoS One. 2016;11(12):e0167883.
15. Ljungstrom L, Enroth H, Claesson BE, Ovemyr I, Karlsson J, Fröberg B, et al. Clinical evaluation of commercial nucleic acid amplification tests in patients with suspected sepsis. BMC Infect Dis. 2015;15:199.
16. Dubourg G, Raoult D. Emerging methodologies for pathogen identification in positive blood culture testing. Expert Rev Mol Diagn. 2016;16(1):97-111.
17. Korber F, Zeller I, Grunstaudl M, Willinger B, Apfalter P, Hirschl AM, et al. SeptiFast versus blood culture in clinical routine: a report on 3 years experience. Wien Klin Wochenschr. 2017;129(11):427-34.
18. Deepa Gotur B. Sepsis diagnosis and management. J Med Sci Health. 2017;3(3):1-12.
19. Dierkes C, Ehrenstein B, Siebig S, Linde HJ, Reischl U, Salzberger B. Clinical impact of a commercially available multiplex PCR system for rapid detection of pathogens in patients with presumed sepsis. BMC Infect Dis. 2009;9(1):1-7.
20. Trung NT, Thau NS, Bang MH. PCR-based Sepsis@ Quick test is superior in comparison with blood culture for identification of sepsis-causative pathogens. Sci Rep. 2019;9(1):1-7.
21. Jacobi J. Pathophysiology of sepsis. Am J Health Syst Pharm. 2002;59(Suppl 1):S3-8.
22. Turenne CY, Witwicki E, Hoban DJ, Karlowsky JA, Kabani AM. Rapid identification of bacteria from positive blood cultures by fluorescence-based PCR-single-strand conformation polymorphism analysis of the 16S rRNA gene. J Clin Microbiol. 2000;38(2):513-20.
23. Jordan JA, Jones-Laughner J, Durso MB. Utility of pyrosequencing in identifying bacteria directly from positive blood culture bottles. J Clin Microbiol. 2009;47(2):368-72.
24. Kotsaki A, Giamarellos-Bourboulis EJ. Molecular diagnosis of sepsis. Exp Opin Med Diagnos. 2012;6(3):209-19.
25. Sinha M, Jupe J, Mack H, Coleman TP, Lawrence SM, Fraley SI. Emerging technologies for molecular diagnosis of sepsis. Clin Microbiol Rev. 2018;31(2):e00089-17.
26. Han SS, Jeong YS, Choi SK. Current scenario and challenges in the direct identification of microorganisms using MALDI TOF MS. Microorganisms. 2021;9(9):1917.
27. Kim S, Kim J, Kim HY, Uh Y, Lee H. Efficient early diagnosis of sepsis using whole-blood PCR–reverse blot hybridization assay depending on serum procalcitonin levels. Front Med. 2020;7:390.
28. Van den Brand M, Van den Dungen FA, Bos MP, Van Weissenbruch MM, van Furth AM, De Lange A, et al. Evaluation of a real-time PCR assay for detection and quantification of bacterial DNA directly in blood of preterm neonates with suspected late-onset sepsis. Crit Care. 2018;22(1):1-10.
29. Ginn AN, Halliday CL, Douglas AP, Chen SC. PCR-based tests for the early diagnosis of sepsis. Where do we stand? Curr Opin Infect Dis. 2017;30(6):565-72.
30. Yealy DM, Huang DT, Delaney A, Knight M, Randolph AG, Daniels R, et al. Recognizing and managing sepsis: what needs to be done?. BMC Med. 2015;13(1):1-10.
31. Peters RP, Savelkoul PH, Vandenbroucke-Grauls CM. Future diagnosis of sepsis. Lancet. 2010;375(9728):1779-80.
32. Scott LJ. Verigene® gram-positive blood culture nucleic acid test. Mol Diagn Ther. 2013;17(2):117-22.
33. McFall C, Salimnia H, Lephart P, Thomas R, McGrath E. Impact of early multiplex FilmArray respiratory pathogen panel (RPP) assay on hospital length of stay in pediatric patients younger than 3 months admitted for fever or sepsis workup. Clin Pediatr. 2018;57(10):1224-6.
34. Loonen AJ, de Jager CP, Tosserams J, Kusters R, Hilbink M, Wever PC, et al. Biomarkers and molecular analysis to improve bloodstream infection diagnostics in an emergency care unit. PloS One. 2014;9(1):e87315.

SECTION 3

Pulmonology/Ventilation

CHAPTER 15

Role of High-flow Nasal Cannula: Has It Change the Outcome?

Ahsan Ahmed, Ahsina Jahan Lopa, Anirban Bose

INTRODUCTION

High-flow nasal cannula (HFNC) has rapidly gained its popularity during COVID pandemic for managing patients with acute respiratory failure due to severe COVID pneumonia. When ventilators were not available and all intensive care unit (ICU) beds were full, it had helped a lot of patients with acute hypoxemic respiratory failure (AHRF) to be managed in high dependency unit (HDU) bed and thus reduced the burden of ICU and ventilator beds in an already exhausted healthcare system. It has distinct advantage over the other oxygen delivery devices because of its unique effects on respiratory physiology. This review summarizes available data and addresses the wide spectrum of its clinical uses.

PHYSIOLOGY

During spontaneous breathing, inspired air is warmed and humidified in nose, pharynx, larynx, and trachea. Conventional oxygen delivery devices deliver cold gas which causes drying up and desiccation of airway mucosa, impaired bronchociliary clearance, and bronchoconstriction. Bubble humidifier is incapable of delivering required humidity to delivered gas particularly when patient's minute volume and peak inspiratory flow rate are high. HFNC delivers adequately heated and humidified gas with an active humidifier. There is better airway clearance, improved mucociliary function and metabolic cost of the breathing reduced by heated and humidified gas of HFNC.[1]

Alveolar oxygenation depends upon delivered gas flow rate, fraction of inspired oxygen (FiO_2), device interface, and inspiratory flow rate. Inspiratory flow rate is increased in acute respiratory failure. Low flow devices can provide maximum 15 L/min flow and FiO_2 up to 100% but higher inspiratory rate dilutes the inspired gas. Intermediate flow device such as Venturi mask can provide fixed FiO_2 compromising total flow. On the other hand, HFNC can provide up to 60 L/min flow and FiO_2 up to 100%, independent of flow, provided device flow must be greater than patient's inspiratory flow.[1] Conventional oxygen delivery system delivers unstable and lower than predicted FiO_2 while HFNC overcomes this shortcoming.[2] HFNC offers resistance to expiratory flow causing increased airway pressure in flow-dependent manner.[3] Pharyngeal pressure is increased in mouth closed position than mouth open position.[3] Pharyngeal pressure with HFNC is also affected by sex and body mass index (BMI).[3,4] End expiratory lung volume (EELV) is increased with HFNC, linearly with flow.[4] HFNC reduces anatomical dead space by flow-dependent clearance of carbon dioxide.[5]

With all these mechanisms, HFNC can reduce respiratory rate, minute ventilation, partial pressure of arterial carbon dioxide ($PaCO_2$), and pH constant; while improves oxygenation with increase in positive end-expiratory pressure (PEEP), reduces work of breathing, and improves patient comfort.[6]

CLINICAL SCENARIOS FOR USING HIGH-FLOW NASAL CANNULA

After its successful use in COVID patients, HFNC is also being tried in many other clinical entities of acute hypoxemic respiratory failure. It has shown to be beneficial in patients in severe acute respiratory distress syndrome (ARDS), for preoxygenation of hypoxic patients before intubation, procedures such as bronchoscopy, prevention of reintubation, and even in a subset of patients with hypercapnic respiratory failure. In spite of significant physiological benefits, robust data on outcome, especially mortality benefit, is lacking.

ACUTE HYPOXEMIC RESPIRATORY FAILURE

Multiple observational studies showed improvement of oxygenation status with HFNC in AHRF with very limited data on reduction in mechanical ventilation and mortality.

FLORALI trial, a multicenter open-label trial, compared the effect of HFNC, noninvasive ventilation (NIV) or conventional oxygen therapy (COT) via nonrebreathing face mask in patients with nonhypercapnic AHRF with no previous history of lung disease. The study showed no

difference in intubation rate in HFNC group compared to other two groups. However, Dyspnea Score, number of days on ventilator, and 90-day mortality are less in the HFNC group. In post-hoc analysis, reduced intubation rate is found in a subgroup with PaO_2/FiO_2 ratio <200.[7]

Rochwerg et al. in a recent meta-analysis found HFNC reduced the need of endotracheal intubation but not mortality.[8] Monro-Somerville et al. in another meta-analysis did not find any difference in intubation rate and mortality benefit between HFNC and usual care group.[9]

Meta-analysis of studies done in patients at emergency unit did not find any benefit of HFNC group compared with COT and NIV groups in terms of intubation requirement, treatment failure, hospitalization, and mortality.[10]

In immunocompromised patients with AHRF, NIV used as first-line therapy has been questioned recently in a meta-analysis by Wang et al. Though there was no significant difference in short-term mortality in the HFNC group over COT or NIV group but lower intubation rate than COT and a shorter length of ICU stay than NIV were observed in the HFNC group.[11]

In patients with do not intubate (DNI) status, HFNO also found to have shown successful oxygenation to many of them.[12]

HYPERCAPNIC RESPIRATORY FAILURE

Noninvasive ventilation is a first line of treatment for hypercapnic respiratory failure but poor tolerance is a limiting issue. Physiologically, HFNC can increase mean airway pressure, decrease dead space ventilation, thus increase in tidal volume, decrease respiratory rate, reduce hypercapnia, and reduce work of breathing. HFNC can also be used for oxygen therapy during breaks off NIV, as an alternative to NIV or as oxygen therapy device in mild-to-moderate respiratory acidosis and tolerated better than NIV.[13]

A single randomized controlled trial on using HFNC in breaks off NIV showed no reduction in time spend on NIV but improvement in comfort, dyspnea control, and respiratory rate.[14]

PREVENTION OF REINTUBATION

Noninvasive ventilation is used traditionally to prevent reintubation after weaning from mechanical ventilation. Physiological effects of HFNC can also prevent reintubation across a spectrum of patients with critical illness. Hernandez et al. showed that HFNC was not inferior to prevent reintubation in high-risk group patients compared to NIV. Patients in HFNC group had less respiratory failure, better tolerance, and improved secretion clearance.[15]

BiPOP study showed HFNC was noninferior to prevent reintubation and mortality.[16] In lung resection surgery, in comparison to COT, HFNC was associated with better oxygenation, less requirement of NIV, and reintubation.[17]

PREOXYGENATION

Patients with AHRF admitted in ICU frequently require endotracheal intubation. Both NIV and HFNO are used frequently for preoxygenation before intubation. HFNO also can be used for apnoeic oxygenation during laryngoscopy. OPTINIV trial showed adding HFNC for apnoeic oxygenation to NIV prior to orotracheal intubation effectively reduced severe desaturation than using NIV alone.[18]

BRONCHOSCOPY

Desaturation can occur during bronchoscopy due to procedural sedation and partial occlusion of airway by bronchoscope. NIV is used successfully to prevent desaturation but mask tolerance is poor and manipulation of bronchoscope is difficult. HFNC is a good alternative for prevention of desaturation during bronchoscopic procedure with better patient compliance.

COVID-19 SCENARIO

High flow nasal cannula is widely used successfully to treat COVID-19 infected patients suffering from AHRF. There are multiple case reports that emphasize the success story of HFNC to prevent intubation. Surviving Sepsis Campaign guideline recommends to use HFNC over NIV for AHRF after failed trial of COT, although evidences are very limited.[19] Main two major limiting factors for using HFNC are generation of aerosol and inability to address progress of disease that may delay intubation.

CONCLUSION

In spite of being a relatively newer device, HFNC finds its place to treat patients with AHRF. HFNC was tried in every segment of AHRF due to its appealing physiological property. Generated data were heterogeneous and still not adequate to show a clear mortality benefit. Further studies are needed to define optimum device settings and to assess defined outcome in well-characterized patient population.

REFERENCES

1. Spoletini G, Alotaibi M, Blasi F, Hill NS. Heated humidified high-flow nasal oxygen in adults: Mechanisms of action and clinical implications. Chest. 2015;148(1):253-61.
2. Ritchie JE, Williams AB, Gerard C, Hockey H. Evaluation of a humidified nasal high-flow oxygen system, using oxygraphy, capnography and measurement of upper airway pressures. Anaesth Intensive Care. 2011;39(6):1103-10.
3. Groves N, Tobin A. High flow nasal oxygen generates positive airway pressure in adult volunteers. Aust Crit Care. 2007;20(4):126-31.
4. Corley A, Caruana LR, Barnett AG, Tronstad O, Fraser JF. Oxygen delivery through high-flow nasal cannulae increase end-expiratory lung volume and reduce respiratory rate in post-cardiac surgical patients. Br J Anaesth. 2011;107(6):998-1004.

5. Mauri T, Turrini C, Eronia N, Grasselli G, Volta CA, Bellani G, et al. Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure. Am J Respir Crit Care Med. 2017;195(9):1207-15.
6. Itagaki T, Okuda N, Tsunano Y, Kohata H, Nakataki E, Onodera M, et al. Effect of high-flow nasal cannula on thoracoabdominal synchrony in adult critically ill patients. Respir Care. 2014;59(1):70-4.
7. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015;372(23):2185-96.
8. Rochwerg B, Granton D, Wang DX, Helviz Y, Einav S, Frat JP, et al. High flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: a systematic review and meta-analysis. Intensive Care Med. 2019;45(5):563-72.
9. Monro-Somerville T, Sim M, Ruddy J, Vilas M, Gillies MA. The effect of high-flow nasal cannula oxygen therapy on mortality and intubation rate in acute respiratory failure: a systematic review and meta-analysis. Crit Care Med. 2017;45:e449-56.
10. Tinelli V, Cabrini L, Fominskiy E, Franchini S, Ferrante L, Ball L, et al. High flow nasal cannula oxygen vs. conventional oxygen therapy and noninvasive ventilation in emergency department patients: a systematic review and meta-analysis. J Emerg Med. 2019;57(3):322-28.
11. Wang Y, Ni Y, Sun J, Liang Z. Use of high-flow nasal cannula for immunocompromise and acute respiratory failure: a systematic review and meta-analysis. J Emerg Med. 2020; 58(3):413-23.
12. Peters SG, Holets SR, Gay PC. High-flow nasal cannula therapy in do-not-intubate patients with hypoxemic respiratory distress. Respir Care. 2013;58(4):597-600.
13. Millar J, Lutton S, O'Connor P. The use of high-flow nasal oxygen therapy in the management of hypercarbic respiratory failure. Ther Adv Respir Dis. 2014;8(2):63-64.
14. Spoletini G, Mega C, Pisani L, Alotaibi M, Khoja A, Price LL, et al. High-flow nasal therapy vs standard oxygen during breaks off noninvasive ventilation for acute respiratory failure: a pilot randomized controlled trial. J Crit Care. 2018;48: 418-25.
15. Hemandez G, Vaquero C, Colinas L, Cuena R, González P, Canabal A, et al. Effect of postextubation high-flow nasal cannula vs noninvasive ventilation on reintubation and postextubation respiratory failure in high-risk patients: a randomized clinical trial. JAMA. 2016;316(15):1565-74.
16. Stephan F, Barrucand B, Petit P, Rézaiguia-Delclaux S, Médard A, Delannoy B, et al. High-flow nasal oxygen vs noninvasive positive airway pressure in hypoxemic patients after cardiothoracic surgery: a randomized clinical trial. JAMA. 2015;313(23):2331-9.
17. Yu Y, Qian X, Liu C, Zhu C. Effect of high-flow nasal cannula versus conventional oxygen therapy for patients with thoracoscopic lobectomy after extubation. Can Respir J. 2017;2017:7894631.
18. Jaber S, Monnin M, Girard M, Conseil M, Cisse M, Carr J, et al. Apnoeic oxygenation via high-flow nasal cannula oxygen combined with non-invasive ventilation preoxygenation for intubation in hypoxaemic patients in the intensive care unit: the single-centre, blinded, randomised controlled OPTINIV trial. Intensive Care Med. 2016;42(12):1877-87.
19 Alhazzani W, Moller MH, Arabi YM, Loeb M, Ng Gong M, Fan E, et al. Surviving sepsis campaign: Guidelines on the management of critically ill adults with corona virus disease 2019 (COVID-19). Intensive Care Med. 2020;46(5):854-87.

16

CHAPTER

Awake Proning

Shrikant Sahasrabudhe, Sauren Panja, Saswati Sinha

INTRODUCTION

Prone positioning (PP) has been shown to reduce mortality in mechanically ventilated patients with moderate-to-severe acute respiratory distress syndrome (ARDS). The improvement in oxygenation with PP was demonstrated over four decades ago[1] but it was only recently demonstrated in the PROSEVA trial[2] that early institution and prolonged sessions of prone ventilation (>16 hours) significantly reduced mortality in these patients. This has been corroborated further in a meta-analysis[3] and a Cochrane review[4] thereby placing PP as a strong recommendation in international guidelines on ARDS management. PP refers to placing a patient face down and it is said to improve oxygenation by improving ventilation-perfusion (VQ) matching. Due to its positive physiological effects, it has also been tested in spontaneously breathing patients who are not intubated which is known as "awake proning." Although there have been studies reporting the use of awake proning in the past, the interest in the same has been rekindled with sudden surge of cases of acute respiratory failure during the COVID-19 pandemic which have overwhelmed the capacity of healthcare systems. Our aim is to address the current evidence, indications, the technical aspects, and the overall utility of awake proning in the present scenario.

PHYSIOLOGIC RATIONALE OF PRONE POSITIONING

- *Improvement of V/Q mismatch* and shunt by reducing alveolar overdistension in the nondependent areas as well as collapse of alveoli in dependent areas. Also there is less compression of dorsal regional lung units leading to homogenization of transpulmonary pressures.
- *Facilitates drainage of secretions* from the posterior lung
- *Reduction of ventilator-induced lung injury (VILI) and patient self-inflicted lung injury (P-SILI)*: There is also a proposed theory of reductions in VILI in ARDS patients put forward by Albert way back in 1997.[5] Similarly patients with acute respiratory failure who are spontaneously breathing have high respiratory drives which can contribute to P-SILI. Reduction of respiratory effort by PP through improved gas exchange may help ameliorate further lung damage.
- *Decreasing lung compression*: More uniform distribution of tidal volume and end expiratory lung volume, thus reducing the cyclical opening and closing of alveoli (reduced atelectrauma)[6]

CURRENT EVIDENCE ON AWAKE PRONING

Although PP is now an integral part of the standard of care due to its proven efficacy not only in improving gas exchange in moderate-to-severe ARDS, data on awake spontaneously breathing patients is scarce.

NON-COVID-19 PATIENTS

There have been studies in the pediatric population which have shown improvement in oxygenation and lung mechanics in spontaneously breathing infants with pneumonia with prone ventilation.[7,8] Similarly there have been several case reports and observational studies on the impact of awake proning in adults with hypoxemic respiratory failure. Valter et al. reported a rapid increase in PaO_2 and ability to avoid intubation in all four patients who were subjected to PP with good tolerance and found no adverse effects.[9] In another study of 15 adult patients (nine of whom were immunocompromised) with acute hypoxemic respiratory failure, Scaravilli et al. found that prone position was both safe and feasible and improved oxygenation.[10] Awake proning when combined with high-frequency percussive ventilation (a form of noninvasive ventilation) has also been found to enhance airway opening, limit potential VILI, and improve clearance of secretions in post-lung transplant recipients. It has been found to improve lung exchange, reduce the work of breathing and respiratory rate and the number of bronchoscopies.[11] Ding et al. in a multicenter cohort study in two teaching hospitals studied

20 patients with moderate-to-severe ARDS and aimed to determine whether early institution of PP with high flow nasal cannula (HFNC) or noninvasive ventilation (NIV) could avoid intubation. The main causes of ARDS were influenza and other viral pneumonia. Average duration of prone position was 4 hours per day. Intubation was avoided in 11 patients. All patients with PF ratio <100 mm Hg on NIV required intubation, thereby concluding that early PP with HFNC in moderate ARDS may avoid intubation but patients with severe ARDS are not appropriate candidates for HFNC/NIV and awake proning.[12]

COVID-19 DISEASE

In view of a dearth of effective definitive therapy for COVID-19, the management is centered mainly on optimizing supportive care. Since acute hypoxemic respiratory failure and ARDS is a common presentation of SARS-CoV2 infection, recent guidelines by the UK Intensive Care Society advocate awake proning to become standard of care for suspected or confirmed Covid-19 patients requiring oxygen >28%.[13] These are a result of extrapolation from studies of mechanically ventilated with ARDS in whom prone ventilation is an evidence-based practice.

Although limited data on the utility of awake proning exists in spontaneously breathing patients, it is now recommended that hospitalized patients with COVID-19 who require supplemental oxygen which may include high flow nasal oxygen, NIV, or even low flow oxygen are encouraged to spend as much time as possible in prone position. Awake proning has shown to improve oxygenation and in some cases reduce intubation rates.

A randomized controlled multinational meta-trial including patients from six superiority trials including patients on HFNC for acute hypoxemic respiratory failure due to COVID-19 were assigned to awake PP or standard of care. Hospitals from Canada, France, Ireland, Mexico, USA, and Spain participated in the study. 1,126 total patients were enrolled with 567 in the awake prone and 559 in the standard of care group. Primary outcome was defined as "treatment failure" which was a composite outcome of intubation or mortality within 28 days of enrollment. Treatment failure occurred in 40% of the awake prone group versus 46% in the standard of care [relative risk (RR) 0.86, 95% confidence interval (CI) 0.75–0.98]. The hazard ratio for intubation was 0.75 (95% CI 0.62–0.91) and that for mortality was 0.87 (95% CI 0.68–1.11) within 28 days whereby indicating that awake proning reduces the risk of treatment failure by reducing intubation rates without any increased risk of harm.[14]

A prospective before - after single center study conducted in a French hospital included 24 nonintubated patients with confirmed COVID-19 infection and requiring oxygen supplementation and chest computed tomography (CT) findings with posterior lesions. Arterial blood gases were obtained before PP, during PP, and 6–12 hours after turning to supine position. The main outcome was the proportion of responders defined as a 20% increase in PaO_2 between pre-PP and during PP. Secondary outcomes included persistent responders (persistent 20% PaO_2 increase between pre-PP and after supination), variation of PaO_2 and $PaCO_2$ between pre-PP, during PP, and after resupination and feasibility (ability to sustain PP >1 hour and <3 hours). Tolerance was monitored using visual analog scale. Two-thirds of the patients could tolerate PP for >3 hours. 40% of those who tolerated PP showed improved oxygenation however the response was sustained in only half of these patients after return to supine position.[15]

Another single center study from Italy included 56 patients with confirmed COVID-19 infection on supplemental oxygen or NIV aimed to assess the feasibility and physiological effects of PP which was maintained for a minimum of 3 hours. PP was feasible in 83.9% patients and oxygenation substantially improved (PaO_2:FiO_2 ratio—180.5 mm Hg [standard deviation (SD) 76.6] in supine to 285.5 mm Hg (SD 112.9) in prone position, $p < 0.0001$). However, this improvement was sustained only in 50% of patients on resupination. Responders had a higher level of inflammatory markers and shorter duration between hospitalization and PP. There was no differences in the rates of intubation among responders and nonresponders (30 versus 26%, $p = 0.74$). Hence, PP was found to be feasible but improvement in oxygenation was sustained in only half of the patients.[16]

Another systematic review and meta-analysis by Reddy et al.[17] included 758 patients from 25 observational studies with an aim to evaluate the impact of PP on oxygenation and clinical outcomes in spontaneously breathing patients. Despite significant heterogeneity in the location, duration, frequency, and respiratory support, there was significant improvement in oxygenation. PaO_2:FiO_2 ratio (mean difference 39, 95% CI 25–54), SpO_2 (mean difference 4.74%, 95% CI 3–6%), PaO_2 (mean difference 20 mm Hg, 95% CI 14–25) were higher in the prone group. Respiratory rate decreased in the prone position. 24% of patients required intubation and mortality was 13%. Location of prone position (ICU vs. non-ICU) did not affect the intubation rate and there were no serious adverse events reported whereby concluding that awake proning improves oxygenation, although its impact on clinical outcomes such as mortality or intubation needs further evaluation in randomized trials.

Table 1 depicts the results from several studies on awake PP in COVID-19.

TECHNICAL ASPECTS OF AWAKE PRONING

Indications

All hospitalized patients with suspected/confirmed COVID-19 requiring supplemental oxygen [low flow oxygen, high flow oxygen (HFNC) or NIV] to achieve a SpO_2 92–96%.

TABLE 1: Evidence during COVID-19.[18]

	Name of study	*Type*	*No. of PTS*	*Interventions*	*Avoid invasive ventilation*	*Mortality benefits*
1	3 Chinese Hospitals	Case report	79	PP + HFNC	Yes	–
2	Jiangsu province Experience	Observational		Awake PP	Yes	Yes
3	ED in New York City	Pilot Observational Cohort study	50	Awake PP	No	–
4	Elharsar et al.	Single center prospective	88	Awake PP	Yes	–
5	Sartini and colleagues	1 day cross sectional study	15	PP with CPAP	Yes	–
6	Singapore study	Observational	10	Awake PP	No	–
7	Coppo and colleagues	Prospective, Observational	56	Awake PP with CPAP or O_2	No	No
8	Columbia University	Observational	29	O_2–NC and NRBM	No	No

(CPAP: continuous positive airway pressure; HFNC: high-flow nasal cannula; NC: nasal cannula; NRBM: non-rebreather mask; PP: prone positioning)
Source: Adapted with permission from Sodhi K, Chanchalani et al, IJCCM

Contraindications

- Severe respiratory distress (RR >35/min, $PaCO_2$ >48 mm Hg (6.5 kPa)
- Immediate need for intubation
- Persistent shock or arrhythmias
- Altered mental status/agitation
- Spinal instability
- Raised intracranial pressure (ICP) and seizures
- Recent sternotomy or tracheal surgery
- Major abdominal surgery
- Morbid obesity
- Anterior thoracostomy/air leaks
- *Pregnancy*: Second/third trimester.

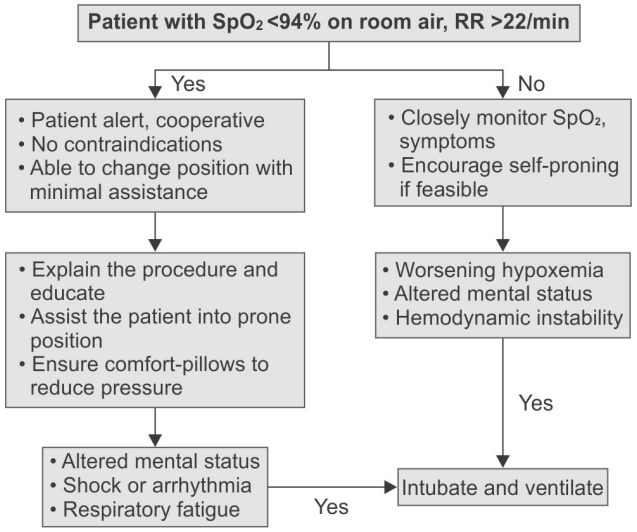
THE PROCEDURE OF AWAKE PRONING (FLOWCHART 1)

- Explain the procedure to the patient.
- The attending staff needs to be trained in the procedure and capable of monitoring the patient.
- Provision to identify failure of awake PP and escalation to invasive ventilation should be present.
- Ensure oxygen and airway adjuncts and the SpO_2 probe are in place from time to time.
- An alarm bell should be available near the patient and explained to him/her.

Timed position changes can be done as follows:

- 30 minutes to 2 hours lying prone (bed flat)
- 30 minutes to 2 hours on right side (bed flat)
- 30 minutes to 2 hours sitting up (30–60°) by adjusting head end of the bed
- 30 minutes to 2 hours lying on left side (bed flat)
- 30 minutes to 2 hours prone again
- Continue to repeat the cycle.

Flowchart 1: Process and steps of awake proning.



(RR: relative risk)

MONITORING OF THE PATIENT

- Ensure that the patient is comfortable and care to avoid pressure injury.
- Closely monitor vitals, sensorium, and signs of respiratory distress.
- Clear protocol to identify failure of awake proning and alert the critical care team must exist.
- Watch closely for desaturation, hemodynamic instability, and arrhythmia.

COMPLICATIONS

- Venous stasis
- Pressure sores
- Dislodgement of venous access
- Nerve compression

- Arrhythmia
- Hypoxia
- Vomiting
- Exposure of medical personnel.

FUTURE DIRECTIONS

Several randomized controlled trials (RCTs) are ongoing which aim to address the effect of awake proning not only on oxygenation but also on how it may impact patient-centered outcomes some of which are mentioned below.

- *OPTIPRONE study*: PP during high flow oxygen therapy in acute hypoxemic respiratory failure (NCT 03095300).
- *Pro Cov*: PP in spontaneously breathing nonintubated COVID-19 patients (NCT 04344106).
- *APPROVE-CARE*: Awake PP to reduce invasive ventilation in COVID-19 induced acute respiratory failure (NCT 04347941).
- *COVI-PRONE*: Awake prone position in hypoxemic patients with coronavirus disease 19 (NCT 04350723).

CONCLUSION

Awake proning seems to be a safe, simple, and a low cost intervention which can be performed in several areas in the hospital even outside the critical care areas. By improving oxygenation at least in the patients with moderate ARDS and by its propensity to reduce the intubation rates in a carefully selected set of patients, it has the potential to reduce the demand on invasive mechanical ventilation. Thus, it may ease the pressure on the intensive care services as well as avoid the complications associated with invasive ventilation. The results from the ongoing trials will likely further elucidate the unresolved issues associated with this maneuver.

REFERENCES

1. Bryan AC. Conference on the scientific basis of respiratory therapy. Pulmonary physiotherapy in the pediatric age group. Comments of a devil's advocate. Am Rev Respir Dis. 1974;110(6 Pt 2):143-4.
2. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. N Eng J Med. 2013;368(23):2159-68.
3. Sud S, Friedrich J, Adhikari N, Taccone P, Mancebo J, Polli F, et al. Effect of prone positioning during mechanical ventilation on mortality among patients with acute respiratory distress syndrome: a systematic review and meta-analysis. CMAJ. 2014;186(10):381-90.
4. Bloomfield R, Noble D, Sudlow A. Prone position for acute respiratory failure in adults. Cochrane database of systematic reviews. 2015;2015(11):CD008095.pub2
5. Cornejo RA, Diaz JC, Tobar EA, Bruhn AR, Rames CA, Gonzalez RA, et al. Effects of prone positioning on lung protection in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2013;188(4):440-8.
6. Glenny RW, Lamm WJ, Albert RK, Robertson HT. Gravity is a minor determinant of pulmonary blood flow distribution. J Appl Physiol. 1991;71(2):620-9.
7. Chaisupamongkollarp T, Preuthipan A, Vaicheeta S, Chantarojanasiri T, Kongvivekkajornkij W, Suwanjutha S. Prone position in spontaneously breathing infants with pneumonia. Acta Paediatr. 1999;88(9):1033-4.
8. Tulleken JE, van der Werf TS, Ligtenberg JJM, Fijen JW, Zijlstra JG. Prone position in a spontaneously breathing near-drowning patient. Intensive Care Med. 1999;25(12):1469-70.
9. Valter C, Christensen AM, Tollund C, Schønemann NK. Response to the prone position in spontaneously breathing patients with hypoxemic respiratory failure. Acta Anaesthesiol Scand. 2003;47(4):416-8.
10. Scaravilli V, Grasselli G, Castagna L, Zanella A, Isgrò S, Lucchini A, et al. Prone positioning improves oxygenation in spontaneously breathing nonintubated patients with hypoxemic acute respiratory failure: A retrospective study. J Crit Care. 2015;30(6):1390-4.
11. Feltracco P, Serra E, Barbieri S, Milevoj M, Michieletto E, Carollo C, et al. Noninvasive high-frequency percussive ventilation in the prone position after lung transplantation. Transplant Proc. 2012;44(7):2016-21.
12. Ding L, Wang L, Ma W, He H. Efficacy and safety of early prone positioning combined with HFNC or NIV in moderate to severe ARDS: a multi-center prospective cohort study. Crit Care. 2020;24:28.
13. Bamford P, Bentley A, Dean J, Whitmore D, Wilson-Baig N. Ics guidance for prone positioning of the conscious COVID patient. 2020.
14. Ehrmann S, Li J, Ibarra-Estrada M, Perez Y, Pavlov I, McNicholas B, et al. Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial. Lancet Respir Med. 2021;9(12):S2213-2600.
15. Elharrar X, Trigui Y, Dols AM, Touchon F, Martinez S, Prud'homme E, Papazian L. Use of prone positioning in nonintubated patients with COVID-19 and hypoxemic acute respiratory failure. JAMA. 2020;323(22):2336-8.
16. Coppo A, Bellani G, Winterton D, Di Pierro M, Soria A, Faverio P, et al. Feasibility and physiological effects of prone positioning in non-intubated patients with acute respiratory failure due to COVID-19 (PRON-COVID): a prospective cohort study. Lancet Respir Med. 2020;8(8):765-74.
17. Ponnapa Reddy M, Subramaniam A, Afroz A, Billah B, Lim ZJ, Zubarev A, et al. Prone positioning of nonintubated patients with coronavirus disease 2019-a systematic review and meta-analysis. Crit Care Med. 2021;49(10):e1001-14.
18. Sodhi K, Chanchalani G. Awake proning: Current evidence and practical considerations. Indian J Crit Care Med. 2020;24(12):1236-41.

CHAPTER 17

Utility of ROX Score in Predicting HFNC Failure

Harjit Dumra, Tushar Patel, Mukesh Patel

INTRODUCTION

Heated humidified high-flow nasal cannula (HFNC) has revolutionized management of acute hypoxemic respiratory failure (AHRF) patients. Physiologic studies have shown that as compared to conventional oxygen therapy, high flow in HFNC generates a positive end-expiratory pressure (PEEP) effect leading to increased end-expiratory lung volume (EELV) and tidal volume all of which contributes to improved ventilation, oxygen delivery, decreased work of breathing (WOB), better airway secretion clearance, and improved patient comfort.[1]

In 2015, Frat et al. published the FLORALI trial where they randomized over 300 patients who had AHRF to receive conventional oxygen therapy, noninvasive ventilation or HFNC. In this study, use of HFNC was associated with lower risk for intubation particularly in a subset of patients with partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2) < 200 mm Hg. This was also associated with improved ventilator free days and lower mortality risk. This clearly indicated that HFNC was a safe and effective tool in reducing the need for mechanical ventilation (MV).[1,2] All this evidence has led to HFNC being given a strong recommendation for use in patients with hypoxemic respiratory failure in the recently published guidelines in Intensive Care Medicine in 2020 as well as in 2021 update of the Surviving Sepsis Campaign Guideline.[3,4]

However, one of the most difficult decisions in the intensive care unit (ICU) is to decide when to intubate and initiate MV in a spontaneously breathing patient with acute respiratory failure (ARF). While HFNC might decrease the need for MV in quite a number of patients, it can also lead to undue delay in intubation in some. This could lead to adverse outcomes. The problem with HFNC is that we are flying blind. While on invasive or noninvasive MV there's an interface which provides clinicians with immense amount of patient data that not only helps in modifying ventilator settings but also guides clinicians in real time about which direction the patient is heading. The lack of such an interface makes it extremely challenging to do so on HFNC. Hence, there is an urgent need to identify accurate predictors for initiating MV in spontaneously breathing patients with ARF.

Some of the common variables which indicate clinical worsening and need for MV in patients of ARF on HFNC include: (1) worsening oxygenation [PaO_2 < 60 mm Hg, saturation of peripheral oxygen (SpO_2) < 90% with HFNC flow > 30 L and FiO_2 of 100%), (2) respiratory acidosis [pressure of arterial carbon dioxide ($PaCO_2$) >50 mm Hg, venous partial pressure of carbon dioxide ($PvCO_2$) > 55 mm Hg, pH < 7.25), (3) respiratory rate (RR) > 30 breaths/minute, (4) persistence of thoracoabdominal asynchrony, (5) retained secretions, and (6) lack of decrease in the RR after HFNC. In addition to these respiratory parameters, some small retrospective studies have also shown that additional organ failures such as hemodynamic, neurological disturbance [Glasgow Coma Scale (GCS) < 12], and high Sequential Organ Failure Assessment (SOFA) score could also predict HFNC failure.[5,6] All of these till date, however, have not been discriminant enough to unequivocally identify patients who would require subsequent intubation.

Hence, there is a pressing need for an objective decision making tool which can provide a solution to this day-to-day dilemma and standardize decision making. For a considerable period of time, we have relied on various indices in the ICU, to guide patient management at bedside. The respiratory rate and oxygenation (*ROX) index* is once such tool which is easy, feasible, and reliably predicts need for MV in patients of hypoxemic respiratory failure on HFNC.[5]

WHAT DOES RESPIRATORY RATE AND OXYGENATION STAND FOR?

The acronym ROX stands for respiratory rate and oxygenation. The ROX index is defined as ratio of SpO_2/FiO_2 to the RR. It was introduced for the first time by Roca et al. when they published the results of their prospective observational study. This study carried out over a period of 4 years, included 157 patients with severe pneumonia and

ARF on HFNC treatment. In this study, a ROX index > 4.88 measured after 12 hours of HFNC treatment was associated with a considerable decrease in need for MV and hence could identify patients who could continue to receive HFNC beyond 12 hours.[1,2,5] This index was more accurate at predicting HFNC failure then either of the two variables (i.e., SpO_2/FiO_2, and RR) independently.[2]

FURTHER IMPROVING THE RESPIRATORY RATE AND OXYGENATION INDEX

So is one study enough to prove the functionality of the ROX index?

Roca et al. published a validation study in 2019, involving 191 patients with pneumonia and ARF and further delineated other parameters for the ROX index. The authors found that ROX was better than looking at SpO_2/FiO_2, RR, $PaCO_2$, flow, SpO_2, FiO_2, and lactate to predict the need for MV. ROX index > 4.88 at 2 hours had a hazard ratio of 0.434, at 6 hours hazard ratio of 0.304, and at 12 hours hazard ratio of 0.291, clearly indicating a lower risk of intubation on HFNC. HFNC failure was indicated by a ROX index of <2.85 at 2 hours, <3.47 at 6 hours, and <3.85 at 12 hours **(Table 1)**.[2] Those patients who had a smaller increase in ROX index values over a 12-hour period were more likely to fail therapy.[1]

RESPIRATORY RATE AND OXYGENATION SCORE MARGIN FOR FAILURE OVER TIME

The diagnostic accuracy of ROX was superior to SpO_2/FiO_2 or RR with an area under receiver operating characteristic (AUROC) of 0.74, 0.83, and 0.87 at 12, 18, and 24 hours, respectively, which means acceptable, outstanding, and outstanding.

Zhen Junhai et al. recently published a meta-analysis which included nine studies with 1,933 patients. Out of these, 745 patients had HFNC failure. Their results indicated that sensitivity and specificity of ROX index was 0.67 [95% confidence interval (Cl) 0.57–0.76] and 0.72 (95% Cl 0.65–0.78), respectively. ROX index had low sensitivity and acceptable specificity. They inferred that ROX index is a reasonably reliable marker to identify subset of patients with a higher risk of HFNC failure, with a moderate prediction efficiency.[6]

TABLE 1: ROX score.

Time point (hours of NHF use)	*ROX score*	*Positive predictive value%*
2 hours	<2.85	98
6 hours	<3.47	98–99
12 hours	<3.85	99
>12 hours	<4.88	80

(NHF: nasal high flow; ROX: respiratory rate and oxygenation)

INCREASING FLOW RATE, RESPIRATORY RATE, AND OXYGENATION INDEX CORRELATION

Previous studies have suggested that the flow rate has a significant bearing on oxygenation and RR. Based on this data, Mauri et al. tried to analyze whether increasing the flow rates in patients of AHRF on HFNC might improve the ROX index values. They assessed the data of 57 patients with hypoxemia who were subjected to two 20-minute sessions on HFNC. The first with gas flow rate of 30 L/min and the next with rate of 60 L/min. The results demonstrated that the increase in flow rate from 30 to 60 L/min was clearly associated with trend towards improvement in the ROX index. The patients with more severe disease at baseline were more likely to respond positively to the increasing flow rates. This study brought out two important conclusions. First, that the set flow rate has a strong bearing on the ROX index and improvement in ROX index with increasing flow rates identified severe patients in need of more stringent monitoring. Secondly, standardizing the ROX index measurement at the lowest flow rate of 30 L/min may help in predicting the success or failure of HFNC much better.[1]

IS ROX INDEX RELIABLE IN COVID-19?

A recent systemic review and meta-analysis published by Prakash et al. looked over this question. Their review analyzed data of 1,301 patients from eight retrospective or prospective studies. A significant challenge posed by coronavirus disease-2019 (COVID-19) to the ROX index is that COVID patients have been on HFNC for days and weeks unlike patients included in studies by Roca et al, who looked at ARF patients for shorter time frames. They found that the ROX index was excellent at predicting the need for intubation. The AUC of ROX index was 0.81 for predicting (95% CI 0.77–0.84) HFNC failure. It had a reasonable sensitivity of 0.70 and a specificity of 0.79.[7]

CAN ROX INDEX BE RELIABLY USED IN PATIENTS ON HFNC IN THE WARDS?

During the coronavirus pandemic, HFNC has extensively been used outside the ICU because[6] of paucity of beds. Vega et al. in a retrospective multicentric study tried to analyze how accurate was the ROX index in predicting HFNC failure in patients treated in wards and whether it would compare favorably to the previously suggested thresholds. Their analysis concluded that the 12 hours ROX index with an area under curve (AUC) of 0.7916 (CI 95% 0.6905–0.8927) was the best predictor of intubation. The best threshold was 5.99 (specificity 96% and sensitivity 62%). Their analysis clearly indicated that although the ROX index may be useful in guiding intubation in patients with COVID-19 and ARF outside the ICU, a different threshold value 5.99 (vs. 4.88)

predicted successful outcomes and this could possibly be secondary to the different mechanisms of hypoxia in COVID-19 patients.[8]

CAN ROX INDEX BE RELIABLY USED IN IMMUNOCOMPROMISED HOSTS?

In a secondary analysis of randomized trial[9] in 302 immunocompromised patients receiving HFNC, Lemiale et al. showed that the ROX index with the threshold value of 4.88 was a poor predictor of need for intubation with an AUC of 0.623. However in a multivariate analysis, a higher value of ROX index was better at predicting a lower rate of intubation with an odds ratio (OR) of 0.89. This trial highlighted that although the ROX index is not a very strong predictor of intubation in immunocompromised patients with AHRF, it still is a very important variable. The index seems to have a good performance for risk stratification.[5,10]

HOW CAN THESE RESULTS BE APPLIED BY THE CLINICIAN?

Most of the studies focusing on the use of HFNC in AHRF have shown that by and large most intubations occur between 12th and 24th hours after initiating HFNC. Hence, the optimal use of HFNC is in this time frame.

Predicting High-flow Nasal Cannula Success

The ROX index > 4.88 at 2, 6, and 12 hours means that clinicians are in the safe zone.

Predicting High-flow Nasal Cannula Failure

Intubation is most likely the correct way to go in patients with ROX < 2.85 at 2 hours, < 3.47 at 6 hours, and < 3.85 at 12 hours.

Gray Zone

There is actually a gray zone between the 3.85 and 4.88 at the 12 hour mark. Clinical judgment reigns supreme here. Options are to try and improve oxygenation by proning or increasing the flow rates. The ROX index should be reassessed within 1–2 hours. If the score has improved the chances of intubation are less, on the contrary if the ROX index has decreased the likelihood of intubation is high. In case of no change, close monitoring of the patient with serial assessment of ROX index every 1–2 hours is recommended.[2]

LIMITATIONS OF RESPIRATORY RATE AND OXYGENATION INDEX

Predicting the probability of intubation remains challenging and may depend on several factors particularly hemodynamic and neurological dysfunctions and respiratory parameters included in the ROX index. Besides these, oxygenation needs, other organ dysfunctions and ARF etiology have also been associated with risk of intubation. Undoubtedly in patients with severe disease, intubation should not be delayed.[10]

The ROX index is likely to be useful clinically because it requires few data points and is simple to calculate on the bedside. It has a positive predictive value for success of >80% between 12 and 20 hours postinitiation, when most of the intubations occur.

The ROX index which includes primarily respiratory parameters only reflects the WOB. There are several other factors which when combined with ROX might improve its prediction ability. Tachycardia is one such factor. In a recent study published in 2020, Ken Junyang Goh et al. reported that ROX-HR, i.e., ratio of ROX index over heart rate (HR) > 8, calculated at 6 and 10 hours after initiating HFNC outperformed the ROX index in predicting HFNC failure.

Last but not the least, the ROX index was developed and validated in subsets of patients with pneumonia/acute respiratory distress syndrome (ARDS) with hypoxemic respiratory failure. The score has not been tested in other cohorts. Also, close bedside observation and clinical judgment is central to decision making regarding intubation in hypoxemic patients with borderline respiratory reserve and scores such as the ROX index only add to our ability to predict failure—it cannot, in isolation be considered the gold standard.[9]

A key feature to the accuracy of the ROX index is avoiding hyperoxia. Excessive oxygen can lead to a falsely low SpO_2/FiO_2 ratio vitiating the benefits of the ROX index. Hence, target saturations during oxygenation should not exceed 90–94%.

STRENGTHS OF RESPIRATORY RATE AND OXYGENATION INDEX

The ROX index is a clinically simple bedside applicable tool. It has a high positive predictive value of nearly 80% when used between 12 and 24 hours, a time frame when most intubations occur.[9] Furthermore, ROX index is a noninvasive tool where no blood samples from patients are required. Hence, its use can decrease the amount of arterial blood gases (ABGs) performed on acute hypoxic respiratory failure patients. Besides these, ROX has also been found to be beneficial as an independent prognostic index for 28-day mortality. It has also been suggested to be a better marker of clinical deterioration in COVID-19 as compared to the National Early Warning Score 2 (NEWS2) and has in addition been found to be useful in predicting continuous positive airway pressure (CPAP) success.[6]

TAKE HOME POINTS

- The S/F ratio can be utilized as an alternative to the P/F ratio.
- The ROX index is a simple noninvasive accurate, bedside tool to quickly assess patients for possible HFNC failure.

- The ROX index should be used complementary to clinical judgment and other assessment tools for appropriate care of patients with AHRF on HFNC.

REFERENCES

1. Brown C, Saihi K, Arnal J-M, Grooms D. (2020). Can we predict the failure of HFNC in patients with acute hypoxemic respiratory failure? [online] Available from: https://www.hamilton-medical.com/en_IN/News/Newsletter-articles/Article~2020-10-16~Can-we-predict-the-failure-of-HFNC-in-patients-with-acute-hypoxemic-respiratory-failure%3F~16e8531b-13ef-42b1-9ef4-892db42db24b~.html. [Last accessed March, 2022].
2. Roca O, Caralt B, Messika J, Samper M, Sztrymf B, Hernández G, et al. An Index Combining Respiratory Rate and Oxygenation to Predict Outcome of Nasal High-Flow Therapy. Am J Respir Crit Care Med. 2019;199(11):1368-76.
3. Rochwerg B, Einav S, Chaudhuri D, Mancebo J, Mauri T, Helviz Y, et al. The role for high flow nasal cannula as a respiratory support strategy in adults: a clinical practice guideline. Intensive Care Med. 2020;46(12):2226-37.
4. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al, Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47(11):1181-1247.
5. Roca O, Messika J, Caralt B, García-de-Acilu M, Sztrymf B, Ricard JD, et al. Predicting Success of High Flow Nasal Cannula in Pneumonia Patients with Hypoxemic Respiratory Failure: The Utility of the ROX Index. J Crit Care. 2016;35:200-5.
6. Junhai Z, Jing Y, Shijin G, Beibei C, Li L. The value of ROX index in predicting the outcome of high flow nasal cannula: a systematic review and meta-analysis. Respir Res. 2022; 23:33.
7. Prakash J, Bhattacharya PK, Yadav AK, Kumar A, Tudu LC, Prasad K. ROX index as a good predictor of high flow nasal cannula failure in COVID-19 patients with acute hypoxemic respiratory failure: A systematic review and meta-analysis. J Crit Care. 2021;66:102-8.
8. Vega ML, Dongilli R, Olaizola G, Colaianni N, Sayat MC, Pisani L. COVID-19 Pneumonia and ROX index: Time to set a new threshold for patients admitted outside the ICU. Authors' reply. Pulmonology. 2021; 2021;27(5):475-6.
9. Hill NS, Ruthazer R. Predicting Outcomes of High-Flow Nasal Cannula for Acute Respiratory Distress Syndrome. An Index that ROX. Am J Respir Crit Care Med. 2019;199(11): 1300-02.
10. Lemiale V, Dumas G, Demoule A, Pène F, Kouatchet A, Bisbal M, et al. Performance of the ROX index to predict intubation in immunocompromised patients receiving high-flow nasal cannula for acute respiratory failure. Ann Intensive Care. 2021;11:17.

CHAPTER 18

Selecting the Right Noninvasive Ventilation Interface

Ranajit Chatterjee, Sivakumar MN, Rekha Das

INTRODUCTION

COVID-19 pandemic led to exponential growth in the usage of noninvasive ventilation (NIV) and high-flow nasal cannula (HFNC). Successful usage of NIV depends on selecting right patient and right interface. NIV failure rate varies between 18 and 40% and is associated with increased mortality. Reasons for NIV failure include:

- Etiology of acute respiratory failure
- *Patient*: Selection and cooperation
- Staff experience
- Interface selection.

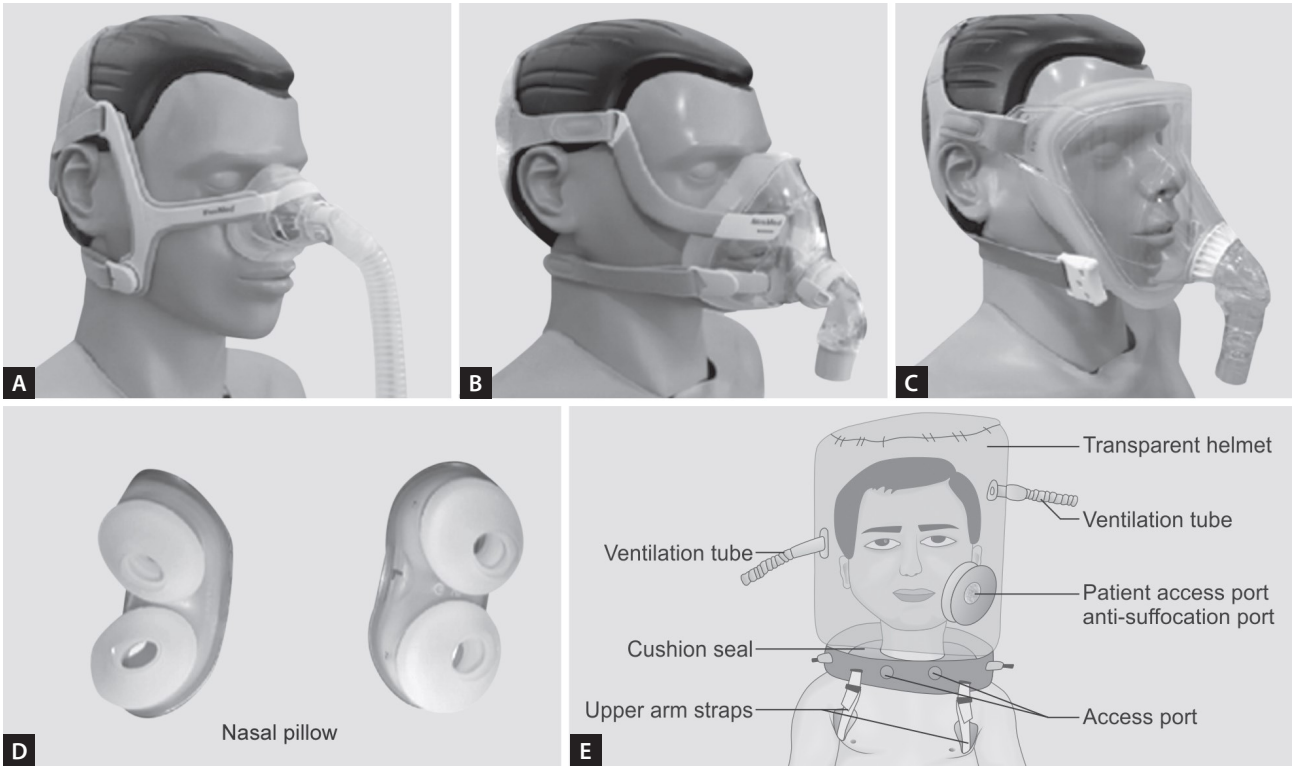
This review discusses the various available interfaces and how to choose the right one. As there is an evolving interest over helmet mask during the pandemic, its usage will be discussed in detail.

Different types of interfaces available are as follows **(Figs. 1A to E)**:

- Oral mask
- Nasal pillow mask
- Nasal mask
- Oronasal mask (face mask)
- Total face mask
- Helmet

ORAL MASK

Oral mask fits inside the mouth between teeth and lips. It is cumbersome and not routinely used.



Figs. 1A to E: Types of mask. (A) Nasal; (B) Oronasal; (C) Total face mask; (D) Nasal pillow; (E) Helmet mask.

NASAL PILLOW MASK

This mask fits on the rim of the nostrils. It is mainly used in stable patients (e.g., sleep disorder). In stable patients when other interfaces are not tolerated or has a complication such as skin breakdown nasal pillow can be tried.

NASAL MASK

This mask covers the nose and rests on the upper lip, side of nose, and nasal bridge. In an acute situation, lot of patients tend to do mouth breathing, which lead to air leak and failure of noninvasive ventilation. However, nasal mask improves patient comfort and hence can be tried in prolonged usage.

Randomized controlled trial by Kwok[1] et al. showed that both nasal and oronasal masks performed similarly with regard to improving vital signs (heart rate and respiratory rate) and gas exchange but the nasal mask was less well tolerated than the oronasal mask in acute situations. In the study conducted by Girault[2] et al. comparing oronasal mask with nasal mask, failure occurred significantly more often in the nasal mask group and air leak was also more prevalent. However, with prolonged use, respiratory discomfort and complications were more frequent in those using an oronasal mask.

ORONASAL MASK (FACE MASK)

This mask covers nose, mouth and rest on chin, nasal bridge, sides of nose and mouth. Well tolerated and has a success rate better then nasal mask in exacerbation of chronic obstructive pulmonary disease (COPD) and pulmonary edema. A randomized control trial conducted by Sadeghi[3] et al. comparing oronasal mask with a total face mask, no differences were noted between the two masks with acceptance and comfort being similar in both groups. In patients with acute respiratory failure (ARF) who are breathing through mouth, an oronasal or total face mask is considered to be the most suitable and effective interface.

In acute hypercapnic respiratory failure, initial few days oronasal mask may be used to reduce leak and then they can be replaced or changed over to nasal mask to reduce complications and respiratory discomfort.[2] Therefore, the oronasal mask is the most commonly used interface in patients with ARF. This was revealed in a large web-based survey conducted in North America and Europe, which showed that an oronasal mask was used in 70% of the patients, followed by total face mask, nasal mask, and helmet.[4]

TOTAL FACE MASK

This mask covers the entire face. It is a commonly used interface other than oronasal minimizes air leak, maximizes NIV delivery, thereby results in better carbon dioxide (PCO_2) reduction.

HELMET AS INTERFACE

Face mask is the principal interface used in NIV. However, face mask is associated with multiple problems such as claustrophobia, eye and skin irritation, nasal congestion, and sore throat. It is also associated with issues such as air leaks, nasal bridge, and face ulcers. All these complications lead to frequent NIV failures. It must be appreciated that different shapes of face cannot be ventilated with limited size of face mask. These limitations have led to the emergence of helmet as an alternative interface. Helmet obviates much of these problems. It has the advantage of better tolerance, gives better patient autonomy (patient can look around, speak, drink, cough, wear glasses, and even read), air leaks are rare, and there are no skin lesions compared to face mask.

Helmet Structure

Helmet is made up of rigid transparent plastic shell with a soft elastic membrane which adheres to the patient torso providing comfort and neck seal. Some helmets have additional inflatable neck cushion to give adequate seal. There are inspiratory and expiratory ports. The helmet also has two accessory ports. These ports can be used for passage of nasogastric tubes and for providing additional flow, if necessary. The helmet is fixed with the help of two soft armpit support with underarm straps. There is a patient access port also called antisuffocation port. The helmet is available in six adult sizes and they are selected by measuring the neck circumference of the patient.

Helmet Function

It is essential to demonstrate the function of the helmet to the patient to gain their confidence. Once the patient is sufficiently assured, the neck circumference of the patient is measured, and an appropriate size helmet is selected. A ventilator which can generate a continuous higher flow levels should be used for ventilating the patient with helmet as interface. The inspiratory and expiratory ports are attached to the two limbs of the circuit. Bacterial/viral filters should be placed in both inspiratory and expiratory limb. A positive end-expiratory pressure (PEEP) [expiratory positive airway pressure (EPAP)] + pressure support (PS) [inspiratory positive airway pressure (IPAP) – EPAP] mode is to be selected, with a PEEP of 10 cmH_2O and PS of 10–15 cmH_2O. As the internal volume is large, it takes a longer time to achieve target level PS. The inspiratory trigger should be kept at 2 L/min, with a fast rise time (50–100 ms). The expiratory sensitivity should be adjusted to achieve minimum depressurization time and it is kept anywhere between 25 and 50%.

Helmet—Problems and Solutions

Four main problems preclude the use of helmet successfully which are as follows:

- *CO_2 re-breathing*: Large dead space
- Noise
- *Asynchrony*: Due to slow pressurization and depressurization times, inspiratory and expiratory trigger delay
- Claustrophobia.

CO_2 rebreathing is due to the large internal volume of the helmet. To overcome this, set high inspiratory flow (>50 L/min) and raise bias flow to 10 L/min. The end tidal carbon dioxide ($EtCO_2$) probe may be kept in a quiet place inside the helmet (just above the inflated cushion) to measure the CO_2h (CO_2 tension inside helmet). Flow should be adjusted to keep the CO_2h values around 5 mm Hg. The issue of CO_2 rebreathing precludes the usefulness of helmet in hypercapnic failure patients.

A lot of noise is generated while helmet ventilation is on as compared to face mask (100 vs. 70 dB). This problem can be mitigated by using ear plugs for patient.

Vargas et al. suggested increasing PEEP and PS levels by 50% than that used in face mask and using fastest pressurization time. They used PEEP 7–8 cmH_2O, PS 12–15 cmH_2O and pressurization time of 50 ms. When used with specific settings, helmet NIV provided equal effect on unloading of inspiratory muscles, decreasing the work of breathing (WOB) and improved the inspiratory trigger delay.[5] Such high PEEP will not be tolerated by patients on face mask.

An optimized setup for helmet noninvasive ventilation was proposed by Majoli et al. to improve PS delivery and patient-ventilator interaction. The authors proposed a high PEEP of 10 cmH_2O, inflated cushion (120–150 cmH_2O), low resistance circuit by reducing its length to 65 cm, and a fast rise time to achieve optimum synchrony.[6]

A meta-analysis of NIV with helmet versus controlled strategy in patients of ARF by Liu et al. comprising of 11 controlled studies and 621 patients revealed that there was lower mortality in the helmet group (17.53 vs. 30.67%), with no failure rate (0 vs. 38%) with helmet. In patients of NIV with face mask, 24–64% had to change the mask and most common reason for nonadaptation of the mask was the shape of the face. Subgroup analysis revealed lower mortality in hypoxemic ARF patients and lower intubation rates (both hypercapnic and hypoxemic patients) with fewer complications in the helmet group.[7] The improved tolerance with the helmet group leads to uninterrupted NIV application which is crucial, especially in the initial phase of acuter respiratory failure, thus obviating mechanical ventilation and its associated complications. Effect of helmet on partial pressure of carbon dioxide (PCO_2) level depends on the type of respiratory failure and the mode of ventilation used. Patients generating high CO_2 may be countered by giving high fresh gas flows and higher inspiratory pressures.

Patel et al. successfully used NIV with helmet in ARDS patients. Treatment with helmet NIV resulted in a significant reduction of intubation rates (61.5 vs. 18.2%, P <0.001). The number of ventilator-free days was significantly higher in the helmet group (28 vs. 12.5, P <0.001). There was also a statistically significant reduction in 90-day mortality (34.1 vs 56.4%, P = 0.02) with helmet NIV.[8] The higher PEEP used in the helmet group (8 vs. 5.1 cm) might be a possible explanation to this success. Patients on face mask cannot tolerate high PEEP/EPAP. This frequently leads to discomfort and leak, leading to NIV failure. Helmet has been used in COVID-19 pandemic, a multicenter randomized control trial with four intensive care unit (ICU) and 109 patients failed to show any difference in the number of days free of respiratory support within 28 days of enrolment. However, the rate of intubation was significantly lower in the helmet group as well as the number of ventilator free days.[9]

Helmet and Contamination

The recent coronavirus disease (COVID) pandemic has raised the serious question of contamination of healthcare workers while using NIV. It has been found that the dispersion of exhaled air is negligible with helmet specially if it is used with double circuit, appropriate filters, and proper neck seal with inflated cushions. Whereas NIV via face mask with an IPAP of 18 cmH_2O and EPAP of 5 cmH_2O disperses exhaled air up to 92 cm, whereas NIV via helmet with an IPAP of 18 cmH_2O and EPAP of 10 cmH_2O has negligible dispersion with an inflated neck cushion. Those helmets without a neck cushion disperse up to 27 cm with similar settings.[10]

Helmet has emerged as an alternative to facemask as an interface, especially in hypoxemic failure. Apprehension of CO_2 rebreathing limits its use in hypercapnic failure. However, with optimum settings, it is comparable to face mask even in hypercapnic failure. It is well tolerated, reduced the requirement of intubation with less complications, and has potential to cause less contamination of healthcare personnel.

Factors to be taken into consideration while selecting interface:

- Patient preference, tolerance, comfort, and fit
- Type of respiratory failure
- Shape of patient face, mouth, and nose
- Dead space.

In acute setting, good mask fit and care are more important than patient comfort for success of NIV. Dyspnea, respiratory rate, and arterial blood gas do not significantly differ between interfaces. Advantages and disadvantages of various interfaces are given in **Table 1**.

TABLE 1: Advantages and disadvantages of various interfaces.

Variables	*Nasal*	*Oronasal*	*Full face mask*	*Helmet*
Comfort	+++	++	+	+
Claustrophobia	+	++	+++	+++
Rebreathing	+	++	++	+++
Permits speech, food, and expectoration	++	+	+	++
Air leak	++	+	+	+
Acute settings	+	++	++	++

+ Possible, ++ Most likely, +++ Very likely

FITTING THE INTERFACE

Right interfaces have to be identified for each patient in given situation. Fitting gauge provided by the manufactures can be used to select the appropriate interface size **(Fig. 2)**. Securing the interface too tight leads to skin breakdown and decrease patient tolerance. After fixing head gear and strap, you should be able to pass two fingers between the strap and face. Excessive pressure on nose (or) face to be avoided. Mask should not encroach on corners of eye (or) lip.

An interface of correct size largely obviates leaks, eye irritation, nasal congestion, and nasal and oral dryness. *Skin erosions and ulcers* develop when NIV is used for a longer period. These ulcers are more common over the nasal bridge and over the cheek where the mask lining is in direct contact with the facial skin. This is one of the most common reasons of noncompliance and failure of NIV.

The following measures will help to prevent skin sores and ulcers:

- Use correct size face masks
- Avoid excessive tightening of headgear
- Use pressure sore dressings at the area of contact, especially over nasal bridge and cheek.

Air leak is another issue with the face mask. An ill-fitted mask may cause leak. These unintentional leaks may lead to eye irritation, dryness of mouth, and throat as well as sleep disturbances. Leaks leads to asynchrony, fall in SpO_2 and eventual failure of NIV. Intentional leaks, via vents in the masks, or circuit, is deliberately created to prevent rebreathing.

Try different mask type or size, if there are large leaks. When changing to a different interface, trigger compatibility with circuit and PS to be verified.

TYPES OF VENTILATOR AND INTERFACE CHOICE

Application of NIV can be done through either a closed dual limb circuit, an open single limb circuit, or a closed single limb circuit with an exhalation port **(Table 2)**. Closed dual limb circuit has separate tubes for inspiration and expiration and used along with a nonvented mask.

In open single limb circuit, vented mask is used. In closed single limb circuit, a nonvented mask is used along with an exhalation port in the circuit. Clinicians and respiratory therapist must have the adequate knowledge about the type of interface **(Figs. 3A and B)** and the circuit in which it is to be used. If nonvented mask is used in a closed single limb circuit without an exhalation port, it will be catastrophic.

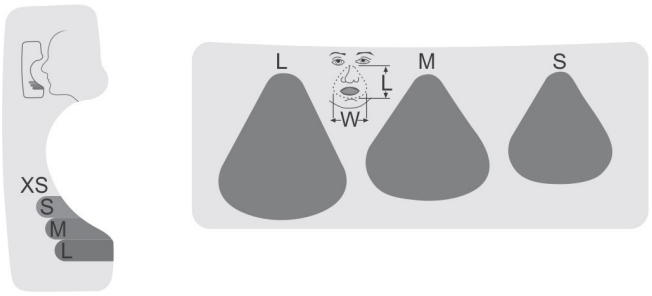
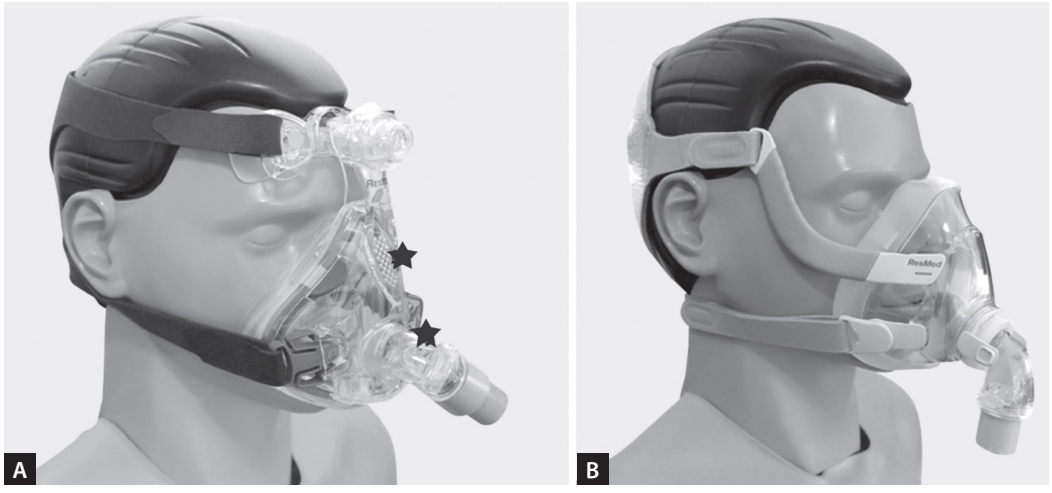


Fig. 2: Fitting gauge to select appropriate interface size.

TABLE 2: Types of circuit and interface selection.

Types of circuit	*Circuit features*	*Type of mask*
Closed dual limb circuit	Separate inspiratory and expiratory limb	Nonvented mask
Open single limb circuit	Single limb circuit	Vented mask
Closed single limb circuit	Single limb circuit with exhalation port	Nonvented mask



Figs. 3A and B: Types of masks. (A) Vent mask; (B) Non-vent mask ★ Vent.

The amount of oxygen delivered to the patient depends on the *site of oxygen* delivery.

If oxygen is directly delivered in the mask, much of it is lost through exhalation vents or due to the unintentional leaks. Ventilators which can precisely monitor and deliver fraction of inspired oxygen concentration (FiO_2) should be the modality of choice compared to stand alone bilevel positive airway pressure (BiPAP).

The *ventilator modes* used may also influence the outcome of NIV. It has been found that neutrally adjusted ventilator assist (NAVA) decreases patient ventilator asynchrony when compared to pressure support ventilation (PSV) mode across all spectrum of interface. When NAVA is used with face mask, trigger delay and asynchrony index (AI) was significantly reduced compared to PSV.[11] When used with a helmet the AI was >10% in PSV trials compared to NAVA. Also, the mechanical expiratory time was significantly shorter with NAVA compared to PSV.[12]

HUMIDIFICATION

Delivery of cold gases causes nasal dryness, thick secretions, increased work of breathing, and delayed weaning. This is more common with invasive ventilation but may also affect patients on prolonged NIV. Though heat moist exchangers (HME) are widely used as it is economical and convenient. However, it increases dead space and work of breathing of patients. Heated humidifiers are a natural choice in these situations. However, heated humidifiers might cause condensation inside the helmet (fog effect).

CONCLUSION

COVID-19 pandemic had further reiterated the paramount importance and benefits of NIV. Though success of NIV depends on multiple factors, selection of appropriate interfaces is the most important. As there are no ideal interfaces, choosing an interface requires through evaluation of patients features, mode of ventilation, and type of respiratory failure.[13]

Noninvasive ventilation is thus a valuable complement in patient management and, based on available evidence, oronasal and face masks are the preferred mode of interface in patients with ARF. Though the helmet is a promising alternative, it requires high positive airway pressures, further studies are required to identify ideal patient population to use the helmet as NIV interface.

REFERENCES

1. Kwok H, McCormack J, Cece R, Houtchens J, Hill NS. Controlled trial of oronasal versus nasal mask ventilation in the treatment of acute respiratory failure. Crit Care Med. 2003;31(2):468-73.
2. Girault C, Briel A, Benichou J, Hellot MF, DacharaouiF, Tamion F, et al. Interface strategy during non-invasive positive pressure ventilation for hypercapnic acute respiratory failure. Crit Care Med. 2009;37(1):124-31.
3. Sadeghi S, Fakharian A, Nasri P, Kiani A. Comparison of comfort and effectiveness of total face mask and oronasal mask in non-invasive positive ventilation in patients with acute respiratory failure: a clinical trial. Can Respir J. 2017;2017:2048023.
4. Crimi C, Noto A, Princi P, Esquinas A, Nava S. A European survey of noninvasive ventilation practices. Eur Respir J. 2010;36(2):469-75.
5. Vargas F, Thille A, Lyazidi A, Campo FR, Brochard L. Helmet with specific settings versus facemask for noninvasive ventilation. Crit Care Med. 2009;37(6):1921-8.
6. Majoli F, Iotti G A, Curro I, Pozzi M, Via G, Venti A, et al. An optimized set-up for helmet noninvasive ventilation improves pressure support delivery and patient–ventilator interaction. Intensive Care Med. 2013;39(1):38-44.
7. Liu Q, Gao Y, Chen R, Cheng Z. Noninvasive ventilation with helmet versus control strategy in patients with acute respiratory failure: a systematic review and meta-analysis of controlled studies. Crit Care. 2016;20(1):265.
8. Patel BK, Wolfe KS, Pohlman AS, Hall JB, Kress JP. Effect of noninvasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome: a randomized clinical trial. J Am Med Assoc. 2016;315(22):2435-41.
9. Grieco DL, Menga LS, Cesarano M, Rosà T, Spadaro S, Bitondo MM, et al. Effect of helmet noninvasive ventilation vs high-flow nasal oxygen on days free of respiratory support in patients with COVID-19 and moderate to severe hypoxemic respiratory failure: the HENIVOT randomized clinical trial. J Am Med Assoc. 325(17):1731-48.
10. Ferioli M, Cisternino C, Leo V, Pisani L, Palange P, Nava S. Protecting healthcare workers from SARS-CoV-2 infection: practical indications. Eur Respir Rev. 2020;29:200068.
11. Piquilloud L, Tassaux D, Bialais E, Lambermont B, Sottiaux T, Roeseler J, et al. Neurally adjusted ventilatory assist (NAVA) improvespatient-ventilator interaction during non-invasive ventilation delivered by face mask. Intensive Care Med. 2012;38(10):1624-31.
12. Cammarota G, Olivieri C, Costa R, Vaschetto R, Colombo D, Turucz E, et al. Noninvasive ventilation through a helmet in postextubation hypoxemic patients: physiologic comparison between neurally adjusted ventilatory assist and pressure support ventilation. Intensive Care Med. 2011;37(12):1943-50.
13. Davidson AC, Banham S, Elliot M, Kennedy D, Gelder C, Glossop A, et al. BTS/ICS guidelines for the ventilatory management of acute hypercapnic respiratory failure in adults. Thorax. 2016;71(Suppl 2):ii1-35.

CHAPTER 19

How to Predict the SILI in Noninvasive Ventilation and High-flow Nasal Cannula?

Manoj Singh, Jay Kothari, Maharshi Desai

INTRODUCTION

Poor lung compliance and need for elevated airway pressure to maintain adequate gas exchange remained the hallmark of acute respiratory distress syndrome (ARDS) since its first description by Ashbaugh and colleagues in 1967.[1] Even after extensive research for >50 years in the field of ARDS, lung-specific treatment is yet to be discovered and mechanical ventilation remained the cornerstone in the management of patient with moderate-to-severe ARDS. When mechanical ventilation was first introduced in 1950s, the primary goal was to correct impairment in gas exchange. Although mechanical ventilation is lifesaving treatment in ARDS, but its use can lead to ventilator-induced lung injury (VILI). The concept of VILI was first introduced in 1970 and now it is well-accepted,[2] although it took a long time to realize that even vigorous spontaneous breathing efforts can cause lung injury. In 2010, a multicenter, double-blind trial was published in New England Journal of Medicine (NEJM) which revealed that early use of neuromuscular blocking agents can improve 90-day mortality in patients with severe ARDS.[3] Since then the possible adverse consequences of spontaneous efforts have been extensively discussed. In 2017, the term P-SILI (patient self-inflicted lung injury) was introduced.[4] P-SILI is a new concept without enough direct evidence, most of the evidence are concluded from other clinical and experimental studies on spontaneously breathing mechanically ventilated patients.[4]

The use of noninvasive ventilation (NIV) and high-flow nasal cannula (HFNC) has been increased dramatically in critical care settings in last decade. Recent COVID-19 pandemic taught us regarding resource management in critical care settings. A large number of patients were managed with noninvasive ventilator support and there was a constant debate among experts regarding early versus late intubation of these patients. P-SILI was considered as one of the factor which may help to decide the one who may require early intubation. In this chapter, we will review the possible mechanism of P-SILI-induced lung injury as well as how we can predict it in patients with noninvasive ventilator support.

MECHANISMS OF PATIENT SELF-INFLICTED LUNG INJURY

Three potential mechanisms of P-SILI are suggested: (1) Increased lung stress/strain and inhomogeneous distribution of air, (2) increased in lung perfusion, and (3) patient ventilator asynchronies during noninvasive positive-pressure ventilation (NPPV).

1. *Increased lung stress or strain and in-homogeneous distribution of ventilation*: Stress is defined as the force applied per unit lung area. It is represented by the transpulmonary pressure. It is the difference between alveolar pressure and pleural pressure, estimated by esophageal pressure (Pes). Strain is defined as the change in volume divided by the initial lung volume (functional residual capacity).[5] Lung strain is directly proportional to stress and it shows overstretching.[6] When we compare spontaneous breathing to positive-pressure ventilation, spontaneous breathing looks safer by our traditional beliefs as the airway pressure is lower during spontaneous breathing as compared to invasive mechanical ventilation. But this low airway pressure does not mean low transpulmonary pressure (PL), a pressure across the lung. Inspiratory effort is the major determinant of PL in spontaneously breathing patients. In ARDS, due to poor lung compliance, higher inspiratory efforts are needed to generate similar tidal volume. Such high inspiratory efforts create more negative pleural pressure and in turn PL in dependent regions of the lung. This is the reason for inhomogeneous distribution of volume and pressure across the vertical gradient.[7,8] Due to heterogeneity in pleural pressure distribution, inspiratory pendelluft phenomenon occurs in which there is intratidal shift of gas from nondependent to dependent lung regions, even before actual inspiratory flow starts which causes regional overdistension of dependent regions. Which is independent from the size of the inspired tidal volume (i.e., the overstretch volume comes from the healthy aerated lung, and not from the ventilator). Experimental

studies showed that pendelluft may further aggravate the lung damage.[9]

2. *Increase in lung perfusion*: As we have already discussed, spontaneous breathing generates a more negative pleural pressure. This can ultimately increase transmural vascular pressure and vessel permeability and cause pulmonary edema. Vigorous inspiratory efforts during volume controlled ventilation can cause pulmonary edema; we call it negative pressure pulmonary edema.[10]
3. *Patient ventilator asynchronies*: Patient ventilator asynchronies contribute to poor outcome in ventilated patients. Ineffective efforts and double trigger are the most common type. Two back-to-back inspirations occur following a single respiratory effort in double triggering. This is harmful as more tidal volume will be delivered. It is common in patients with higher respiratory drive.[11]

EARLY DETECTION OF TREATMENT FAILURE

Delayed intubation of spontaneously breathing patients with hypoxemic acute respiratory failure is associated with an excess mortality. It is obvious that patients with more severe clinical condition will have higher chances of treatment failure with NIV. PaO_2/FiO_2 <200 mm Hg before treatment and higher SAPS II (Simplified Acute Physiology Score II) (>35) are associated with increased risk of being intubated.[12,13] Improvement in gas exchange after 1 hour of NIV application is also an important tool which can help to identify patients who may require intubation. PaO_2/FiO_2 ratio between 145 and 175 mm Hg after 1 hour of NIV is independently associated with risk of NIV failure and need for intubation.[12,14] On NIV with low level of pressure support, the expiratory tidal volume of >9–9.5 mL/kg of predicted body weight with p/f ratio <200 mm Hg can predict NIV failure with good sensitivity and specificity.[15] It has been found in previous studies that patients with tachycardia, tachypnea, acidosis, hypoxemia, and altered mental status have higher probability of NIV failure.[16] Recently a comprehensive scale (HACOR) was developed using five parameters to predict NIV failure: Heart rate, acidosis, consciousness, oxygenation, and respiratory rate. Patients with a HACOR score of >5 had a very high risk of NIV failure.[17]

TECHNIQUES TO ENHANCE SUCCESS OF NONINVASIVE APPROACH

High-flow Nasal Cannula

Introduction of HFNC has revolutionized the area of noninvasive management of hypoxic respiratory failure. HFNC can match patient's inspiratory flow requirement and can deliver up to 60 L/min of fully heated and humidified air through air oxygen blender.[18] High flow reduces anatomical dead space by CO_2 washout from upper airway and thereby reduces work of breathing and inspiratory efforts. In comparison to NIV or standard oxygen therapy, HFNC has shown to have reduced mortality, more ventilator-free days, and lower risk for intubation in subsets of patients with PaO_2/FiO_2 ≤200 mm Hg or in those who were immunocompromised.[19] The ROX index (ratio of pulse oximetry/FiO_2 to respiratory rate) has been validated to predict HFNC therapy outcomes in patients with hypoxic respiratory failure. Patients with ROX Index >4.88 after 2 hours of treatment likely avoid intubation, while those with a ROX <2.85, <3.47, and <3.85 after 2, 6, and 12 hours of HFNC are at high risk of treatment failure.[20]

Use of Positive End-expiratory Pressure

High positive end-expiratory pressure (PEEP) reduces the amount of atelectatic lung which allows more homogeneous distribution of inspiratory efforts. It helps to control the injurious inflation caused by spontaneous efforts. High PEEP increases the end-expiratory lung volume and thereby reduces the force generated by diaphragm. Higher PEEP also improves gas exchange, which helps to reduce respiratory drive.[21] ROSE (Reevaluation Of Systemic Early Neuromuscular Blockade) trial which was published in 2019, found that among patients who were treated with high PEEP strategy, no difference in mortality was found between neuromuscular blocker group and control group.[22]

CONCLUSION

The type of noninvasive device, timing, and duration should be carefully customized as per patient's clinical requirement. Bedside monitoring of patient has no substitute. While noninvasive approach sound convincing as it avoids invasive approach at the same time, we should be careful as spontaneous breathing itself can cause lung injury and increase mortality. Early detection of failure of noninvasive approach is also equally important. Vigorous inspiratory efforts generating high expiratory tidal volume can worsen the hypoxemia and lung injury. On NIV support, patient's spontaneous effort should be carefully monitored. If vigorous spontaneous effort continues even after initiation of NIV, necessary steps should be taken to minimize the injury generated by patient's own efforts to maintain physiology. A patient struggling to breathe is an indication to see for treatment of acidosis, careful use of sedation and analgesia, or early intubation. P-SILI not studied on NIV/HFNC is an actual thing happening in front of our eyes in day-to-day clinical practice in hypoxemic respiratory failure. Scoring systems and further studies will identify this process early and give us clear path for future treatment paradigm.

REFERENCES

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet. 1967;2(7511):319-23.

2. Greenfield LJ, Ebert PA, Benson DW. Effect of positive pressure ventilation on surface tension properties of lung extracts. Anesthesiology. 1964;25(3):312-6.
3. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med. 2010;363(12):1107-16.
4. Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. Am J Respir Crit Care Med. 2017;195(4):438-42.
5. Hubmayr RD, Kallet RH. Understanding pulmonary stress-strain relationships in severe ARDS and its implications for designing a safer approach to setting the ventilator. Respiratory Care. 2018;63(2):219-26. 10.4187/respcare.05900.
6. Marchioni A, Tonelli R, Rossi G, Spagnolo P, Luppi F, Cerri S, et al. Ventilatory support and mechanical properties of the fibrotic lung acting as a "squishy ball". Ann Intensive Care. 2020;10(1):13.
7. Bellani G, Grasselli G, Teggia-Droghi M, Mauri T, Coppadoro A, Brochard L, et al. Do spontaneous and mechanical breathing have similar effects on average transpulmonary and alveolar pressure? A clinical crossover study. Crit Care. 2016;20(1):142.
8. Yoshida T, Amato MBP, Grieco DL, Chen L, Lima CAS, Roldan R, et al. Esophageal manometry and regional transpulmonary pressure in lung injury. Am J Respir Crit Care Med. 2018;197(8):1018-26.
9. Coppadoro A, Graci A, Giovannoni C, Rabboni F, Eronia N, Bronco A, et al. Occurrence of pendelluft under pressure support ventilation in patients who failed a spontaneous breathing trial: an observational study. Ann Intensive Care. 2020;10(1):39.
10. Kantor DB, Hirshberg EL, McDonald MC, Griffin J, Buccigrosso T, Stenquist N, et al. Fluid balance is associated with clinical outcomes and extravascular lung water in children with acute asthma exacerbation. Am J Respir Crit Care Med. 2018;197(9):1128-35.
11. de Haro C, Ochagavia A, López-Aguilar J, Fernandez-Gonzalo S, Navarra-Ventura G, Magrans R, et al. Patient-ventilator asynchronies during mechanical ventilation: current knowledge and research priorities. Intensive Care Med Exp. 2019;7(Suppl 1):43.
12. Antonelli M, Conti G, Esquinas A, Montini L, Maggiore SM, Bello G, et al. A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. Critical Care Med. 2007;35(1):18-25.
13. Madotto F, Rezoagli E, Pham T, Schmidt M, McNicholas B, Protti A, et al. Hyperoxemia and excess oxygen use in early acute respiratory distress syndrome: insights from the LUNG SAFE study. Crit Care. 2020;24(1):125.
14. Antonelli M, Conti G, Moro M, Esquinas A, Gonzalez-Diaz G, Confalonieri M, et al. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. Intensive Care Med. 2001;27(11):1718-28.
15. Frat JP, Ragot S, Coudroy R, Constantin JM, Girault C, Prat G, et al. Predictors of intubation in patients with acute hypoxemic respiratory failure treated with a noninvasive oxygenation strategy. 2, 2018, Critical Care Med. 2018;46(2):208-15.
16. Yoshida Y, Takeda S, Akada S, Hongo T, Tanaka K, Sakamoto A. Factors predicting successful noninvasive ventilation in acute lung injury. J Anesth. 2008;22(3):201-6.
17. Duan J, Han X, Bai L, Zhou L, Huang S. Assessment of heart rate, acidosis, consciousness, oxygenation, and respiratory rate to predict noninvasive ventilation failure in hypoxemic patients. Intensive Care Med. 2016;43:192-9.
18. Papazian L, Corley A, Hess D, Fraser JF, Frat JP, Guitton C, et al. Use of high-flow nasal cannula oxygenation in ICU adults: a narrative review. Intensive Care Med. 2016;42(9):1336-49.
19. Frat JP, Ragot S, Girault C, Perbet S, Prat G, Boulain T, et al. Effect of non-invasive oxygenation strategies in immuno-compromised patients with severe acute respiratory failure: a post-hoc analysis of a randomised trial. Lancet Respir Med. 2016;4(8):646-52.
20. Roca O, Caralt B, Messika J, Samper M, Sztrymf B, Hernández G, et al. An index combining respiratory rate and oxygenation to predict outcome of nasal high-flow therapy. Am J Respir Crit Care Med. 2019;199(11):1368-76.
21. Laghi F, Shaikh HS, Morales D, Sinderby C, Jubran A, Tobin MJ. Diaphragmatic neuromechanical coupling and mechanisms of hypercapnia during inspiratory loading. Respir Physiol Neurobiol. 2014;198:32-41.
22. National Heart, Lung, and Blood Institute PETAL Clinical Trials Network; Moss M, Huang DT, Brower RG, Ferguson ND, Ginde AA, et al. Early neuromuscular blockade in the acute respiratory distress syndrome. N Engl J Med. 2019;381:785-8.

CHAPTER 20

Peri-intubation Complications and Management

Vandana Sinha, Brajendra Lahkar

INTRODUCTION

Tracheal intubation is a high-risk procedure commonly performed in critically ill patients in intensive care unit (ICU) and emergency departments. Peri-intubation period is defined by different authors as 60 minutes after the initiation of airway management[1] or 30 minutes prior to/after intubation,[2] or it is taken as within 30 minutes from the beginning of intubation procedures.[3] Risk of complications during this period is much higher in critically ill patients as compared to those intubated in operating room.[3] Major adverse events in peri-intubation period, such as cardiovascular instability, cardiac arrest, and severe hypoxia, are much more common than actually anticipated and these events are observed to the tune of 42, 3.1, and 9.3%, respectively.[4] The 28-day mortality of patients with these major adverse events (37.7%) are higher than those without events (24.6%) with an absolute difference of 13.1% [95% confidence interval (CI), 9.5–16.3%, P <0.001].[4]

Being prepared for possible complications during peri-intubation period is of prime importance in critically ill patients. Adhering to an "intubation care bundle" where simple component such as preoxygenation or having two operators during intubation or confirmation of endotracheal placement by capnography etc. has resulted in significant reduction of life-threatening complications (21 vs. 34%).[5] In this chapter, we are going to discuss some of the important peri-intubation complications and their management.

RISK FACTORS[6]

- Poor airway assessment
- Poor planning for airway management and for failure of intubation
- Multiple intubation attempts
- Inappropriate use of a supraglottic airway (SGA) device
- Obesity
- Failure to correctly interpret capnography and recognize esophageal intubation
- Anesthesia for head and neck surgery
- Intubation in the emergency department or ICU.

COMPLICATIONS AND MANAGEMENTS

Hemodynamic Instability

Cardiovascular instability in the form of hypotension occurs in about 42.6% of ICU cases during peri-intubation period.[4] Cardiac arrest is encountered in 3.1% of cases and half of them do not survive (47.3%). Atrial fibrillation, bradycardia, and ventricular tachycardia comprise of almost three-fourth cases of arrhythmias encountered during peri-intubation period.

The very act of intubation causes a change in breathing dynamics that is deleterious to the patient's hemodynamic status. Switching from negative pressure to positive pressure ventilation (PPV) causes an instant decrease in the venous return by increasing right atrial pressures. Decreased venous return leads to decreased preload which is integral to maintaining hemodynamic stability in critically ill patients. Physiologic stress, whether for sepsis, fluid overload, respiratory failure, or a variety of other indications, increases the work of breathing making it hard for patients to breathe prior to intubation attempt. Due to catecholamine surge during stress, vascular tone, stroke volume, heart rate, and ultimately cardiac output (CO) are augmented. When any induction agent is given, the sympathetic state is reversed resulting in decrease in catecholamine hence decreasing blood pressure. When combined with reduced venous return following PPV, these patients are set up for hypotension and possibly worst outcome. Hence selection of induction agent is important. While there is no perfect induction agent, some certainly have few distinct advantages.

Steps to prevent hypotension:

- *Peri-intubation intravenous (IV) fluids*: Jaber et al.[5] included 500 mL of crystalloid bolus in pre-intubation period, after excluding cardiogenic pulmonary edema, in their study of intubation care bundle and reported positive outcome. The PREPARE study on the other hand did not show any difference in outcome between those who received fluid bolus and the group who did not.[7]
- *Pressor support*: Shock Index (heart rate/systolic blood pressure) should be calculated, if >1, there is high risk of life-threatening hypotension which should be treated

by appropriate fluid resuscitation along with use of vasopressors/inotropes. Epinephrine as it possesses both α and β agonist [increases systemic vascular resistance (SVR) and CO] is the pressor of choice to give bolus dose.[8]

Dose of epinephrine: 0.5–2 mL every 2–5 minutes (5–20 μg). This is equivalent to dose of epinephrine given via infusion (5–20 μg/min).

- *Induction agent*: The dose of induction agent may be more important than choice of agent.
  - Avoid propofol and benzodiazepines for their potential hypotensive effect.
  - Ketamine is an attractive option for hemodynamically tenuous patients as least cardiodepressant. Ketamine has a negative inotropy but this is offset by an increase in heart rate, arterial pressure, and CO in patients with intact autonomic nervous system (ANS). It can achieve induction in subsympatholytic dose, 0.5 mg/kg, too.
  - Fentanyl and midazolam in low doses for induction is an alternative but onset is very slow in patients with shock.
  - Etomidate is the most hemodynamically neutral agent used for rapid sequence induction (RSI) and this makes it a useful medication for hypotensive patients. The concern is with the possible transient adrenocortical suppression with its use and increase in the risk of multiorgan system dysfunction by a small amount but evidence suggests that this is not harmful in most clinical settings.[9]

Hypoxia

Severe hypoxia (SPO_2 <80%) is the second most common (9.3%) major complication encountered during peri-intubation period.[4] Use of sedative and neuromuscular blocking agents just before intubation renders patient apnoeic and clinician has to promptly ventilate him by bag mask ventilation (BMV) and intubating with an endotracheal tube (ETT) as early as possible. If it is delayed, hypoxia will set in leading to hypotension, arrhythmia, brain damage, cardiac arrest, and death.

Classic oxyhemoglobin dissociation curve **(Fig. 1)** is a plot of different SpO_2 values at varying PaO_2 levels. It demonstrates the saturation of hemoglobin at different levels of partial pressure of oxygen. It also depicts the rate of fall of oxygen saturation at different points in the curve. At PaO_2 of 90 mm Hg (point 3), the curve is flat and SpO_2 approaching 100%. Once PaO_2 drops below 60 mm Hg (where SpO_2 is still maintained at around 90%), small drops in PaO_2 is associated with large drops in SpO_2. This is the steep part of the curve. This physiologic curve manifests itself in clinical practice. If patient has a SpO_2 of 100% at time of intubation, they will desaturate slowly until reaching an SpO_2 around 93%, at which point they will desaturate progressively faster. In other words, they "fall off the curve." Preventing desaturation will prevent peri-intubation hypoxia hence keeping SpO_2 around 100% for long enough to fill up the physiologic "Buffer" and cause denitrogenation make sense. Breathing 100% O_2 will completely remove the nitrogen in lungs with oxygen. Denitrogenation is the principle behind the role of preoxygenation. A commonly used and readily available technique for apneic oxygenation involves the use of standard nasal cannulae. The patient is typically preoxygenated using nasal cannulae simultaneously with face mask oxygen, with nasal oxygen continued during intubation after the face-mask is removed. In critically ill patients, the functional residual capacity (FRC) is reduced in proportion to the severity of the airspace diseases and associated shunt reduces the availability to resaturate the hemoglobin.[10] Noninvasive ventilation for preoxygenation in hypoxic respiratory failure is safer, reduces the rate of desaturation by 15%, and better than high flow nasal insufflation in patient with PaO_2/FiO_2 ratio <200.[10]

Steps to optimize peri-intubation saturation are as follows:

- Use of second provider to make a good mask seal
- *Position*: Optimal positioning **(Fig. 2)** improves upper airway patency and access, and may reduce aspiration risk. Ear is aligned at the same plan with sternal notch, neck is extended and face parallel with the ceiling.

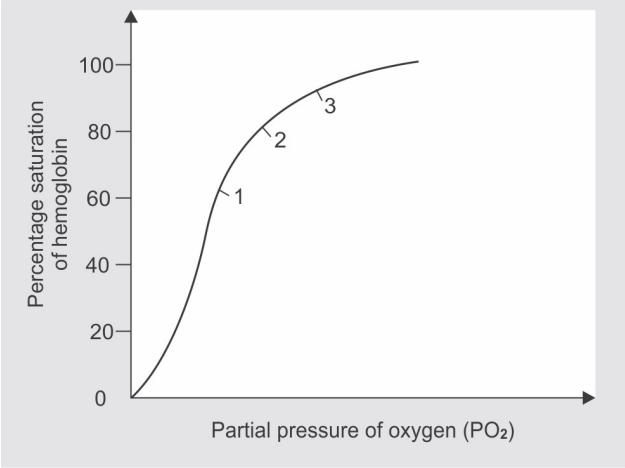


Fig. 1: Oxyhemoglobin dissociation curve showing different points of desaturation rate.

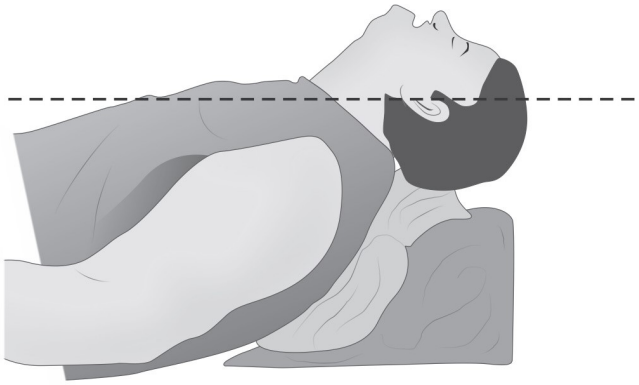
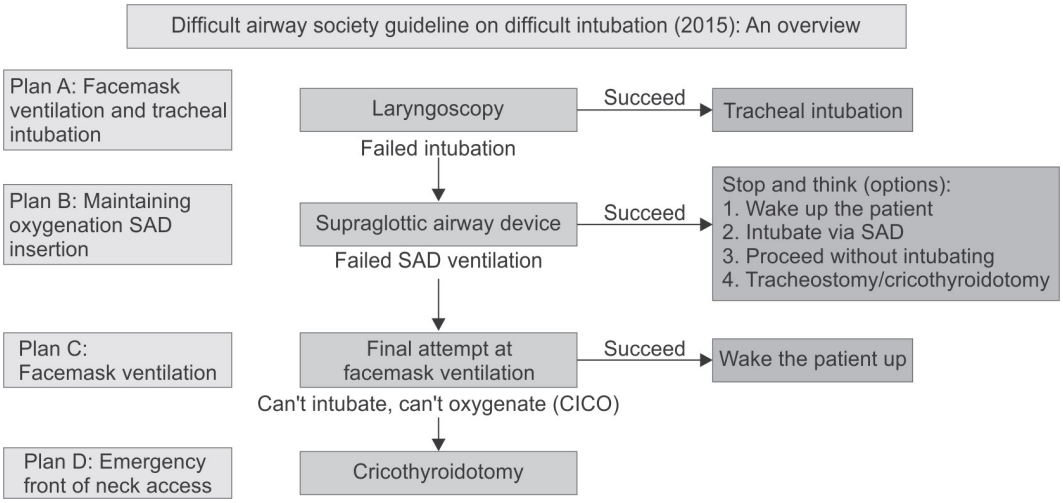


Fig. 2: Optimal position for intubation.

Flowchart 1: Difficult Airway Society (DAS) guideline overview.



(SAD: supraglottic airway device)

Source: Adopted from Difficult Airway Society guideline 2015.[11]

- *Waveform capnography*: Before, during, and after intubation not only to confirm tube placement but also to measure the tidal volume, indirectly.
- Clearing airway of secretions/vomitus
- *Apnoeic oxygenation*: Oxygen delivery through standard nasal cannula or humidified high flow nasal oxygenation (HFNO) system has shown to decrease desaturation during intubation. HFNO causes dead space wash out, maintains positive end expiratory pressure (PEEP), and a constant FiO_2 and thereby decrease the risk of desaturation during intubation.

Planning for unanticipated difficult airway is mandatory. Recommendations given in Difficult Airway Society guidelines on difficult intubation (2015) as described in **Flowchart 1**, should be kept in mind.

Pulmonary Hypertension Decompensation

Deteriorating acidosis can cause seizure, coma, cardiac arrhythmia, and arrest. If underlying cause is respiratory acidosis, rapid improvement can be achieved by increasing alveolar ventilation. This leads to decreasing $PaCO_2$ and correcting respiratory acidosis. If metabolic acidosis is the cause of acidosis, compensatory respiratory alkalosis from alveolar hyperventilation becomes critical for preservation of acid–base homeostasis.

Traumatic Complications

- *Pressure-induced injuries*: As ETT occupies posterior aspect of larynx, it exerts pressure on the surrounding tissues such as medial surfaces of arytenoids, vocal processes, cricoarytenoid joints, cricoid cartilage, posterior glottis, and interarytenoid region. When the pressure from ETT exceeds capillary pressure, microcirculation of mucosa and mucoperiosteum of these structures are interrupted, leading to ischemia and necrosis.
- Supraglottic region may become edematous but rarely sustain serious damage. Tracheal injuries have significantly reduced due to usage of low-pressure cuffs.[12] The injuries sustained results in hoarseness of voice due to:
  - Vocal cord edema
  - Lacerations
  - Epiglottic hematoma.
- Vocal cord paralysis is secondary to compression of anterior branch of recurrent laryngeal nerve between the ETT cuff and thyroid cartilage in subglottic larynx (0.03% incidence).[12] Unilateral paralysis, where left vocal cord is more commonly involved,[12] is present immediately after extubation and present with hoarseness of voice and dysphonia.
- Traumatic dental injury involves mostly upper incisors but multiple teeth may be injured too. Difficult intubation is the major risk factor for dental injury.

Aspiration

Pulmonary aspirations of gastric contents in patients with compromised laryngeal protective reflexes can lead to complications such as hypoxia, respiratory failure, acute respiratory distress syndrome (ARDS), and even cardio respiratory arrest and death. The types of pulmonary syndromes include acid-associated pneumonitis, particle-associated aspirations, or bacterial infections. Most common injury is aspiration pneumonitis. Predisposing conditions consistent with upper gastrointestinal tract stasis, effect of medications on lower esophageal sphincter, level of consciousness, loss of protective reflexes, and providers expertise, all contribute to the risk. RSI is one approach that was developed to quickly achieve a protected airway in emergency or high-risk cases while minimizing the risk of regurgitation of gastric contents. Though initial systemic reviews concluded that cricoid pressure is a benign practice

and should be used in RSI, it should be released if pressure is creating difficulties in securing the airway.[13] It should be noted that recent meta-analysis has failed to support that cricoid pressure increases protection from aspiration and it may actually increase difficulty of intubation.[14]

GENERAL MANAGEMENT

The following measures taken during the intubation can alleviate the risks and complications and also prevent pressure induced injuries:

- *Measures taken before intubation*: Routine assessment for potentially difficult intubation cases
  - Proper size tube
  - Proper technique
  - Experience of the performer
- *Measures during intubation*:
  - *Direct vision*: Using intubation assisting devices (Bougie, video laryngoscope, and flexible bronchoscopy)
  - Appropriate cuff pressure <20 cmH_2O
    - Fixation of ETT with tapes/devices
- Measures after intubation:
  - Suctioning of oral and ETT secretions
  - Assessment of skin integrity around lips and checking adhesive tapes frequently.

CONCLUSION

Risk of complications during peri-intubation period is real and complications can lead to serious consequences. As more than two failed attempts at endotracheal intubation increases the risk of complication and death, it should be done by experienced personnel. Good training and careful preparations are most essential for successful first attempt endotracheal intubation and prevention of complications.

REFERENCES

1. Heffner AC, Swords DS, Neale MN, Jones AE. Risks for peri-intubation cardiac arrest. Resuscitation. 2013;84(11):1500-4.
2. Panchal AR, Satyanarayan A, Bahadir JD, Hays D, Mosier J. Efficacy of bolus-dose phenylephrine for peri-intubation hypotension. J Emerg Med. 2015;49(4):488-94.
3. Russotto V, Myatra SN, Laffey JG. What's new in airway management of the critically ill. Intensive Care Med. 2019;45(11):1615-8.
4. Russotto V, Myatra SN. Intubation practices and adverse peri-intubation events in critically ill patients from 29 countries. JAMA. 2021;325(12):1164-72.
5. Jaber S, Jung B, Corne P, Sebbane M, Muller L, Chanques G, et al. An intervention to decrease complications related to endotracheal intubation in the intensive care unit: A prospective, multiple-center study. Intensive Care Med. 2010;36(2):248-55.
6. Cook TM, Woodall N, Harper J, Benger J. Fourth National Audit Project. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society, II: intensive care and emergency departments. Br J Anaesth. 2011;106(5):632-42.
7. Janz DR, Casey JD, Semler MW, Russell DW, Dargin J, Vonderhaar, DJ, et al. Pragmatic Critical Care Research G. Effect of a fluid bolus on cardiovascular collapse among critically ill adults undergoing tracheal intubation (PrePARE): a randomised controlled trial. Lancet Respir Med. 2019;7(12):1039-47.
8. Weingart S. EMCrit Podcast 205. Push-Dose Pressors Update 2009 [online] Available from: https://emcrit.org/emcrit/bolus-dose-pressors/.[Last accessed February 2022].
9. Bruder EA, Ball IM, Ridi S, Pickett W, Hohl C SO. Single induction dose of etomidate versus other induction agents for endotracheal intubation in critically ill patients. Cochrane Database Syst Rev. 2015;8(1):CD010225.
10. Mosier JM, Sakles JC, Law JA, Brown III CA, Brindley PG. "Tracheal Intubation in the Critically Ill. Where We Came from and Where We Should Go", Am J Respir Crit Care Med. 2020;201(7):775-88.
11. Frerk C, Mitchell VS, McNarry AF, Mendonca C, Bhagrath R, Patel A, et al. Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults. Br J Anaesth. 2015;115(6):827-48.
12. Touman AA, Stratakos GK. Long-term complications of tracheal intubation. In: Erbay RH, editor. Tracheal Intubation. 2018. DOI:10.5772/intechopen.74160.
13. Nason KS. Acute intraoperative pulmonary aspiration. Thorac Surg Clin. 2015;25(3):301-30.
14. White L, Thang C, Hodsdon A, Melhuish T, Vlok R. Cricoid pressure during intubation: A systematic review and meta-analysis of randomised controlled trial. Heart Lung. 2020;49(2):P175-80.

CHAPTER 21

Impact of Obesity on Difficult Weaning

Anand Tiwari, Kapil Zirpe

INTRODUCTION

Obesity and overweight are defined by world health organization (WHO) as conditions in which excess fat accumulation may impair health. The body mass index (BMI) calculated as (weight/height in m^2) is the basis for WHO classification of obesity **(Table 1)**.

Obesity prevalence has increased globally over the last 50 years, reaching pandemic proportions.[1] Obesity raises the risk of developing various disease such as type 2 diabetes, fatty liver disease, hypertension, myocardial infarction stroke, dementia, osteoarthritis, and obstructive sleep apnea, as a result percentage of obese patients admitted to the intensive care unit are likely to rise.[2] Obesity not only increases the risk of more severe disease requiring intensive care admission but also need for mechanical ventilation as evident from studies in patients with trauma,[3] traumatic brain injury,[4] H1N1 pneumonia,[5] and recently ongoing pandemic affecting patient with COVID-19.[6] Obesity is a significant risk factor for major complications, morbidity and mortality associated with intubation and mechanical ventilation. There are specific problems faced while ventilating these subgroups of patients. Difficult weaning and increase length of stay is evident in patients with obesity requiring mechanical ventilation.[7]

This chapter/update attempts to summarize the effects of obesity on the lung mechanics and its impact on weaning. The author also advocates the practice point while ventilating an obese patient at the end of the chapter **(Fig. 1)**.

TABLE 1: World Health Organization (WHO) classification of obesity.

Type	*BMI (kg/m^2)*
Underweight	<18.5
Normal weight	18.8–24.9
Overweight	25–29.9
Obesity class 1 (moderate)	30–34.9
Obesity class 2 (severe)	35–39.9
Obesity class 3 (very severe)	>40

(BMI: body mass index)

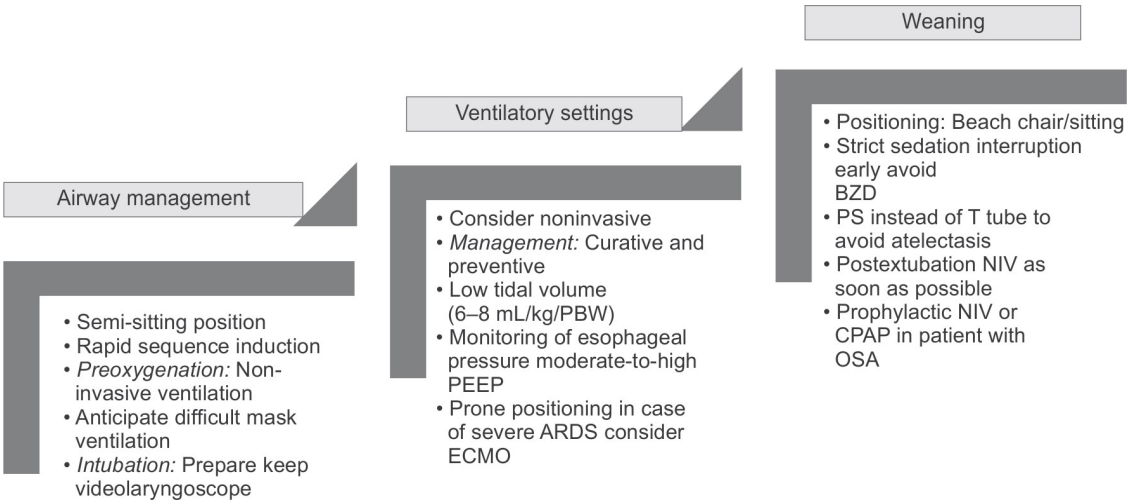


Fig. 1: Practice points for mechanical ventilation in obese patient.
(ARDS: acute respiratory distress syndrome; CPAP: continuous positive airway pressure; ECMO: extracorporeal membrane oxygenation; NIV: noninvasive ventilation; OSA: obstructive sleep apnea; PBW: predicted body weight; PEEP: positive end-expiratory pressure)

RESPIRATORY PHYSIOLOGICAL CHANGES IN OBESITY

Respiratory mechanics are affected in obesity. Central obesity poses greater challenge on the respiratory mechanics compared to gynoid obesity. As depicted in **Figure 2** central obesity results in cephalic displacement of diaphragm resulting in decrease in expiratory reserve volume and functional residual capacity (FRC). The increased amount of fat tissue into posterior chest wall and abdomen (changes that occur in central obesity) leads to increased abdominal pressure and work of breathing. Probability of hypoxemia is increased due to atelectasis and small airway closure and decreased ventilation to perfusion ratio at lung bases.[8]

MEASURABLE PRESSURES AND PRESSURE DIFFERENCES IN RESPIRATORY MECHANICS

Obesity leads to increase in transthoracic pressure which is often higher than in patient without obesity. Elevated thoracic pressure causes rise in plateau pressure and not the increase in transpulmonary pressure with lung overdistension.

As shown in **Figure 3**, when transpulmonary pressure (alveolar minus esophageal, surrogate for pleural pressure measured by esophageal manometry) equals zero, normal FRC is maintained. Negative transpulmonary pressure leads to atelectasis and decrease in lung compliance. This phenomenon is observed in obesity where pleural pressure becomes positive resulting in negative transpulmonary pressure. Atelectasis develops in tandem with negative transpulmonary pressure and is reversed when it becomes zero or positive. This highlights the importance of positive end-expiratory pressure (PEEP) which by increasing alveolar pressure results in positive transpulmonary pressure and avoids alveolar derecruitment.[9]

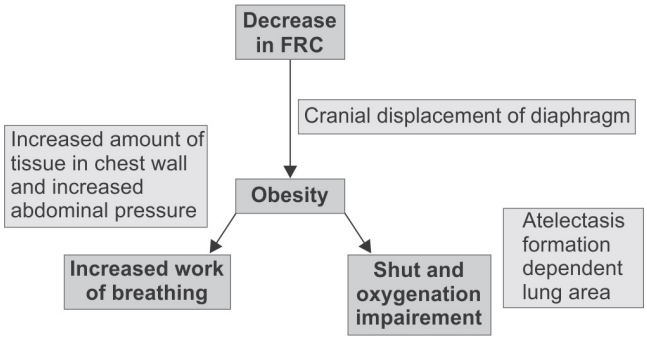


Fig. 2: Effects of obesity on respiratory physiology.
(FRC: functional residual capacity)

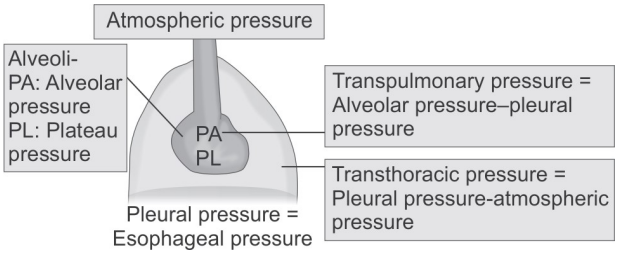


Fig. 3: Measurable pressures and pressure differences in respiratory.

WEANING AND EXTUBATION IN OBESE PATIENTS

Obesity constitutes one of the most difficult patients' populations to wean from ventilatory support.

Best Modality to Wean

Numerous randomized controlled trials (RCTs) have been conducted to discover the optimal method for weaning from ventilatory support. The investigations by Brochard et al.[10] and Esteban et al.[11] are widely considered as the two landmark studies that established spontaneous breathing trials (SBTs) as the ideal strategy to weaning.

As previously stated, people with obesity have a much higher work of breathing (WOB) due to their negative transpulmonary pressure. According to Mahul et al.[12] findings, whether pressure support, PEEP, or both are used during weaning evaluation, the work of breathing (WOB) improves. We do not disagree with Mahul et al.,[12] but we would interpret their data differently. In obese patients with risk of atelectasis, authors suggest pressure support with sufficient PEEP as mode of weaning and avoidance of T tube trials.[12]

Sedation Practices

Kress et al.[13] and Girard et al.[14] pioneered the concept of a spontaneous awaking trial accompanying an SBT. Patients were randomly assigned to one of two groups: those who received continued sedation and those who did not receive any sedation prior to the SBT. Patients in the spontaneous awaking group required less time to wean from ventilatory support and spent less time in the intensive care unit.

In line with the above evidence, we suggest stopping sedation in obese patient as early as possible and benzodiazepines should be restricted even more compared to lean patient to avoid prolonged release of these sedative drugs which redistributes from excess fat in obese patient.

Use of Prophylactic and Curative Noninvasive Ventilation

Use of prophylactic noninvasive ventilation (NIV) post-extubation and even as a curative therapy for acute respiratory failure in obese patient is advocated as evident from various studies[14-18] summarized in **Table 2**.

Positioning

Obese patients might suffer substantial physiologic impairment and physical harm if they are improperly

TABLE 2: Summary of published studies on assessing NIV ventilation (prophylactic/curative) in patients with obesity.

Study (First author)	*Design*	*Patient population*	*Comparisons*	*Outcome*
El solh AA[15]	• Prospective • Prophylactic NIV	Prophylactic NIV in extubation of patient with BMI > 35	(n)-124 patients 62 with prophylactic NIV postextubation 62 with conventional oxygen therapy (control)	16% absolute risk reduction in respiratory failure in first 48 hours postextubation
Duarte AG[16]	• Retrospective • Curative NIV	Patient with morbid obesity and acute respiratory failure	(n)-50 patients 33 treated with NIV 17 with invasive mechanical ventilation (IMV)	• Avoided intubation in 21 patients • Hospital mortality was higher in IMV and failed NIV group
Lemyze M[17]	• Prospective observational • Curative NIV	• Patient with BMI > 40 • Diagnosed with OHS (obesity hypoventilation syndrome) and acute respiratory failure	(n)-76 patient on NIV	Failure of NIV in 13 patient had poor outcome despite escalation to endotracheal intubation and ventilation
Neligan PJ[18]	• RCT (randomized controlled trial) • Prophylactic NIV	Patient with morbid obesity and OSA for laparoscopic bariatric surgery	(n)-40 patients 20 in CPAP after extubation 20 in supplemental oxygen group	Less reduction in FVC and PEFR in CPAP group
Stéphan F[19]	• Post hoc analysis of RCT • Prophylactic and curative NIV	Patient with obesity extubation after cardiothoracic surgery	(n)-231 patients 136 in NIV group 135 in HFNC group	Treatment failure did not significantly differ between groups

(CPAP: continuous positive airway pressure; FVC: forced expiratory volume; HFNC: high-flow nasal cannula; IMV: invasive mechanical ventilation; NIV: noninvasive ventilation; OSA: obstructive sleep apnea; PEFR: peak expiratory flow rate)

positioned. The supine position is hazardous for obese people because the intra-abdominal pressure is abnormally raised in this position when compared to nonobese patients. This results in a decrease in lung volume and, as a result, hypoxemia. The term "obese supine death syndrome" was developed by Tsueda et al.[20] Some morbidly obese patients with limited cardiac reserve may not tolerate the supine posture and are at danger of cardiac arrest, thus the intensivist must be aware of proper positioning of obese patient to avert complications. Optimum body position suggested for weaning is reverse Trendelenburg or beach chair/sitting position which improves respiratory compliance and gas exchange.

Obesity Paradox

Obesity appears to have a protective effect in critically ill individuals and is associated with a lower mortality. This phenomenon is generally known as "obesity paradox."[21] Several theories have evolved to explain why obese patients may have a higher chance of survival:[22] (1) adipose tissue may serve as a nutritional reserve, slowing catabolism in severe illness; (2) adipocyte-secreted hormones (leptin and interleukin-10) may have immunomodulatory effects; (3) during sepsis, high cholesterol and lipid levels may be beneficial by binding endotoxins; and (4) outcome-improving effects of special drugs, such as statins or angiotensin-converting enzyme inhibitors, which are frequently prescribed for obese individuals.

CONCLUSION

Obesity has a negative impact on the respiratory system and ventilatory control due to altered physiology and respiratory mechanics. Weaning from mechanical ventilation and extubation in obese patients poses additional challenges for clinicians. Obese ventilated patient should never be nursed in supine position and optimal PEEP should be used to prevent lung collapse. Sedation with benzodiazepines should be avoided due to accumulation in fat stores with redistribution and slow release thus causing negative impact on weaning and newer short-acting agent like dexmedetomidine may be chosen. Sedation to stop as early as possible when compared to lean patient. In light of current evidence, positioning the obese patient in reverse Trendelenburg's position and application of NIV immediately after extubation probably facilitates weaning from invasive mechanical ventilation. Noninvasive ventilation appears as ideal choice to be considered both for prophylactic and curative purpose for treating acute respiratory failure in obese patient.

REFERENCES

1. Blüher M. Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol. 2019;15(5):288-98.

2. Abdelaal M, le Roux CW, Docherty NG. Morbidity and mortality associated with obesity. Ann Trans Med. 2017;5(7):161.
3. Bell T, Stokes S, Jenkins PC, Hatcher L, Fecher AM. Prevalence of cardiovascular and respiratory complications following trauma in patients with obesity. Heart Lung. 2017;46(5): 347-50.
4. Cone JT, Benjamin ER, Alfson DB, Demetriades D. Isolated severe blunt traumatic brain injury: effect of obesity on outcomes. J Neurosurg. 2020;134(5):1667-74.
5. Fezeu L, Julia C, Henegar A, Bitu J, Hu FB, Grobbee DE, et al. Obesity is associated with higher risk of intensive care unit admission and death in influenza A (H1N1) patients: a systematic review and meta-analysis. Obes Rev. 2011;12(8):653-9.
6. Lemyze M, Courageux N, Maladobry T, Arumadura C, Pauquet P, Orfi A, et al. Implications of obesity for the management of severe coronavirus disease 2019 pneumonia. Crit Care Med. 2020;48(9):e761-e767.
7. Chauhan N. Complications Associated with Invasive Mechanical Ventilation in Obese Patients. In: Esquinas AM, Lemyze M (Eds). Mechanical Ventilation in the Critically Ill Obese Patient. Switzerland AG: Springer Cham; 2018. pp. 151-6.
8. Dixon AE, Peters U. The effect of obesity on lung function. Expert Rev Respir Med. 2018;12(9):755-67.
9. Fumagalli J, Berra L, Zhang C, Pirrone M, Santiago RR, Gomes S, et al. Transpulmonary pressure describes lung morphology during decremental positive end-expiratory pressure trials in obesity. Crit Care Med. 2017;45(8):1374-81.
10. Brochard L, Rauss A, Benito S, Conti G, Mancebo J, Rekik N, et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. Am J Respir Crit Care Med. 1994;150(4):896-903.
11. Esteban A, Frutos F, Tobin MJ, Alía I, Solsona JF, Valverdu V, et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. N Engl J Med. 1995;332(6):345-50.
12. Mahul M, Jung B, Galia F, Molinari N, de Jong A, Coisel Y, et al. Spontaneous breathing trial and post-extubation work of breathing in morbidly obese critically ill patients. Crit Care. 2016;20(1):1-2.
13. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med. 2000;342(20):1471-7.
14. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet. 2008;371(9607):126-34.
15. El Solh AA, Aquilina A, Pineda L, Dhanvantri V, Grant B, Bouquin P. Noninvasive ventilation for prevention of post-extubation respiratory failure in obese patients. Eur Respir J. 2006;28(3):588-95.
16. Duarte AG, Justino E, Bigler T, Grady J. Outcomes of morbidly obese patients requiring mechanical ventilation for acute respiratory failure. Crit Care Med. 2007;35(3):732-7.
17. Lemyze M, Taufour P, Duhamel A, Temime J, Nigeon O, Vangrunderbeeck N, et al. Determinants of noninvasive ventilation success or failure in morbidly obese patients in acute respiratory failure. PloS One. 2014;9(5):e97563.
18. Neligan PJ, Malhotra G, Fraser M, Williams N, Greenblatt EP, Cereda M, et al. Continuous positive airway pressure via the Boussignac system immediately after extubation improves lung function in morbidly obese patients with obstructive sleep apnea undergoing laparoscopic bariatric surgery. J Am Soc Anesthesiol. 2009;110(4):878-84.
19. Stéphan F, Bérard L, Rézaiguia-Delclaux S, Amaru P. High-flow nasal cannula therapy versus intermittent noninvasive ventilation in obese subjects after cardiothoracic surgery. Respir Care. 2017;62(9):1193-202.
20. Tsueda K, Debrand M, Zeok SS, Wright BD, Griffin WO. Obesity supine death syndrome: reports of two morbidly obese patients. Anesth Analg. 1979;58(4):345-7.
21. Hutagalung R, Marques J, Kobylka K, Zeidan M, Kabisch B, Brunkhorst F, et al. The obesity paradox in surgical intensive care unit patients. Intensive Care Med. 2011;37(11): 1793-9.
22. Rice TW. Obesity in acute lung injury: the "weight" is over. Chest. 2007;131(2):333-4.

CHAPTER 22

Selecting Appropriate Humidification (Active and Passive)

Sharmili Sinha, Ranajit Chatterjee, Bhuvna Ahuja

INTRODUCTION

Humidification is the process of increasing the moisture content of air. In clinical practice, it has considerable significance especially in the critical care setting. Whenever a patient is artificially ventilated, a lot of dry air or oxygen is introduced in the environment of upper and lower airway. Exposure to dry gas damages the respiratory epithelium causing cytoplasmic, nuclear, and ciliary damage. This leads to decreased mucus clearance manifested by increased work of breathing, atelectasis, thick and dehydrated secretions, and cough and/or bronchospasm. The consequence is far reaching, leading to increased chances of ventilator-associated pneumonia (VAP), delayed weaning, and increase mortality. Thus, it is imperative to humidify gases whenever delivered to a patient mechanically. The chapter will deal with the various aspects of humidification in clinical practice.

PHYSIOLOGICAL ASPECTS OF HUMIDIFICATION

Humidity, the amount of water vapor present in the air, is measured by absolute humidity (AH) and relative humidity (RH). Whereas AH is the weight of water present in a given volume of gas and it is usually expressed in mg/L, RH is expressed in percentage as it is the ratio of the actual weight of water vapor AH relative to the gas capacity to keep water at a specific temperature. Thus, AH is temperature independent, whereas RH is inversely related to temperature. So, with decrease in temperature RH increases and water condensate into liquid droplets. This effect is observed when water accumulates in tubing and increases resistance of the circuit and consequently the work of breathing of the patient. The AH and the RH requirement varies in different part of airways. The requirement increases as we move from upper to the lower airways. In nose and mouth, it is 50% RH with AH of 10 mg/L at 22°C, in hypopharynx, it is 95% RH with AH of 28 to 34 mg/L at 29–32°C and when it reaches the mid-trachea, the requirement increases to 100% RH with AH of 36–40 mg/L at 31–35°C.[1] A point 5 cm below the carina is known as the isothermic saturation boundary (ISB), where the RH is 100% and temperature of the airway is 37°C. This point shifts much below the carina after endotracheal intubation (ET). Thus, the lower respiratory tract, which is already weak in maintaining humidification and secretion clearance compared to upper respiratory counterpart, becomes overburdened. This situation is further exacerbated if cold and dry air is delivered through the endotracheal (ET) tube to the lower airways. The airway of patients on noninvasive ventilation (NIV) suffers the same fate though to a lesser extent. This makes humidification essential during mechanical ventilation.

CLASSIFICATION

Humidifiers are broadly classified into two types **(Table 1)**:

1. *Active*: Use external resources to achieve humidification. It can be further subdivided into:
   a. Bubble
   b. Passover
   c. Inline
   d. Counterflow vaporizers

   The details of all these types are outside the scope of this chapter.
2. *Passive*: Uses patients own resources (temperature and hydration) to achieve humidification. These are heat moist exchangers (HMEs).

   They are subdivided into:
   a. Hydrophobic
   b. Hydrophobic hygroscopic (HH)
   c. Pure hygroscopic

Certain hygroscopic salts such as calcium or lithium chloride, having a chemical affinity to attract water particles and thus increasing the humidification capacity of the HME, are added inside the hydrophobic HME.

TABLE 1: Different types of humidifier techniques.

Active humidifier	*Passive humidifier (heat and moisture exchangers)*
• Bubble humidifier • Passover humidifier • Inline vaporizers • Counterflow vaporizers	• Hydrophobic • Hydrophobic hygroscopic • Pure hygroscopic

INDICATIONS

- Patients on mechanical ventilation—either tracheostomized or with ET tube:
  - Patients on artificial airway on mechanical ventilation should receive continuous humidification of inspired gases.
  - When providing active humidification to patients who are invasively ventilated, it is suggested that the device provides a humidity level between 33 and 44 mg H_2O/L and gas temperature between 34 and 41°C at the circuit Y-piece, with an RH of 100%.[2]
  - When providing passive humidification to patients undergoing invasive mechanical ventilation, it is suggested that the HME provides a minimum of 30 mg H_2O/L.[2]
- *Patients on prolonged NIV:*
  - Passive humidification is not recommended for NIV.[2]
  - HME should be used when used for short periods <96 hours.
  - HME should be used during transport of patients.

A Cochrane database systemic review failed to show any mortality difference between the two procedures.[3] Even the apprehension of HH causing more VAP compared to HME has been questioned and found to be fallacious.[4] It is suggested that HMEs are not used as a prevention strategy for VAP.

CONTRAINDICATIONS

Humidification should not be performed or cautiously performed in these following situations:

- Frank bloody, thick, or copious secretions
- When patient[2] is on low tidal volume ventilation, e.g., lung protective ventilation or expired tidal volume is <70% of delivered tidal volume, e.g., tracheoesophageal fistula, uncuffed ET
- Patients of hypothermia with body temperature <32°C[5]
- Patients generating high minute volumes >10 L/min[6]
- To be switched off during nebulization
- Relatively cautious use in NIV, especially in presence of leaks where it increases dead space and $PaCO_2$.

COMPLICATIONS

The procedure, though looks apparently innocuous, is not without complications. It may cause hypothermia (HME or inadequately set HH) or even hyperthermia due to overheating by HH.

Hydrophobic hygroscopic may cause fogging of the helmet in NIV helmet. The increase in dead space leads to increased work of breathing and CO_2 retention. The overheated atmosphere inside the lung may cause thick dry mucus leading to increased resistive work. The situation aggravates in patients who are not properly hydrated. It also leads to increased risk of patient ventilator asynchrony. The heating element is a potential source of accidental burns amongst caregivers.

INFECTION CONTROL

Strict vigilance should be kept maintaining asepsis while using a heated humidifier device. Sterile water should be used, and asepsis should be maintained while filling the humidifier reservoir. The condensed water is source of infection and should be despised with outmost care and should not be drained back to the reservoir. The circuit if soiled should be changed. The HME can be used for 24 hours and in some cases up to 7 days if not soiled by patient's secretions.[7]

APPROPRIATE SELECTION OF HUMIDIFIER

Selection of an appropriate humidifier is crucial. It requires patient individualization of the type of humidifier used. There have been several studies which guides toward the use of humidification technique. According to American Association of Respiratory Care (AARC) clinical practice guidelines 2012, humidification performance plays an important role in selection of a humidifier.

Hydrophobic hygroscopics should provide an AH level between 33 and 44 mg H_2O/L, whereas HMEs should provide a minimum of 30 mg H_2O/L.[8]

Initial use of HMEs showed increased chances of ET occlusion. Hence studies were formulated to test HMEs performance in intensive care setting. Cohen et al. reported 15 cases of ETT occlusion when a hydrophobic heat moisture exchange filter (HMEF) was used, whereas only one case with bubble humidifiers was demonstrated. It was later found that with HMEs, most patients required minute ventilation higher than 10 L/min.[9]

A clinical trial reported comparison between HMES and HH. It was found in the study six patients in HMEs group developed ETT occlusion whereas none of the patients in HH group had ETT occlusion.[10]

Roustan et al. in their study also found higher incidence of ETT occlusions with HMEs as compared to HH.[11] In both the abovementioned studies, hydrophobic HMEs type was used. Therefore, based on the studies combined use of HH HMEs could be more appropriate, when passive humidification is applied to the patient.[12]

Another randomized controlled trial (RCT), compared HH HME, hydrophobic HME, HH, and with minute ventilations of 10.8, 11.6, and 10.2 L/min, respectively. After 72 hours, the mean diameter of the ETTs had decreased by 6.5 mm with the hydrophobic HME, 2.5 mm with hygroscopic hydrophobic HME, and 1.5 mm with an HH.[13]

As far as HME duration of use is concern, it was found that it should be changed every 24 hours to prevent ET occlusion. Djedaini et al. demonstrated that there was no increase in the resistance of hygroscopic hydrophobic HMEs if they were changed every 48 hours versus every 24 hours.[14] Hygroscopic hydrophobic HMEs in another study showed better results, compared to other types of HMEs. HMEs are not recommended for hypothermic (temperature <32°) patients since it requires absorption of heat for its functioning. This was showed by Lellouche et al. RCT.[15]

In most of the studies, it was found that incidence of ETT occlusion was higher with the use of HMEs compared to HH. Hence, HMEs should be avoided in patients having thick secretions.

HMEs have adverse effects on ventilator parameters.

Effect on Ventilator Mechanics

There is increase in dead space causing decrease alveolar ventilation, which further causes rise in $PaCO_2$. This may lead to inadvertent lung injury so as to keep adequate alveolar ventilation.

Addition of dead space in spontaneously breathing patients with the use of HMEs may cause increase in work of breathing.[16]

Incidence of Ventilation Associated Pneumonia with the Use of Humidifier

Cook et al. meta-analysis (1998) found lower VAP rates with HME than with use of HH humidifiers.[17] But a recent meta-analysis which included 13 RCTs did not find any significance difference in the incidence of VAP, with HMEs and HH humidifier.[18]

There was evident heterogeneity in the trials included in the meta-analysis. Such heterogeneity is also reflected on different guidelines. British Society for Antimicrobial Chemotherapy (2008), recommends the use of HMEs over HHs to reduce the incidence of VAP. The Centers for Disease Control and Prevention (CDC) recommendations did not favor HMEs over HHs, and the American Thoracic Society stated that HMEs cannot be regarded as a tool for prevention of VAP.[19] In 2009, various European societies in their joint statement recommended use of HMEs over HH. Later in the same year, VAP guidelines committee of Canadian critical care group found no difference in VAP incidence with use of any of humidifiers.[20] Therefore still there is significant gray area for appropriate humidifier which may prevent or lessen incidence of VAP. Clinically use of HH is preferred over HMEs in patients having viscous secretions and in patients who stay on mechanical ventilator for a prolonged duration. In a systemic review, it was found that $PaCO_2$ and minute ventilation were found to be lower with the use of HH compared with HMEs in patients with limited respiratory reserve.[3] Important drawback with HH is increased incidence of nosocomial infections because of formation of condensate in the circuit **(Box 1)**.[21]

BOX 1: Grades of recommendations for humidification.

Following are the recommendations of GRADE (Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria.[2] Level of evidence mentioned along with each recommendation

- Humidification is recommended on every patient receiving invasive mechanical ventilation (1A)
- Active humidification is suggested for NIV, as it may improve adherence and comfort (2B).
- When providing active humidification to patients who are invasively ventilated, it is suggested that the device provide a humidity level between 33 and 44 mg H_2O/L and gas temperature between 34 and 41°C at the circuit Y-piece, with an RH of 100% (2B).
- When providing passive humidification to patients undergoing invasive mechanical ventilation, it is suggested that the HME provide a minimum of 30 mg H_2O/L (2B).
- Passive humidification is not recommended for NIV (2C).
- When providing humidification to patients with low tidal volumes, such as when lung-protective ventilation strategies are used, HMEs are not recommended because they contribute additional dead space, which can increase the ventilation requirement and $PaCO_2$ (2B).
- It is suggested that HMEs are not used as a prevention strategy for ventilator-associated pneumonia (2B).

CONCLUSION

Critically ill patients on mechanical ventilation need humidification as a key intervention. Depending upon the source of heat and humidity, humidifier may be active or passive. Its selection depends on the clinical scenario of the patient. Appropriate selection of humidifiers are crucial as it might have wide ranging consequences on patient's morbidity and mortality.

KEY POINTS

- Humidification is essential for patients on noninvasive and invasive ventilation.
- Choosing type of humidification depends on existing clinical context.
- Both active and passive humidifiers have their own indications and contraindications.
- These need to be changed at regular intervals.
- Either active or passive humidification have not proven superior to each other in preventing or reducing the incidence of VAP.

REFERENCES

1. Cairo JM. Mosby's Respiratory Care Equipment, 9th edition. St. Louis: Mosby, Elsevier; 2013.
2. Restrepo DR, Walsh KB. Humidification during invasive and noninvasive mechanical ventilation. Resp Care. 2012; 57(5):782-8.
3. Kelly M, Gillies D, Todd DA, Lockwood C. Heated humidification versus heat and moisture exchangers for ventilated adults and children. Cochrane Database Syst Rev. 2010;(4):CD004711.
4. Gillies D, Todd AD, Foster P Jr, Batuwitage TB. Heat and moisture exchangers versus heated humidifiers for mechanically ventilated adults and children. Cochrane Database Syst Rev. 2017;9(9):CD004711.
5. Branson RD. Secretion management in the mechanically ventilated patient. Respir Care. 2007;52(10):1328-42.
6. Prat G, Renault A, Tonnelier JM, Goetghebeur D, Oger E, Boles JM, et al. Influence of the humidification device during acute respiratory distress syndrome. Intensive Care Med. 2003;29(12):2211-5.
7. Hedley RM, Allt-Graham J. A comparison of the filtration properties of heat and moisture exchangers. Anaesthesia. 1992;47(5):414-20.
8. American Association for Respiratory Care, Restrepo RD, Walsh BK. Humidification during invasive and noninvasive mechanical ventilation: 2012. Respiratory Care. 2012;57(5):782-8.
9. Cohen IL, Weinberg PF, Fein IA, Rowinski GS. Endotracheal tube occlusion associated with the use of heat and moisture exchangers in the intensive care unit. Crit Care Med. 1988;16(3):277-9.
10. Vandenbroucke-Grauls CM, Teeuw KB, Ballemans K, Lavooij C, Cornelisse PB, Verhoef V. Bacterial and viral removal efficiency, heat and moisture exchange properties of four filtration devices. J Hosp Infect. 1995;29(1):45-56.
11. Roustan JP, Kienlen J, Aubas P, Du Cailar J. Comparison of hydrophogic heat and moisture exchangers with heated humidifier during prolonged mechanical ventilation. Intensive Care Med. 1992;18(2):97-100.
12. Mebius C. A comparative evaluation of disposable humidifiers. Acta Anaesthesiologica Scandinavica. 1983;27(5):403-9.
13. Villafane MC, Cinnella G, Lofaso F, Isabey D, Harf A, Lemaire F, et al. Gradual reduction of endotracheal tube diameter during mechanical ventilation via different humidification devices. Anesthesiology. 1996;85(6):1341-9.
14. Djedaini K, Billiard M, Mier L, Le Bourdelles G, Brun P, Markowicz P, et al. Changing heat and moisture exchangers every 48 hours rather than 24 hours does not affect their efficacy and the incidence of nosocomial pneumonia. Am J Respir Crit Care Med. 1995;152(5):1562-9.
15. Lellouche F, Qader S, Taille S, Lyazidi A, Brochard L. Underhumidification and over-humidification during moderate induced hypothermia with usual devices. Intensive Care Med. 2006;32(7):1014-21.
16. Campbell RS, Davis Jr K, Johannigman JA, Branson RD. The effects of passive humidifier dead space on respiratory variables in paralyzed and spontaneously breathing patients. Respiratory Care. 2000;45(3):306-12.
17. Cook D, de Jonghe B, Brochard L, Brun-Buisson C. Influence of airway management on ventilator-associated pneumonia: evidence from randomized trials. J Am Med Assoc. 1998; 279(10):781-7.
18. Siempos II, Vardakas KZ, Kopterides P, Falagas ME. "Impact of passive humidification on clinical outcomes of mechanically ventilated patients: a meta-analysis of randomized controlled trials. Crit Care Med. 2007;35(12):2843-51.
19. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Resp Crit Care Med. 2005;171(4): 388-416.
20. Muscedere J, Dodek P, Keenan S, Fowler R, Cook D, Heyland D. Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: prevention. J Crit Care. 2008;23(1):126-37.
21. Kirton OC, DeHaven B, Morgan J, Morejon O, Civetta J. A prospective, randomized comparison of an in-line heat moisture exchange filter and heated wire humidifiers: rates of ventilator-associated early-onset (community-acquired) or late-onset (hospital-acquired) pneumonia and incidence of endotracheal tube occlusion. Chest. 1997;112(4):1055-9.

CHAPTER 23

Identifying Pulmonary Embolism in Bedside Where Computed Tomography Pulmonary Angiography is not Possible

Deepak Govil, Anant Pachisia, Divya Pal

INTRODUCTION

Pulmonary embolism (PE) causes up to 180,000 deaths per year in the United States and ranks as the third most common cause of cardiovascular death. Multidetector computed tomography pulmonary angiography (CTPA) is the investigation of choice of imaging patient with suspected PE.[1] Often doing a CTPA in a critically ill patient is not only challenging but also can be time-consuming. Thus, where CTPA is not possible, by diagnosing PE at the bedside, we can shorten the time to correct diagnosis and decrease the morbidity/mortality.

IDENTIFICATION AT THE BEDSIDE

Currently, PE is diagnosed by using clinical presentation, d-dimer, and CTPA pathway. However, instead of CTPA, a triple point of care ultrasound (POCUS) assessing heart, lung, and deep vein thrombosis (DVT) can be a useful tool to evaluate suspected PE in critically ill patients.

CLINICAL FEATURES

Acute PE is a well-recognized cause of sudden cardiac death.[2] The common clinical manifestations of massive/submassive PE include unilateral/bilateral lower limb or upper limb swelling following immobility, dyspnea, hypoxia, pleuritic chest pain, cough, hemoptysis, and hemodynamic instability. Chest pain is a common symptom generally arising from pulmonary infarct.[3] Acute PE can be classified as given in **Table 1**.[4]

TABLE 1: Pulmonary embolism classification.

Classification	*Characteristics*	*In hospital mortality*
Massive	Hemodynamic instability present	25–65%
Submassive	No hemodynamic instability, but right ventricular (RV) strain present	3%
Nonmassive	No RV strain or hemodynamic instability	<1%

DIAGNOSTIC WORKUP (TABLE 2)

D-dimer

The simultaneous activation of coagulation and fibrinolysis in acute thrombosis causes elevation of plasma levels of D-dimer. In acute PE, it has high negative predictive value but poor positive predictive value. Thus, a normal D-dimer may exclude acute PE but elevated D-dimer values are not diagnostic of it.[1] The specificity of D-dimer decreases with age reaching just 10% for patients with age of >80 years.[5] Using age-adjusted D-dimer values for patients >50 years, i.e., age × 10 μg/L increases the number of patients in whom PE can be excluded without increasing false negative findings.[6]

Troponins

Serum troponin levels are often elevated in acute PE, but they are prognostic rather than being diagnostic. They may be early markers for right ventricular dysfunction and elevated levels predict an adverse outcome.[7]

Brain Natriuretic Peptide

Right ventricle (RV) pressure overload causes myocardial stretch leading to rise in the levels of brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP). Elevated BNP levels thus have limited diagnostic importance but do reflect the severity of RV dysfunction.[8,9]

Electrocardiography

Electrocardiography (ECG) changes in an acute PE can vary from sinus tachycardia to changes indicative of RV strain, i.e., T wave inversion in V1-V4, QR pattern in V1, S1Q3T3 pattern, or an incomplete/complete right heart block.[10] Incidence of S1Q3T3 pattern is reported in just 12–50% patients of acute PE and is nonspecific.[11]

TABLE 2: Electrocardiography (ECG), chest X-ray, and ultrasound findings in acute pulmonary embolism.

ECG	*Chest X-ray*	*Ultrasound*
• Sinus tachycardia • *Right heart strain pattern:* – Complete/incomplete RBBB – Right axis deviation – T wave inversion in right precordial +/– inferior leads • $S_1Q_3T_3$ pattern	• Westermark sign (regional oligemia) • Hampton sign (Peripheral-wedge opacity) • Pleural effusion • Fleischner sign (enlarged pulmonary artery) • Palla sign (enlarged right descending pulmonary artery) • Vascular redistribution	• *Echocardiography* • *Right ventricular strain:* – *Right ventricle*: Shape and size – Abnormal septal motion – McConnell's sign – Tricuspid regurgitation – Decreased tricuspid annular systolic excursion – Decreased S' – Pulmonary artery mid-systolic notching – 60/60 sign – Speckle tracking demonstrating right ventricular free wall strain – Thrombus in transit • DVT scan • Lung ultrasound

(DVT: deep vein thrombosis; RBBB: right bundle branch block)

BEDSIDE IMAGING

Chest X-ray

They have very poor sensitivity and specificity in diagnosing acute PE. Bedside chest X-ray (CXR) is done primarily to rule out other causes of hypoxia such as pneumonia, pleural effusion, pneumothorax, pulmonary edema, etc. However the classical and specific finding of acute PE (Westermark sign, Hampton hump, Fleischner sign, and Palla sign) are not commonly encountered.[12,13]

Point of Care Ultrasound

Point of care ultrasound plays an important role in diagnosing acute PE at the bedside in patients who are hemodynamically unstable or severely hypoxic to be shifted for CTPA. It has gained all the more importance in the COVID era because of the increase in incidence of PE.

Acute PE causes sudden rise in pulmonary vascular resistance (PVR), caused by thrombus in the pulmonary vasculature. This causes dilatation of the RV along with decrease in left ventricle (LV) preload which causes decrease in LV outflow and hence hypotension. Increase in RV pressure causes interventricular septum (IVS) to shift toward LV, thus compromising LV filling.

For confirming the diagnosis of PE using POCUS, a three-point examination is required:

1. Echocardiographic signs of RV strain
2. Scanning for DVT
3. Lung ultrasound.

ECHOCARDIOGRAPHIC SIGNS OF RIGHT VENTRICULAR STRAIN

Right Ventricle Shape and Size

Right ventricular dilatation is found in >25% patients with PE.[14] Assessment can be done in apical four-chamber (A4C) view and parasternal short axis (PSAX) view. Normally RV is crescent-shaped in PSAX but as the RV dilates, it becomes circular. Normally, RV is 60% of the size of LV at end diastole. RV size between 60 and 100% and >100% of LV size indicates moderate or severe RV dysfunction[15] **(Fig. 1)**.

The normal RV wall thickness in parasternal long axis view is <4 mm. Any RV wall thickness >5 mm suggests chronic elevation of RV afterload like chronic obstructive pulmonary disease (COPD), cor pulmonale, etc.

McConnell's Sign

McConnell's sign initially proposed in 1996 is defined as RV free wall hypokinesia with preserved apical function. However, later studies have found it to be having poor positive predictive value in diagnosing acute PE.[16,17]

Interventricular Septum

Normally, LV is circular in shape in PSAX, with IVS being concave toward LV in both systole and diastole. Because of

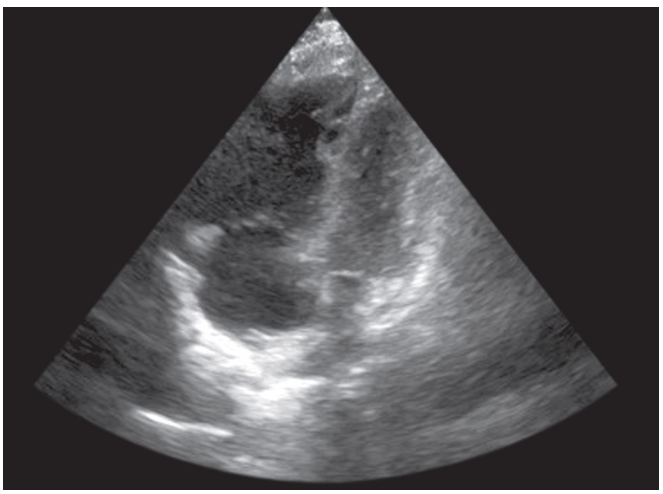


Fig. 1: Right ventricle (RV) dilatation in apical four-chamber view.

sudden pressure rise in RV caused by acute PE, septum is pushed toward LV leading to septal flattening, thus giving LV a "D-shape." The movement of septum also becomes paradoxical, thus being concave toward RV in systole **(Fig. 2)**.

Tricuspid Regurgitation

Continuous wave (CW) Doppler of the tricuspid regurgitation (TR) trace is used to calculate the pressure difference between RV and right atrium. Peak TR velocity (TRmax) <2.8 m/s is normal. Value of 2.9–3.4 m/s in suggestive of intermediate possibility and >3.4 m/s is suggestive of a high probability of pulmonary artery hypertension.[18] TRmax values are not particularly high in acute PE and values between 2.5 and 3 m/s can be normal for an acute PE (assuming no previous chronic pulmonary hypertension) **(Fig. 3)**.

Tricuspid Annular Plane Systolic Excursion

Tricuspid annular plane systolic excursion (TAPSE) is one-dimensional measurement of RV systolic function. In A4C view, RV systolic function is obtained by measuring vertical movement of lateral tricuspid annulus between end of diastole and end of systole using M-mode. It reflects longitudinal contraction of the RV, which contributes 80% of RV output. It has a sensitivity of 80% and specificity of 75% for RV ejection fraction.[19] A value of <16 mm is suggestive of RV dysfunction[1] **(Fig. 4)**.

Decreased S'

S' refers to the systolic excursion velocity of the right ventricular basal free wall. As with TAPSE, this reflects the longitudinal contraction of the right ventricle. In the A4C view when the tissue Doppler sampling gate is placed at 1 cm toward the apex from the lateral tricuspid annulus, the velocity of the basal free wall appears as a positive deflection on the y-axis during systole (S'). A S' <9.5 cm/s indicates right ventricular systolic dysfunction.[20]

Pulmonary Artery Systolic Notch

When assessing pulse wave Doppler flow of the pulmonary artery in the PSAX view (at the level of aortic valve), the pulmonary artery systolic ejection waveform appears as a downward deflection on the y-axis. Normally the waveform typically appear like a "dome." However, in case of pulmonary hypertension, the flow demonstrates a transient decrease in velocity during the pulmonary arterial systolic flow cycle, resulting in the appearance of pulmonary artery mid-systolic notch ("spike and dome" pattern). This has been used to assess for increased PAP in the context of PE. One study reported appearance of a "spike and dome" pattern from early-systolic notching, was 92% sensitive and 99% specific for massive or submassive PEs.[21]

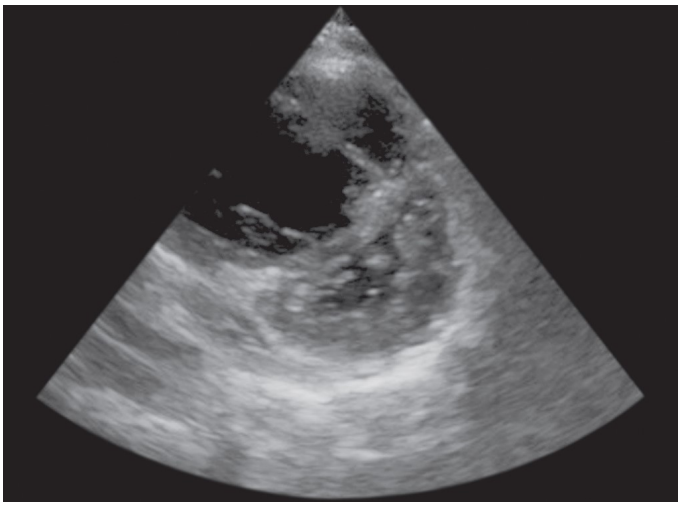


Fig. 2: Flattening of interventricular septum (IVS) with D-shaped left ventricle (LV).

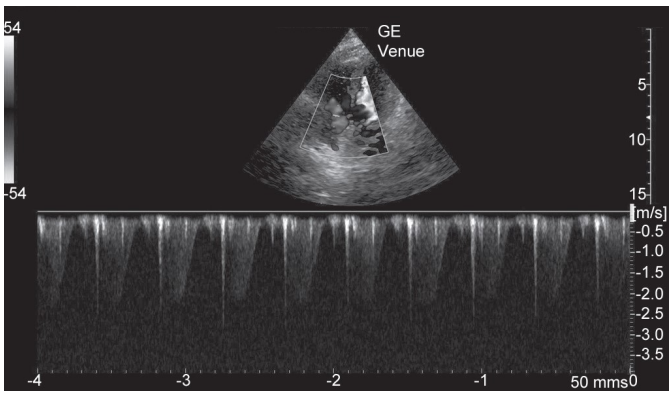


Fig. 3: Tricuspid regurgitation demonstrated using continuous wave (CW) Doppler.

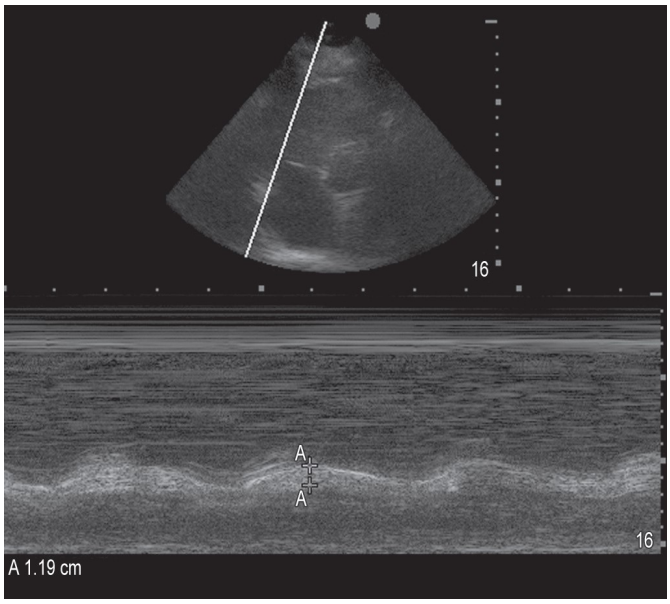


Fig. 4: Tricuspid annular plane systolic excursion (TAPSE) demonstrating right ventricle (RV) dysfunction.

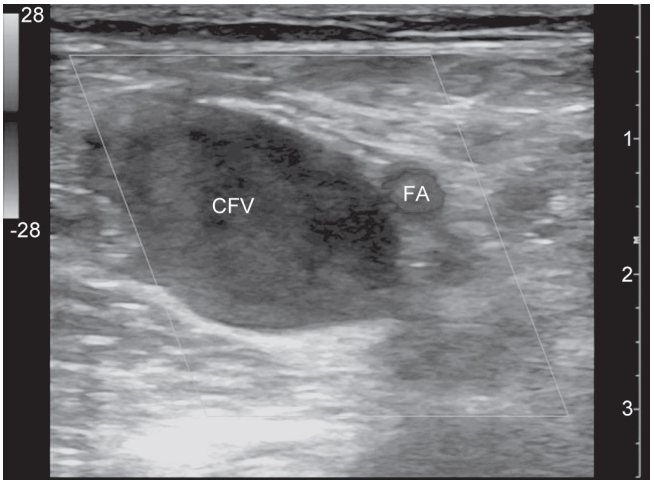


Fig. 5: Common femoral vein (CFV) thrombosis with no flow on color Doppler.

60/60 Sign

60/60 sign is not a sensitive but a very specific sign (94%) for diagnosing acute PE.[22] It has two components:

1. Pulmonary artery systolic pressure (PASP) <60 mm Hg but >30 mm Hg (TR jet velocity <3.9 m/s).
2. Pulmonary flow/RV outflow (RVOT) acceleration times (AT) <60 millisecond (ms).

Right ventricular outflow tract (RVOT) acceleration time is calculated by visualizing RVOT in PSAX basal view **(Fig. 5)**. Pulsed wave (PW) Doppler is aligned with the flow and sample volume is placed at the level of annulus. Normal RVOT AT >90 m/s. For TR jet, CW Doppler is placed at the center of TR flow.

Bernoulli's equation is used to convert TR velocity into pressure.

$$PASP = (Vmax^2 \times 4) + RAP$$

Right atrial pressure (RAP) is calculated by measuring IVC diameter and correlating with central venous pressure. However, recent studies have found that IVC-based assessment of RAP can be highly inaccurate. Thus, whether adding RAP affects PASP calculation is yet to be determined.[23]

Mobile Thrombus

A mobile thrombus can rarely be visualized in IVC, right atrium, RV, or the pulmonary artery.

Speckle Tracking Demonstrating Right Ventricular Free Wall Strain[24]

A new emerging trend in the RV strain evaluation is the use of speckle tracking. Sound waves emitted from the transducer are reflected due to relative difference in the acoustic impedance between different areas of the myocardium. Software in the ultrasonography (USG) machine measures the scatter reflections, interprets these as grey-scale spots, and tracks their frame by frame movement in any direction within image plane. Right ventricular strain refers to the percentage change in myocardium deformation (i.e., in the length of myocardial segment). It correlates closely with right ventricular ejection fraction (RVEF) by magnetic resonance imaging (MRI), sonomicrometry, and radionucleotide studies. In suspected/diagnosed PE, longitudinal strain (i.e., RV contractile pattern) refers to the percentage of free wall systolic shortening from base to apex. Currently, American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) have proposed mean percentage of RV free wall strain as –29% ± 4.5%, with abnormality threshold being –20% (or 20% in magnitude).

SCANNING FOR DEEP VEIN THROMBOSIS

Common femoral vein (CFV) originates at the level of inguinal ligament and bifurcates into greater saphenous vein (GSV) medially and deep femoral vein laterally. After these branch off, CFV becomes superficial femoral vein (SFV), the main deep vein of lower limb. After passing through the adductor canal, it becomes the popliteal vein, which subsequently bifurcates into anterior, posterior tibial, and peroneal vein. CFV and SFV make up the deep venous system of lower limb and thus many identify both these as "femoral vein."

Equipment

Generally, high frequency linear probe (5–12 MHz) is used for scanning the lower limb veins but in patients with obesity or edema, curvilinear probe may be required.

Patient Position

The patient should externally rotate the hip and do slight flexion of the knee joint.

Two-point Deep Vein Thrombosis Scan

Ideally, DVT scan should be performed at 1 cm distance for scanning the entire venous system, but this classical technique is time-consuming. Scanning performed in intensive care unit (ICU) as part of POCUS is the two-point DVT scan. CFV scanning is done from inguinal ligament until it becomes SFV. Popliteal vein scanning is done from where it is parallel to popliteal artery to its trifurcation.

Ultrasonography Scanning Technique

- *Compression test*: First point of compression is at the level of CFV with visualization of the junction of GSV with CFV, as this is an area of high turbulence thus increased risk of DVT formation. Second point of compression if popliteal fossa to compress popliteal vein. Visualize an iso/hypo-echoic structure inside the lumen of the vein, which is suggestive of a thrombus (do not compress as it may

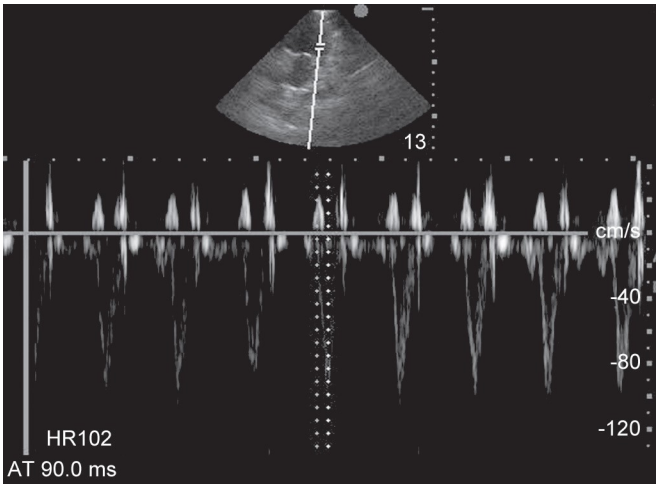


Fig. 6: PVAT measurement in PSAX basal view.
(PVAT: pulmonary velocity acceleration time; PSAX: parasternal short axis)

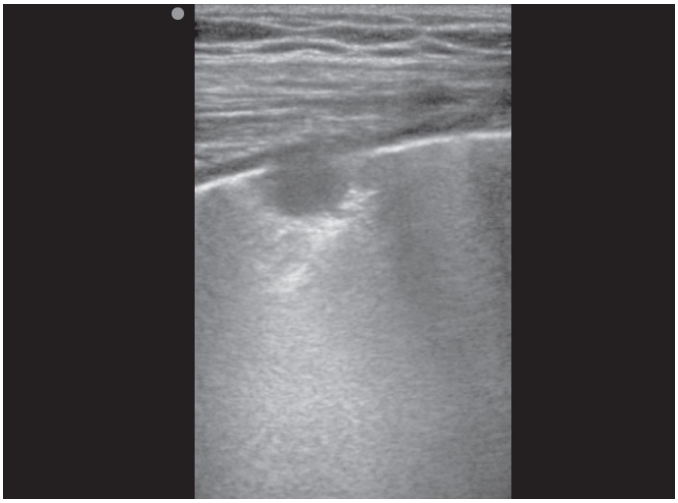


Fig. 7: Lung infarct caused by pulmonary embolism.

embolize) **(Fig. 6)**. However, if it not visualized, apply pressure with the USG probe in transverse orientation so that nearby artery is compressed slightly. Weak or off axis compression results in false positive result.[25] If the compression does not obliterate the lumen, it may be suggestive of a thrombus, thus do not do repeated compressions.

- *Scanning with PW and color Doppler*: The presence of constant color throughout the scanned area of vein on color Doppler along with presence of spontaneous flow on PW Doppler is suggestive of patent vein.
- *Respiratory phasicity*: Presence of biphasic flow, i.e., increase in flow in expiration and decrease in inspiration is again suggestive of patent blood flow through the concerned vein. Monophasic flow pattern is indicative of venous thrombosis.
- *Distal augmentation test*: Squeezing the vein distal to assessment site like compressing the calf muscle will increase the blood flow in the proximal segment of vein. This will result in an increased spike/augmentation on PW Doppler suggestive of patent vein. Following augmentation, a brief Doppler silence is present because the veins become empty after compression and the normal flow starts once vein is refilled with arterial inflow.

LUNG ULTRASOUND

Lung USG is not mentioned in the European Society of Cardiology (ESC) guidelines for PE,[1] but most ICU physicians regularly use it in diagnosing PE. When embolic pulmonary vascular occlusion occurs, it will cause peripheral lung parenchymal necrosis which will be visible on lung USG as a peripheral subpleural consolidation **(Fig. 7)**. A recent systematic review found out that lung ultrasound was 87% sensitive and 81.8% specific in diagnosing PE in patients who were suspected of having PE.[26]

It is also helpful in ruling out other causes of hypoxia like consolidation, lung collapse, pleural effusion, pneumothorax, etc.

PITFALLS OF POINT OF CARE ULTRASOUND IN PULMONARY EMBOLISM

Diagnosis of RV dilatation relies on comparing the size of two ventricles in end diastole. An incomplete or wrong visualization of the two chambers like in patients with COPD, obesity, surgical bandaging, etc., can lead to incorrect diagnosis. Also, chronic RV dilatation needs to be differentiated from an acute RV overload in conditions such as chronic pulmonary hypertension, chronic TR, or pulmonary regurgitation. Adjunctive signs of chronic overload like RV wall thickness (>5 mm), LV status, regional impairments along with relevant history should be taken into consideration. RV infarct can also present with RV dilatation or dysfunction which needs to be differentiated. Thus, when cardiac view is not fully demonstrative on POCUS, conclusions may not be drawn about the diagnosis of PE. A recent systematic review found out that combined cardiopulmonary ultrasound is less sensitive and specific for PE compared to CTPA.[27] More studies are required comparing CTPA and POCUS for diagnosis of PE.

CONCLUSION

Computed tomography pulmonary angiography is not feasible in all the patients especially those with hemodynamic instability or severe hypoxia. POCUS is a very useful and handy tool to diagnose PE at the bedside using three-point examination, i.e., RV strain, DVT, and lungs and thus guide the physician to an effective thrombolytic therapy in high-risk PE.[1]

REFERENCES

1. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41(4):543-603.
2. Courtney DM, Sasser HC, Pincus CL, Kline JA. Pulseless electrical activity with witnessed arrest as a predictor of sudden death from massive pulmonary embolism in outpatients. Resuscitation. 2001;49(3):265-72.
3. Stein PD, Henry JW. Clinical characteristics of patients with acute pulmonary embolism stratified according to their presenting syndromes. Chest. 1997;112(4):974-9.
4. Sista AK, Kuo WT, Schiebler M, Madoff DC. Stratification, imaging, and management of acute massive and submassive pulmonary embolism. Radiology. 2017;284(1):5-24.
5. Righini M, Goehring C, Bounameaux H, Perrier A. Effects of age on the performance of common diagnostic tests for pulmonary embolism. Am J Med. 2000;109(5):357-61.
6. Righini M, Van Es J, Den Exter PL, Roy PM, Verschuren F, Ghuysen A, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. JAMA. 2014;311(11):1117-24.
7. Horlander KT, Leeper KV. Troponin levels as a guide to treatment of pulmonary embolism. Curr Opin Pulm Med. 2003;9(5):374-7.
8. Kiely DG, Kennedy NS, Pirzada O, Batchelor SA, Struthers AD, Lipworth BJ. Elevated levels of natriuretic peptides in patients with pulmonary thromboembolism. Respir Med. 2005;99(10):1286-91.
9. Henzler T, Roeger S, Meyer M, Schoepf UJ, Nance JW Jr, Haghi D, et al. Pulmonary embolism: CT signs and cardiac biomarkers for predicting right ventricular dysfunction. Eur Respir J. 2012;39(4):919-26.
10. Shopp JD, Stewart LK, Emmett TW, Kline JA. Findings from 12-lead electrocardiography that predict circulatory shock from pulmonary embolism: systematic review and meta-analysis. Acad Emerg Med. 2015;22(10):1127-37.
11. Arshad H, Khan RR, Khaja M. Case Report of S1Q3T3 Electrocardiographic abnormality in a pregnant asthmatic patient during acute bronchospasm. Am J Case Rep. 2017; 18:110-3.
12. Lu P, Chin BB. Simultaneous chest radiographic findings of Hampton's hump, Westermark's sign, and vascular redistribution in pulmonary embolism. Clin Nucl Med. 1998;23(10):701-2.
13. Moore AJE, Wachsmann J, Chamarthy MR, Panjikaran L, Tanabe Y, Rajiah P. Imaging of acute pulmonary embolism: an update. Cardiovasc Diagn Ther. 2018;8(3):225-43.
14. Kurnicka K, Lichodziejewska B, Goliszek S, Dzikowska-Diduch O, Zdonczyk O, Kozlowska M, et al. Echocardiographic pattern of acute pulmonary embolism: analysis of 511 consecutive patients. J Am Soc Echocardiogr. 2016;29(9):907-13.
15. Lai WW, Gauvreau K, Rivera ES, Saleeb S, Powell AJ, Geva T. Accuracy of guideline recommendations for two-dimensional quantification of the right ventricle by echocardiography. Int J Cardiovasc Imaging. 2008;24(7):691-8.
16. Vaid U, Singer E, Marhefka GD, Kraft WK, Baram M. Poor positive predictive value of McConnell's sign on transthoracic echocardiography for the diagnosis of acute pulmonary embolism. Hosp Pract (1995). 2013;41(3):23-7.
17. Casazza F, Bongarzoni A, Capozi A, Agostoni O. Regional right ventricular dysfunction in acute pulmonary embolism and right ventricular infarction. Eur J Echocardiogr. 2005;6(1):11-4.
18. Parasuraman S, Walker S, Loudon BL, Gollop ND, Wilson AM, Lowery C, et al. Assessment of pulmonary artery pressure by echocardiography-A comprehensive review. Int J Cardiol Heart Vasc. 2016;12:45-51.
19. Alerhand S, Hickey SM. Tricuspid annular plane systolic excursion (TAPSE) for risk stratification and prognostication of patients with pulmonary embolism. J Emerg Med. 2020;58(3):449-56.
20. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39. e14.
21. Afonso L, Sood A, Akintoye E, Gorcsan 3rd J, Rehman MU, Kumar K, et al. A Doppler echocardiographic pulmonary flow marker of massive or submassive acute pulmonary embolus. J Am Soc Echocardiogr. 2019;32(7):799-806.
22. Kurzyna M, Torbicki A, Pruszczyk P, Burakowska B, Fijałkowska A, Kober J, et al. Disturbed right ventricular ejection pattern as a new Doppler echocardiographic sign of acute pulmonary embolism. Am J Cardiol. 2002;90(5):507-11.
23. Magnino C, Omedè P, Avenatti E, Presutti D, Iannaccone A, Chiarlo M, et al. Inaccuracy of right atrial pressure estimates through inferior vena cava indices. Am J Cardiol. 2017;120(9): 1667-73.
24. Alerhand S, Sundaram T, Gottlieb M. What are the echocardiographic findings of acute right ventricular strain that suggest pulmonary embolism? Anaesth Crit Care Pain Med. 2021;40(2):100852.
25. Soni NJ, Arntfield R, Kory P. Point of Care Ultrasound, 2nd edition. Amsterdam: Elsevier; 2020.
26. Squizzato A, Rancan E, Dentali F, Bonzini M, Guasti L, Steidl L, et al. Diagnostic accuracy of lung ultrasound for pulmonary embolism: a systematic review and meta-analysis. J Thromb Haemost. 2013;11(7):1269-78.
27. Kagima J, Stolbrink M, Masheti S, Mbaiyani C, Munubi A, Joekes E, et al. Diagnostic accuracy of combined thoracic and cardiac sonography for the diagnosis of pulmonary embolism: A systematic review and meta-analysis. PLoS ONE. 2020;15(9):e0235940.

CHAPTER 24

Relevance of Berlin Definition

Rajesh Chawla, Raju Shakya, Aakanksha Chawla Jain

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is not linked to a single etiology and cannot be diagnosed by a single laboratory test. There has always been a challenge in defining ARDS due to the lack of a reference gold standard for diagnosis just like other syndromes such as depression.

Since there is no biomarker that is specific for ARDS, it is likely that many patients with acute hypoxemic respiratory failure with bilateral pulmonary infiltrates from other diseases could be wrongly diagnosed as having ARDS.[1,2]

Misdiagnosis can also occur if clinicians consider qualifying arterial oxygen tension (PaO_2) values recorded during acute events unrelated to the disease process (such as endotracheal tube obstruction, bronchospasm, patient–ventilator asynchrony, and pneumothorax), instead of considering PaO_2 values when patients are clinically stable.

DEFINITIONS OF ACUTE RESPIRATORY DISTRESS SYNDROME

In 1821, Laennec first brought to acknowledgement a condition characterized by pulmonary edema with no evidence of heart failure. It was described with terms such as double pneumonia, post-traumatic lung, and shock lung.[3]

In 1967, Asbaugh et al. declared the term ARDS based on five clinical features: Associated risk factor, severe hypoxemia despite adequate oxygen supplementation, bilateral chest X-ray infiltrates, poor lung compliance, and no evidence of congestive heart failure.[4]

American-European Consensus Conference Definition

In 1994, the first definition of ARDS was proposed by the American European Consensus Conference (AECC)[5] using the four following criteria:

1. Acute onset of hypoxemia.
2. PaO_2 to inspiratory oxygen fraction (FiO_2) ratio ≤200 mm Hg with no minimum positive end-expiratory pressure (PEEP) requirement.
3. Presence of bilateral infiltrates on chest X-ray.
4. Pulmonary artery wedge pressure ≤18 mm Hg or no clinical signs of cardiogenic pulmonary edema.

They also defined a new term "acute lung injury (ALI)" as less severe degree of hypoxemia with PaO_2 to FiO_2 ratio between 300 and 201 mm Hg, that meet all the above criteria similar to ARDS.

After using this criteria for 18 years, there were many queries unanswered such as description of the term "acute," uncertainty of PaO_2/FiO_2 ratio (depending on the ventilator settings), lack of minimum PEEP, and FiO_2 requirements,[6] interobserver variability in chest X-ray interpretation and difficulty in differentiating the presence of hydrostatic pulmonary edema.

Berlin Definition

In 2011, Berlin definition coined the term ARDS as acute diffuse lung injury occurring in patients with a predisposing risk factor that fulfill the following criteria:

- Acute onset within 1 week of a clinical insult or new/worsening respiratory symptoms.
- Presence of bilateral opacities on chest X-ray, not fully explained by effusions lobar/lung collapse, or nodules.
- Respiratory failure not fully explained by fluid overload or heart failure with the need for objective assessment (e.g., echocardiography) to rule out hydrostatic edema.
- Presence of hypoxemia, defined by (PaO_2/FiO_2) ≤ 300 mm Hg, measured with a minimum PEEP of ≥5 cmH_2O and categorized into mild, moderate, and severe ARDS according to the severity of hypoxemia.[7]

IMPROVEMENT OVER THE AMERICAN-EUROPEAN CONSENSUS CONFERENCE DEFINITION IN BERLIN CRITERIA

The Berlin definition had addressed several issues raised over the previous AECC definition.

- Acute onset of hypoxemia is described as respiratory symptoms occurring within 7 days of exposure to a risk factor. A specific time frame of 1 week was considered as almost all patients developed ARDS within 7 days of exposure to the risk factor.

- The confusing terminology of ALI was removed and patients are classified from mild, moderate, to severe ARDS when PaO_2/FiO_2 ratio is equal or less than 300, 200, or 100 mm Hg, respectively. Moreover mortality of 27, 32, and 45% were assigned with increasing severity of hypoxemia (mild, moderate, or severe), respectively.
- A minimum PEEP requirement of 5 cmH_2O has to be administered for the measurement of PaO_2/FiO_2 ratio.
- The need for a predisposing risk factor was included in the definition. The risk factors of ARDS were further classified into direct and indirect risk factors. Direct risk factors (direct injury to lung) include pneumonia, aspiration of gastric contents, lung contusion, inhalation injury, vasculitis and drowning while indirect risk factors include sepsis, trauma, pancreatitis, noncardiogenic shock, drug toxicity, and TRALI (transfusion associated acute lung injury).[8,9]
- The respiratory failure must not be fully explained by fluid overload or heart failure as judged by the clinician or confirmed by echocardiography and does not require the use of pulmonary artery catheter. The AECC definition required pulmonary arterial wedge pressure to not exceed 18 mm Hg in ARDS but higher values were observed in patients with ARDS and moreover the use of pulmonary artery catheter is no longer a routine practice for hemodynamic management.[10]
- The Berlin definition considered radiological abnormalities as bilateral infiltrates not just on chest-X-ray but also on computed tomography (CT) scan, which should not be fully explained by lung collapse, pleural effusions, or nodules.
- Moreover, they categorized ARDS into mild, moderate, and severe as they were associated with increased severity of disease, mortality, and increased number of days on mechanical ventilation.

All these changes resulted in a final definition that is simple to use, more practical with similar predictive validity.

LIMITATIONS OF BERLIN DEFINITION

Autopsy

Diffuse alveolar damage is a hallmark of ARDS, characterized by hyaline membrane, edema, cell necrosis, or fibrosis. An autopsy study revealed that the Berlin criteria did not correlate with the presence of diffuse alveolar damage in more than half of patients with moderate-to-severe ARDS. However, this correlation became significant when patients were categorized by PaO_2/FiO_2 criteria after 24 hours of persistent ARDS.[11]

Change in Acute Respiratory Distress Syndrome Severity beyond 24 Hours of Ventilation

Villar et al. studied patients with moderate-to-severe ARDS under standardized ventilator settings at a PEEP setting of >10 cm of water. On evaluation 24 hours later, >60% of patients with severe ARDS according to Berlin criteria improved and were reclassified to moderate, mild, or non-ARDS.[12]

This proves that a single measurement of PaO_2/FiO_2 ratio at a comparatively low PEEP of 5 cmH_2O has poor specificity for predicting persistent, severe hypoxemia. However, this approach could delay enrollment into clinical studies or initiating necessary treatment and also needs to be supported by more research work.

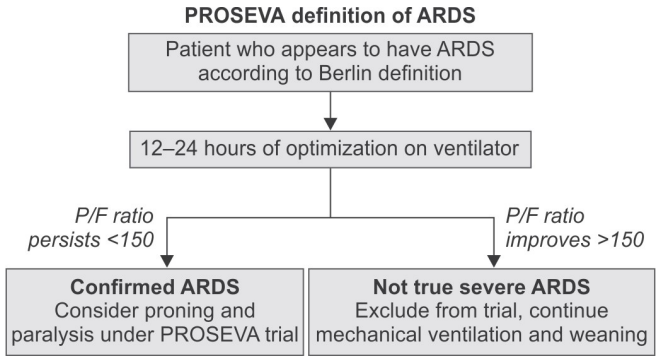
Acute Respiratory Distress Syndrome Overestimation in Pseudo-Acute Respiratory Distress Syndrome Collapse Pattern

Pseudo-ARDS-collapse is respiratory failure mostly due to collapse of the lower lobe seen, especially in patients with morbid obesity. It is the one of the closest mimic to ARDS.[13] Radiologically, pseudo-ARDS-collapse can look similar to true ARDS. Moreover, there is no history of heart failure or volume administration unlike in patients with hypervolemia. The only feature that can reliably differentiate pseudo-ARDS-collapse is resolution with increased mean airway pressure [e.g., airway pressure release ventilation (APRV) or conventional ventilation with high levels of PEEP]. The Berlin definition tried to rule out pseudo-ARDS collapse with inclusion of at least 5 cm PEEP. This is a nominal improvement over the AECC definition, not sufficient enough to recruit a collapsed lung, that too in a morbidly obese patient.

PROSEVA Hidden Definition of Acute Respiratory Distress Syndrome

The PROSEVA trial showed that proning is beneficial in patients with moderate-to-severe ARDS, who persist to have P/F ratio below 150 after 12–24 hours of optimization on the ventilator. Hidden within the foot print of PROSEVA trial is a new definition of ARDS, with an additional condition that PaO_2/FiO_2 ratio remains below 150 despite 12–24 hours of optimization on the ventilator. This would also help to rule out patients with pseudo-ARDS collapse (which show dramatic improvement with positive pressure) in contrast to patients with true ARDS **(Flowchart 1)**.

Flowchart 1: Selection of patients in PROSEVA trial.



(ARDS: acute respiratory distress syndrome)

Underestimation of Acute Respiratory Distress Syndrome in Healthcare Areas with Limited Resources/Kigali Definition of SpO_2/FiO_2 Ratio

The incidence of ARDS was explored in a Rwandan University Hospital by RIVIELLO et al. by using Kigali modification of the Berlin criteria to define ARDS as they had difficult access to arterial blood gas analysis, chest X-ray, and mechanical ventilation.[14]

The Kigali ARDS criteria defines ARDS as the ratio of oxygen saturation to FiO_2 of ≤315 [spO_2 (arterial oxygen saturation measured by pulse oximetry)/FiO_2 ratio ≤315] with no minimum PEEP requirement within the same time frame of 1 week as the Berlin definition. This criterion was based on the study by Rice et al.[15] who showed that SpO_2/FiO_2 ratio values of 235 and 315 correspond to PaO_2/FiO_2 ratio of 200 and 300, respectively. Bilateral chest opacities were evaluated through the routine use of lung ultrasonography, while chest X-rays were only considered when available.

Out of 1,046 patients screened, 88 of 126 hypoxemic patients had SpO_2/FiO_2 ratio of ≤315, and 42 (4%) were ultimately found to have ARDS according to the Kigali definition. None of these patients would have been identified had the Berlin definition been used. This study clearly shows that ARDS is still underestimated and undertreated, especially in low income countries and Berlin definition is not suitable in such settings with limited resources **(Table 1)**.

$PaO_2/(FiO_2 \times PEEP)$ ratio over PaO_2/FiO_2 Ratio

The Berlin definition requires a minimum applied PEEP of 5 cmH_2O, but does not specify an exact PEEP for the measurement of PaO_2.[16] It is, however, well known that PEEP can alter PaO_2 values. Therefore, PaO_2/FiO_2 ratios with lower PEEP settings have tendency for more patients to get categorized into severe ARDS, and those with higher PEEP settings has tendency to get more patients categorized into mild or even no ARDS.[17]

Sunitha et al. hypothesized that since the PaO_2/FiO_2 ratio is closely related to PEEP, it may be redefined by incorporating PEEP into the formula, that led to formulation of $PaO_2/(FiO_2 \times PEEP)$ ratio while maintaining the Berlin definition's severity classification of 100, 200, and 300. Moreover, the addition of PEEP to P/F ratio also takes into consideration the compliance of respiratory system and lung recruitment in assessing the diagnosis and severity of ARDS. They concluded that $PaO_2/(FiO_2 \times PEEP)$ ratio has a greater predictive validity for mortality than PaO_2/FiO_2 ratio in ARDS patients and its prognostic ability progressively increases with higher levels of PEEP.[18]

Inspiratory Oxygen Fraction

Villar et al. in 2007 showed that increasing the FiO_2 to 100% led to about 20% of patients with moderate–severe ARDS to be reclassified into a milder diagnostic category. Other factors that affect PaO_2/FiO_2 ratio include cardiac output, metabolic rate, and hemoglobin concentration.

Thus, PaO_2/FiO_2 ratio is a very labile measurement influenced by a number of factors (PEEP, FiO_2, recruitment, cardiac output, metabolic rate, and hemoglobin concentration).

Deviation from the Root of Cause

The real problem is that once a patient falls under ARDS according to Berlin criteria, the clinician may assume to have come to a diagnosis and defer the search for the underlying etiology.

TABLE 1: American European Consensus Conference (AECC), Berlin and Kigali definition for acute respiratory distress syndrome (ARDS).

	AECC definition	***Berlin definition***	***Kigali modification of Berlin definition***
Timing	Acute onset	Within 1 week of exposure to a risk factor or new or worsening respiratory symptoms	Within 1 week of exposure to a risk factor or new or worsening respiratory symptoms
Oxygenation	PaO_2/FiO_2 ≤200 mm Hg [acute lung injury if PaO_2/FiO_2 between (300–201) mm Hg]	*Mild*: 200 <PaO_2/FiO_2 ≤300 *Moderate*: 100 <PaO_2/FiO_2 ≤ 200 *Severe*: PaO_2/FiO_2 ≤100	SpO_2/FiO_2 ≤315
PEEP requirement	Nil	Minimum PEEP of 5 cmH_2O PEEP is required.	No PEEP requirement, similar to AECC definition
Chest imaging	Bilateral infiltrates on chest X-ray	Bilateral opacities not fully explained by collapse, effusion, or nodules by chest X-ray or CT	Bilateral opacities not fully explained by collapse, effusion or nodules by chest X-ray or ultrasound
Origin of edema	Pulmonary artery wedge pressure <18 mm Hg or no evidence of left atrial hypertension	Respiratory failure not fully explained by fluid overload or heart failure or fluid overload	Respiratory failure not fully explained by fluid overload or heart failure or fluid overload

(CT: computed tomography; PEEP: positive end-expiratory pressure)

It should be kept in mind that ARDS is a syndrome, not a disease and survival depends solely on identification of the root of cause rather than any form of organ support. A favorable course of ARDS is usually associated with resolution of the underlying cause and failing to identify and control it may result in sequential organ failure and death.

CONCLUSION

Although the recent Berlin definition is better than previous ones, there is still a high variability in both epidemiology and clinical outcomes in different healthcare settings.[19]

- The Berlin Definition of ARDS is limited due to wide fluctuations in PaO_2/FiO_2 ratio which occur with varying levels of PEEP and different FiO_2 levels. This may cause a patient to meet the definition of ARDS at one moment and not in the other.
- Pseudo-ARDS collapse patterns do not have severe lung injury and should not be treated on the line of ARDS.
- PROSEVA trial suggests a diagnostic/therapeutic strategy for ARDS. Initial management includes stabilization on the ventilator for 12–24 hours and determine if they respond to recruitment. Patients with persistent severe hypoxemia have true ARDS and may benefit from proning. Alternatively, patients who improve dramatically with recruitment have pseudo-ARDS and do not require proning/paralysis.
- PaO_2/FiO_2 ratio is only one piece of information, which must be interpreted within clinical context. The judgement to take major treatment decisions should not rest entirely on a single measurement of PaO_2/FiO_2.
- The search for newer criteria such as spO_2/FiO_2 ratio, $PaO_2/(FiO_2 \times PEEP)$ ratio, increasing the minimum PEEP requirement to >10 cmH_2O and reclassifying after 24 hours of optimization on the ventilator should be promoted.
- Development of better strategies in the future to diagnose ARDS should be considered, for instance, specific biomarker of inflammation, permeability, and alveolar-capillary membrane disruption, rather than using a clinical criteria alone.[20,21]
- In spite of all the concerns raised, Berlin definition still holds its relevance when combined with proper clinical assessment, although there is space for improvement with further trials and research work.

REFERENCES

1. Guérin C, Thompson T, Brower R. The ten diseases that look like ARDS. Intensive Care Med. 2015;41(6):1099-102.
2. Gibelin A, Parrot A, Maitre B, Brun Buisson C, Mekontso Dessap A, Fartoukh M, et al. (2015) Acute respiratory distress syndrome mimickers lacking common risk factors of the Berlin definition. Intensive Care Med. 2015;42:164-72.
3. Villar J, Blanco J, del Campo R, Andaluz Ojeda D, Díaz Dominguez FJ, Muriel A, et al. Assessment of PaO_2/FiO_2 for stratification of patients with moderate and severe acute respiratory distress syndrome. BMJ Open. 2015;5:e006812.
4. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet. 1967;2(7511):319-23.
5. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Am J Respir Crit Care Med. 1994;149(3 Pt 1):81824.
6. Phua J, Stewart TE, Ferguson ND. Acute respiratory distress syndrome 40 years later: time to revisit its definition. 2008;36(10):2912-21.
7. The ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012;307(23):2526-33.
8. Fanelli V, Vlachou A, Ghannadian S, Simonetti U, Slutsky AS, Zhang H. Acute respiratory distress syndrome: new definition, current and future therapeutic options. J Thorac Dis. 2013;5(3):326-34.
9. Saguil A, Fargo M. Acute respiratory distress syndrome: Diagnosis and management. Am Fam Physician. 2012;85(4):352-8.
10. Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med. 2012;38(10):1573-82.
11. Thille AW, Esteban A, Fernández-Segoviano P, Rodriguez JM, Aramburu JA, Peñuelas O, et al. Comparison of the Berlin definition for acute respiratory distress syndrome with autopsy. Am J Respir Crit Care Med. 2013;187:761-7.
12. Villar J, Pérez-Méndez L, Blanco J, Añón JM, Blanch L, Belda J, et al. A universal definition of ARDS: the PaO_2/FiO_2 ratio under a standard ventilatory setting. A prospective, multicenter validation study. Intensive Care Med. 2013;39(4):583-92.
13. PulmCrit: ARDS vs pseudoARDS Failure of the Berlin definition. [online] Available from: https://emcrit.org/pulmcrit/pseudoards/. [Last accessed February 2022].
14. Riviello ED, Kiviri W, Twagirumugabe T, Mueller A, Banner-Goodspeed VM, Officer L, et al. Hospital incidence and outcomes of the acute respiratory distress syndrome using the Kigali modification of the Berlin definition. Am J Respir Crit Care Med. 2016;193(1):52-9.
15. Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB, et al. Comparison of the SpO_2/FiO_2 ratio and the PaO_2/FiO_2 ratio in patients with acute lung injury or ARDS. Chest. 2007;132(2):410-7.
16. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012;307(23):2526-33.
17. Villar J, Perez-Mendez L, Lopez J, Belda J, Blanco J, Saralegui I, et al. An early $PEEP/FiO_2$ trial identifies diferent degrees of lung injury in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2007;176(8):795-804.
18. Palanidurai S, Phua J, Chan YH, Mukhopadhyay A. P/FP ratio: incorporation of PEEP into the PaO_2/FiO_2 ratio for prognostication and classification of acute respiratory distress syndrome. Ann Intensive Care. 2021;11(1):1-9.
19. Villar J, Blanco J, Añón JM, Santos-Bouza A, Blanch L, Ambrós A, et al. The ALIEN study: incidence and outcome of acute respiratory distress syndrome in the era of lung protective ventilation. Intensive Care Med. 2011;37(12):1932-41.
20. Vincent JL. The Berlin definition met our needs: not sure. Intensive Care Med. 2016;42(5):651-2.
21. Orwoll BE, Sapru A. Biomarkers in pediatric ARDS: future Directions. Front Pediatr. 2016;1(4):1-15.

CHAPTER 25

Hemodynamics in Severe Acute Respiratory Distress Syndrome

Edward Smith, Nitin Arora

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is seen in a quarter of mechanically ventilated patients and is associated with 41.9% intensive care unit (ICU) mortality.[1] A majority of patients with ARDS demonstrate hemodynamic instability.[2] This is commonly associated with right ventricular (RV) failure and is independently associated with even higher mortality.[3] This is a common clinical picture, good understanding, and management will reduce sickness and death in our patients.

PHYSIOLOGY

Ventilation, both spontaneous and mechanical, in the presence and absence of pathology, alters hemodynamics. By its effects on preload, afterload, and cardiac output.

Right Heart

In inspiration during spontaneous ventilation negative intrathoracic pressure increases the pressure gradient from the extrathoracic compartment. This increases flow to the right heart, preload and therefore cardiac output. This is augmented by increased abdominal pressure during the inspiratory phase.[4]

Venous return to the right heart and thus cardiac output is impeded during positive pressure ventilation (PPV). Higher thoracic pressures reduce the intra-/extrathoracic pressure gradient.[5]

Pulmonary vascular resistance (PVR) and RV afterload are almost directly related. PVR is high when ventilating at low pressures due to alveolar collapse and high pressures due to extra-alveolar vessel collapse. There is an ideal midway ventilating pressure with low PVR and high RV output. As ventilating peak pressures increase beyond this point, PVR increases exponentially.[6]

Increased pleural pressure during inspiration in mechanical ventilation decreases RV filling, reducing cardiac output. Conversely expiration produces sufficiently negative pleural pressure to compensate for this deleterious effect as long as the expiratory phase is long enough.[7] In the healthy lung, positive end-expiratory pressure (PEEP) < 15 cm H_2O is unlikely to significantly increase RV afterload or decrease cardiac output.

Left Heart

In the left heart, PEEP will expel blood from the pulmonary vascular bed into the left atrium and ventricle increasing preload and cardiac output. This is if the alveolar pressure does not exceed the pulmonary venule pressure. Magnetic resonance imaging (MRI) study of the left ventricular (LV) end-diastolic volume suggests that alveolar pressure does not exceed pulmonary venule pressure in spontaneous ventilation, but it is more likely to in PPV.[8] The LV preload will also be compromised if RV outflow is compromised by ventilation.

Ventricular interdependence has been demonstrated. The pressure or volume overloaded right ventricle will inhibit the volume and outflow of the left ventricle but not the contractility.[9]

In spontaneous inspiration, a decrease in intrathoracic pressure will create a relatively greater extrathoracic pressure gradient for the left ventricle to pump against. The opposite is true in PPV or as a function of increasing PEEP. Cardiac output can be increased in these scenarios. However, this physiological effect is limited in animal studies, where LV function is compromised. A pathology shared by many ICU patients even if their pulmonary edema is not directly being caused by LV failure.

Anesthetists electively ventilating patients for planned surgeries and will ensure gradual pressure increases, sufficient expiratory phase time and expiratory phase mean expiratory pressure as low as possible to ensure that hemodynamic compromise as a result of ventilation is not seen.

In ARDS, more pressure is required to ensure oxygenation, this can compromise the physiology above and lead to hemodynamic compromise, which the intensivist will need to address.

PATHOPHYSIOLOGY

Microscopic and macroscopic dysfunction in ARDS causes hemodynamic instability.

Pulmonary endothelial vessel and alveolar epithelial damage compromises the integrity of the alveolar capillary unit. Fluid, protein, red blood cells, and neutrophils migrate inappropriately and fill the alveolus. There is associated edema and inflammation.[10]

On a larger scale high ventilator pressures inhibit cardiac function, gaseous derangements and microthrombi cause pulmonary hypertension and disease processes such as sepsis outstrip the supply of the cardiovascular system.[11]

Edema and alveolar dysfunction caused by microscopic complications impede gas exchange and increases shunting leading to arterial hypoxemia and respiratory acidosis. Intensivists will increase ventilating pressures, volumes, and FiO_2 to address these issues.

Oxygenation is prioritized over ventilation. Therefore, the PEEP and inspiratory expiratory (I:E) ratio are likely to be higher. Preload in the right heart is reduced due to high thoracic pressures, the over pressurized lungs can also obstruct the superior vena cava (SVC) at the thoracic inlet.[12] Right heart afterload is increased by pulmonary infiltrates, hypoxic pulmonary vasoconstriction, and then venule collapse by high ventilating pressures. The left heart preload is then inhibited by high pressure in the lungs collapsing pulmonary venules, and poor flow from the struggling right heart. The pressure overloaded right ventricle functionally increases left ventricle afterload by ventricular interdependence. This will result in hemodynamic instability in ARDS.

Pulmonary hypertension often develops in ARDS as a result of hypoxic pulmonary vasoconstriction, acidosis from sepsis or shock, and microemboli. This further contributes to hemodynamic instability.

Hypercarbia is addressed second to hypoxia in ARDS. Yet it is not without harm. Permissive hypercapnia can become excessive. In carbon dioxide toxicity, hypercarbia causes acidosis, increased heart rate, and demands greater contractility. Acidosis increases PVR while systemic vascular resistance (SVR) drops. There is some evidence that outcomes are also poor in patients with severe hypercarbia.[13]

Fluid can be administered as a treatment, in drug dilution, or in feeds, in excess it can further exacerbate pulmonary edema and inhibit gas exchange. The weight of fluid lowers the tidal volumes at which regions of lung tissue can become over distended in ventilation and alter hemodynamics. Patients who are overloaded can be diuresed with loop diuretics which also cause metabolic alkalosis. This can reduce pulmonary edema and increase compliance.[6] Diuresis also reduces the cardiovascular compromise caused by acidosis. Yet diuresis in excess reduces RV preload and causes electrolyte imbalance which can compromise hemodynamics typically by arrhythmias.

Other simultaneous disease states in ARDS can alone cause instability or contribute to the above pathology. They must not be overlooked. They include, by no means exclusively; sepsis, trauma, hemorrhage, pulmonary embolisms (PEs), myocardial infarctions (MIs), and pneumothoraces.

MANAGEMENT

It is important to recognize that currently there are no specific and curative treatments for ARDS. As in much of intensive care medicine, the best treatment involves optimization of a multitude of factors. The two main areas of optimization in ARDS hemodynamic instability are fluid balance and ventilation.

Euvolemia is essential to minimize hypoxia that is due to fluid overloaded lung or hemodynamic compromise from low circulating volumes. In the physiologically compromised patient, these may both still be present at euvolemia. If indicated fluid resus can be with crystalloid, albumin or blood as dictated by the clinical picture.

Ventilator settings can be adjusted with reference to a large range of factors to optimize hemodynamics with consideration of oxygenation and ventilation as well. Compromises are often required.[11]

Assessment

An arterial line is essential giving beat-to-beat information on blood pressure and pulse pressure variation as an indicator of voluemic status in the ventilated patient.[11] This function has its limits including in the low compliance and low tidal volumes seen in ARDS.

Accurate, up-to-date blood gas analysis will mean hypoxia and hypercarbia causing pulmonary hypertension and electrolyte derangements causing hemodynamic instability can be treated promptly.

Central venous pressure (CVP) monitoring via a central catheter aids assessment of the RV function after management changes (in PEEP or vasopressor use). Electrolyte solutions and vaso-active drugs can be administered rapidly and safely. CVP is less useful as an indicator of fluid responsiveness.

Occasionally, the patient with positive pulse pressure variation will not respond to fluid boluses. This can be due to the RVs requirement for greater preload. Echocardiography can guide optimization of preload by assessment of changes following a passive leg raise. RV size calculation and LV contractility assessment is also helpful in excluding other causes of shock such as cardiac tamponade, MI, and PE. More complete assessment can be made by transesophageal rather than the transthoracic route but the intensivist should consider the risk over benefit of an invasive investigation with no guarantee of a direct benefit to the patient.

In selected cases involving sepsis or poor response to treatment a pulmonary artery catheter may be considered. It gives estimates of cardiac output and mixed venous oxygen saturation which can indicate the response to fluid, ventilation, and vasopressors.[11]

Even with euvolemia and optimized ventilator settings hemodynamic instability can persist. Commonly, this can be related to sepsis and strategies could include changing antimicrobial medication or inotropic/vasopressor medication.

Vasopressors

Vasopressors should be used in the euvolemic unstable patient with right-sided heart failure. Noradrenaline is commonly used but levosimendan has also been trialed with good results.

Positive End-expiratory Pressure

Insufficient PEEP will cause alveolar collapse and increase RV strain. Excessive PEEP will distend the lungs and also inhibit RV function.

There is no strong evidence for a single method of PEEP titration, although increased PEEP with increased severity of ARDS is likely to benefit the patient. There is some evidence supporting the pulmonary compliance method for setting PEEP.[14]

Proning

The mechanically ventilated patient with ARDS and refractory hypoxemia will often be proned.[15] Proning will increase intra-abdominal pressure and venous return. It may also improve pulmonary perfusion, decrease hypoxic pulmonary vasoconstriction and reduce RV afterload. However, proning will decrease the compliance of the chest wall. This can increase intrathoracic pressure and inhibit venous return. Thus proning can improve or inhibit good hemodynamics in ARDS.[16]

Pulmonary Vasodilators

There is some evidence that inhaled nitric oxide might benefit patients in whom acute right heart failure has precipitated circulatory failure.[17] Its efficacy in reducing arterial hypoxemia is unproven.

Extracorporeal Membrane Oxygen

Extracorporeal membrane oxygen (ECMO) will support selected patients but can contribute to hemodynamic instability in ARDS as well as improving it.

Veno-venous (VV) ECMO alone can improve hemodynamic instability by improving arterial hypoxemia; it decreases hypoxic pulmonary vasoconstriction and RV strain. Veno-arterial (VA) ECMO is indicated in ARDS refractory hypoxemia with circulatory shock. It plays a larger active role in stabilization of the patients hemodynamic system.[18]

Controversial Strategies

High-frequency oscillatory ventilation has been linked with increased RV strain, and there is insufficient evidence of benefit.[19]

Individual recruitment maneuvers do temporarily reduce arterial hypoxemia; this is often associated with temporary hemodynamic compromise. Recurrent recruitment maneuvers have not been shown to improve patient outcomes.[20] Recurrent recruitment maneuvers, causing lung injury, are often a systematic issue. Where they are repeated by different members of the healthcare team. Institutions should try and avoid this system error.

More anticoagulation has been suggested to reduce the incidence of microthrombi in ARDS. Yet intermediate over prophylactic dose enoxaparin has not been demonstrated to improve outcomes of intensive care patients with COVID-19.

CONCLUSION

Hemodynamic compromise in ARDS is common due to ventilating pressures in the chest, lung tissue and vessel pathology and associated disease processes. Associated morbidity and mortality is high.

Careful management of fluid status, ventilation settings, and patient physiological parameters remains the foundation of best care.

REFERENCES

1. Summers C, Singh NR, Worpole L, Simmonds R, Babar J, Condliffe AM, et al. Incidence and recognition of acute respiratory distress syndrome in a UK intensive care unit. Thorax. 2016;71:1050-1.
2. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA. 2016;315:788-800.
3. Bull TM, Clark B, McFann K, Moss M; National Institutes of Health/National Heart, Lung, and Blood Institute ARDS Network. Pulmonary vascular dysfunction is associated with poor outcomes in patients with acute lung injury. Am J Respir Crit Care Med. 2010;182:1123-8.
4. Mills GH. Respiratory physiology and anaesthesia. BJA CEPD Rev. 2001;1(2):35-9.
5. Santamore WP, Heckman JL, Bove AA. Cardiovascular changes from expiration to inspiration during IPPV. Am J Physiol. 1983;245(2):H307-12.
6. West JB, Dollery CT, Naimark A. Distribution of Blood Flow in Isolated Lung; Relation to Vascular and Alveolar Pressures. J Appl Physiol. 1964;19:713-24.
7. West JB, Luks A. West's Respiratory Physiology: The Essentials. Philadelphia: Wolters Kluwer; 2016.

8. Leithner C, Podolsky A, Globits S, Frank H, Neuhold A, Pidlich J, et al. Magnetic resonance imaging of the heart during positive end-expiratory pressure ventilation in normal subjects. Crit Care Med. 1994;22(3):426-32.
9. Naeije R, Badagliacca R. The overloaded right heart and ventricular interdependence. Cardiovasc Res. 2017;113(12):1474-85.
10. Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. J Clin Invest. 2012;122:2731-40.
11. Vieillard-Baron A, Matthay M, Teboul JL, Bein T, Schultz M, Magder S, et al. Experts' opinion on management of hemodynamics in ARDS patients: focus on the effects of mechanical ventilation. Intensive Care Med. 2016;42(5):739-49.
12. Fessler HE, Brower RG, Shapiro EP, Permutt S. Effects of positive end-expiratory pressure and body position on pressure in the thoracic great veins. Am Rev Respir Dis. 1993;148(6 Pt 1):1657-64.
13. Nin N, Muriel A, Peñuelas O, Brochard L, Lorente JA, Ferguson ND, et al. Severe hypercapnia and outcome of mechanically ventilated patients with moderate or severe acute respiratory distress syndrome. Intensive Care Med. 2017;43:200-8.
14. Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med. 2006;354:1775-86.
15. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368(23):2159-68.
16. Jozwiak M, Teboul JL, Anguel N, Persichini R, Silva S, Chemla D, et al. Beneficial hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2013;188(12):1428-33.
17. Repesse X, Charron C, Vieillard-Baron A. Acute cor pulmonale in ARDS: rationale for protecting the right ventricle. Chest. 2015;147:259-65.
18. Gutsche JT, Mikkelsen ME, McCarthy FH, Miano TA, V ernick WJ, Ramakrishna H, et al. Veno-Venous Extracorporeal Life Support in Hemodynamically Unstable Patients With ARDS. Anesth Analg. 2017;124(3):846-8.
19. Guervilly C, Forel JM, Hraiech S, Demory D, Allardet-Servent J, Adda M, et al. Right ventricular function during high-frequency oscillatory ventilation in adults with acute respiratory distress syndrome. Crit Care Med. 2012;40(5):1539-45.
20. Goligher EC, Hodgson CL, Adhikari NKJ, Meade MO, Wunsch H, Uleryk E, et al. Lung Recruitment Maneuvers for Adult Patients with Acute Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis. Ann Am Thorac Soc. 2017;14(Supplement_4):S304-S311.

CHAPTER 26

Lung Transplant: Lessons for the Intensivist

Suresh Rao KG, Santhosh Vilvanathan, KR Balakrishnan

INTRODUCTION

In patients with end-stage lung disease, lung transplantation is the only option currently available to improve survival and quality of life.[1] Despite many advancements in the surgical techniques, immunosuppression regimens, preservative solutions and technology, early morbidity and mortality remains high in lung transplantation among other solid-organ transplants. Complications such as primary graft dysfunction (PGD), reperfusion injury, infection, bleeding, and anastomotic dehiscence in the early postoperative period adversely affect outcomes.[2] Strict vigilance and early initiation of rescue therapies like extracorporeal membrane oxygenation (ECMO) is vital in improving success after lung transplantation.[3] In this chapter, we briefly review about the immediate postoperative management after lung transplantation.

POSTOPERATIVE MANAGEMENT

Intensive care management can be broadly divided into:

- Stabilization of ventilatory function and oxygenation
- Hemodynamic management
- Immunosuppression
- Anti-infective strategies
- Management of complications.

VENTILATORY MANAGEMENT

The primary goals of ventilatory strategies are to provide adequate minute ventilation and to avoid ventilator-induced lung injuries such as volutrauma, barotrauma, and oxygen toxicity.[4] From the time of bronchial anastomosis, lung protective ventilation is initiated—low tidal volume (4–6 mL/kg ideal body weight) and low driving pressures to limit the plateau pressure below 30 cm H_2O.[5] Lowest acceptable fraction of inspired oxygen (FiO_2) to maintain oxygen saturations >92%, FiO_2 < 40% during reperfusion is ideal to prevent acute lung injury. No particular mode of ventilation is proven to be beneficial in the early postoperative period, though pressure control mode of ventilation with pressure control below 15 and optimal positive end-expiratory pressure (PEEP) is commonly used.[6]

The management should be individualized to achieve to set target goals. Sudden deterioration in oxygenation and decrease in lung compliance are early indicators of graft dysfunction. Differential diagnosis for postoperative hypoxemia includes PGD, anastomotic issues, pneumothorax, atelectasis, fluid overload, cardiac failure, etc. Frequent desaturations may indicate pulmonary hypertensive episodes, should be managed with inhaled nitric oxide or pulmonary vasodilators, sedation, and muscle relaxation.[7] In many instances, sudden hypoxemia and hypercapnia will require emergency bronchoscopic removal of secretions and mucous plugs.

Single lung transplantation done, e.g., emphysema, pose different challenges. The native and donor lungs will have different respiratory mechanics depending on the native lung disease. In chronic obstructive pulmonary disease (COPD) patients, there is high risk of hyperinflation and auto PEEP in the native lungs so lower PEEP is generally employed.

Primary Graft Dysfunction

It is a syndrome of acute severe lung injury which occurs within 72 hours post-lung allograft transplant without any major identifiable cause.[8] It is one of the major causes of morbidity and mortality in early postoperative period with a reported incidence of about 10–25%.[9] It is characterized by progressive hypoxemia and diffuse alveolar infiltrates in chest X-ray.

The International Society for Heart and Lung Transplantation (ISHLT) consensus statement of the working group on PGD,[10] standardized the definition of PGD in 2016 **(Table 1)**. Assessment is carried out at specific time points after reperfusion; within the first 6 hours (T0), post 24 hours (T24), 48 hours (T48), and 72 hours (T72). Ideally, the partial pressure of arterial oxygen (PaO_2)/FiO_2 (P/F ratio) is measured on a FiO_2 of 1.0 and PEEP of 5 cm H_2O.

TABLE 1: Grading of primary graft dysfunction.

Grade	*Pulmonary edema on chest radiograph*	*PaO_2/FiO_2 ratio*
0	No	Any
1	Yes	>300
2	Yes	200–300
3	Yes	<200

(FiO_2: fraction of inspired oxygen; PaO_2: partial pressure of arterial oxygen)

TABLE 2: Postoperative complications after lung transplantation.

Respiratory	*Cardiovascular*	*Surgical*
• Primary graft dysfunction • Pulmonary embolism • Pleural effusions • Transfusion-related acute lung injury (TRALI)	• Right heart dysfunction • Arrhythmias • Myocardial ischemia	• Bleeding • Pulmonary arterial stenosis • Pulmonary venous thrombosis • Bronchial anastomotic dehiscence
Immunological	***Renal***	***Infectious***
• Hyperacute rejection • Acute rejection • Side effects of drugs	Acute kidney injury	• Bacterial pneumonia • Fungal infections • Viral infections (CMV and EBR)

(CMV: cytomegalovirus; EBV: Epstein–Barr virus)

Risk Factors of Primary Graft Dysfunction

Donor-specific risk factors: Donor smoking history >20 pack years, alcohol use, donor age >64 years and <18 years, undersized lungs, traumatic brain injury, and lung contusion increases the risk of PGD.[11]

Recipient-specific risk factors: Patients with diagnosis of idiopathic pulmonary fibrosis, idiopathic pulmonary hypertension, and sarcoidosis undergoing lung transplant have higher risk of PGD.

Obesity [body mass index (BMI) > 25 kg/m^2], left ventricular diastolic dysfunction, preformed autoantibodies, and pleurodesis also increase risk.

Perioperative risk factors: Use of cardiopulmonary bypass, large volume blood transfusion, ischemic time > 8 hours, FiO_2 > 40% during reperfusion, delayed chest closure, and single lung transplant are associated with an increased risk of PGD above grade 2 at 48 or 72 hours post-lung transplantation.[11]

Management

Primary graft dysfunction is a diagnosis of exclusion. Pulmonary edema due to cardiac cause, pneumonia, antibody-mediated rejection, transfusion-related acute lung injury, and occlusion of venous anastomosis must be rule out.

Treatment is mainly supportive with restrictive fluid strategy, lung protective ventilation, antibiotics, and immunosuppression. Particular attention is given to maintain mean pulmonary artery pressures < 30 mm Hg.

Extracorporeal Membrane Oxygenation Post-lung Transplant

Early initiation of ECMO is advised in patients with refractory hypoxemia, ideally within 24 hours after transplantation.[12,13]

Veno venous ECMO (VV ECMO) with ultra-lung protective ventilation (3 mL/kg) may limit ventilator-induced lung injury and improve graft survival. Oxygen supply to the graft via pulmonary arteries is crucial as bronchial arterial blood supply to implanted lung is lacking.

Veno arterial ECMO (VA ECMO) is established in case of severe hemodynamic instability or severe pulmonary hypertensive crisis. As VA ECMO shunts blood away from the lung, maintenance of normal pulmonary artery pressure and pulsatility is essential to prevent graft hypoxia.

In certain situations, VVA ECMO, which combines both VV and VA ECMO techniques, can be utilized to regulate adequate pulmonary perfusion and systemic oxygenation.

Weaning of Mechanical Ventilation

Chest X-ray is done daily in the initial week. Malposition of invasive lines, diaphragmatic position, atelectasis, evidence of rejection like infiltrates/opacities, pleural abnormalities, and pneumonia should be looked for. Bedside lung ultrasound also is particularly helpful. In case of unclear finding, computed tomography without contrast is warranted.

Early extubation is ideal post-lung transplantation. Inhaled nitric oxide at 10–20 ppm, when used to manage pulmonary hypertension post-transplant is generally weaned in 24–48 hours.

Positive end-expiratory pressure is then weaned, followed by FiO_2 according to serial blood gases and hemodynamics.

Early tracheostomy should be considered in patients requiring prolonged mechanical ventilation. Flexible fiber optic bronchoscopy is performed in all patients for better trachea bronchial toileting and to evaluate the integrity of the airways.

Postextubation aggressive respiratory physiotherapy with incentive spirometry and early mobilization is initiated.

HEMODYNAMIC MANAGEMENT

Invasive cardiovascular monitoring is essential, as early postoperative hemodynamics can be very labile. In high-risk cases like elevated pulmonary arterial pressures at the time of transplant or an underlying diagnosis of pulmonary arterial hypertension, pulmonary artery catheters with continuous cardiac output and transesophageal echocardiography (TEE) are used to aid management.[14]

Obstruction of the pulmonary vein flow (due to clot, kinking, or narrow anastomosis) may present with hypoxia. TEE becomes a significant tool in differentiating this condition from other causes such as acute graft rejection or reperfusion injury. Turbulence of flow, pulmonary vein diameter of <0.5 cm, peak systolic flow velocity > 1 m/s, and pulmonary vein-left atrial pressure gradient (PVLAG) ≥10–12 mm Hg support the diagnosis of pulmonary vein stenosis.[15]

Hemodynamic goals are to maintain adequate systemic perfusion and oxygen delivery, by avoiding hypotension and pulmonary hypertension. Sudden increases in pulmonary vascular resistance can lead to right heart failure, should be monitored continuously. Use of pulmonary vasodilators such as nitric oxide, inhaled prostacyclin, and milrinone will reduce the right ventricular afterload and help in right ventricular recovery. Cardiac index of 2.2–2.5 is ideal. Vasopressors and ionotropic agents may be required to support hemodynamics.[16] Caution should be held in using high dose vasopressors as it may compromise airway circulation. Serial lactate levels and mixed venous saturations are measured guided by clinical status.

Arrhythmias

Arrhythmias generally supraventricular in origin are common with a reported incidence of 34–74%.[17] Hemodynamically significant arrhythmias should be cardioverted immediately; otherwise medical management with antiarrhythmic like amiodarone and anticoagulation should suffice.

Fluid Management

Reperfusion pulmonary edema is common after lung transplantation due to leaky capillaries, loss of lymphatic drainage should be managed aggressively. Diuretic infusion is required to maintain a total negative balance.

Volume replacement with colloid (5% albumin) rather than crystalloids should be considered. Hematocrit in the range of 25–30% is maintained. Point-of-care testing of coagulation like thromboelastogram (TEG) should guide blood product replacement.

Postoperative Pain and Sedation Management

Multimodal analgesia with intravenous opioids and regional anesthesia techniques play an important role in reducing morbidity.[18] Thoracic epidural analgesia has shown to reduce the duration of mechanical ventilation and reduction of length of intensive care unit (ICU) stay. Intercostal nerve cryoablation intraoperatively is particularly helpful in patients whom epidural placement is contraindicated. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, ketorolac, and other nephrotoxic drugs should be avoided due to synergistic action with calcineurin inhibitors.

Chest Tube Management

From postoperative day 2 chest tube removal should be considered once there is no air leak/serosanguinous drain < 100 mL/24 hours. This will aid in early mobilization and pulmonary rehabilitation.

Nutritional Support

Early initiation of enteric feeds via nasogastric tube should be done. Probiotics should be avoided in immunosuppressed patients. Swallowing assessment should be done prior to initiation of oral feeds. In case of recurrent nerve injury, vocal cord palsy nasojejunal tube is preferred to prevent gastric aspiration.

Deep Vein Thrombosis and Stress Ulcer Prophylaxis

Prophylactic anticoagulation should be initiated at the earliest as these patients are at moderate risk of venous thromboembolism. Subcutaneous unfractionated heparin is used.

Most patients will have gastrointestinal symptoms such as nausea, vomiting, ileus in the postoperative period due to phrenic nerve, and recurrent laryngeal nerve injuries during surgery and medications. Ulcer prophylaxis, stool softeners, and laxatives should be added to routine medications. However, immune suppressants especially Myfortic can cause loose stools.

Infection and Sepsis Management

Infectious complications contribute substantially to increased postoperative morbidity and mortality following lung transplant. Data suggests that >25% of postoperative deaths are due to infectious cause.[19]

Lung transplant recipients are uniquely high risk for bacterial and fungal infections. High level of immunosuppression is maintained. Allograft denervation leads to decreased mucociliary clearance and absent cough reflex. There is also continuous exposure to environmental pathogens and colonizing organisms from the upper respiratory tract.

Bronchoscopy with bronchoalveolar lavage (BAL) is the most sensitive test to rule out infections. Bacterial pneumonia is the most common infection post-lung transplant.[20] Viral infections in early postoperative period are uncommon. Empirical broad-spectrum antibiotics should be initiated intraoperatively before incision followed up by targeted antibiotics for the BAL cultures of explanted lung from the donor. Antifungal prophylaxis, *Pneumocystis carinii* prophylaxis, and *Cytomegalovirus* prophylaxis are started from postoperative day 2.

IMMUNOSUPPRESSION

Establishment of adequate immunosuppression is crucial for successful outcomes.[21] Induction therapy is used to suppress the T cell-mediated response of the recipient to the donor organ. Triple drug maintenance immunosuppression therapy is considered standard of care after lung transplantation and consists of a calcineurin inhibitor, tacrolimus or cyclosporine; a cell cycle inhibitor, mycophenolate or azathioprine; and a corticosteroid, prednisone. Use of immunosuppression regime should be individualized depending on the comorbidities and balancing the risk of infection.

DAILY INTENSIVE CARE ROUNDS

During daily rounds the critical care physician should thoroughly review all aspects of patient clinical parameters, imaging, and medications. Continuous optimization and adjustment of therapeutic measures should be done in discussion with transplant team. Specific emphasis should be given to radiological imaging, as it provides vital clues to detect early and late complications.

SUMMARY

Immediate postoperative period after lung transplantation requires meticulous attention to detail and instant decision making. These patients may have prolonged ICU stay in the pre- and post-transplant period, critical illness polyneuropathy or myopathy may also occur. They require frequent and intensive physiotherapy as well as occupational therapy.

REFERENCES

1. Meyer KC. Lung transplantation. F1000prime Rep. 2013;5:16.
2. Marczin N, de Waal EEC, Hopkins PMA, Mulligan MS, Simon A, Shaw AD, et al. International Consensus Recommendations for Anesthetic and Intensive Care Management of Lung Transplantation. An EACTAIC, SCA, ISHLT, ESOT, ESTS, and AST Approved document. J Heart Lung Transplant. 2021;40(11):1327-48.
3. Potestio C, Jordan D, Kachulis B. Acute postoperative management after lung transplantation. Best Pract Res Clin Anaesthesiol. 2017;31(2):273-84.
4. Lau CL, Patterson GA, Palmer SM. Critical care aspects of lung transplantation. J Intensive Care Med. 2004;19(2):83-104.
5. Barnes L, Reed RM, Parekh KR, Bhama JK, Pena T, Rajagopal S, et al. Mechanical ventilation for the lung transplant recipient. Curr Pulmonol Rep. 2015;4(2):88-96.
6. King CS, Valentine V, Cattamanchi A, Franco-Palacios D, Shlobin OA, Brown AW, et al. Early postoperative management after lung transplantation: Results of an international survey. Clin Transplant. 2017;31(7).
7. Kao CC, Parulekar AD. Postoperative management of lung transplant recipients. J Thorac Dis. 2019;11(Suppl 14): S1782-S1788.
8. Altun GT, Arslantaş MK, Cinel I. Primary graft dysfunction after lung transplantation. Turk J Anaesthesiol Reanim. 2015;43(6):418-23.
9. Christie JD, Kotloff RM, Ahya VN, Tino G, Pochettino A, Gaughan C, et al. The effect of primary graft dysfunction on survival after lung transplantation. Am J Respir Crit Care Med. 2005;171(11):1312-6.
10. Snell GI, Yusen RD, Weill D, Strueber M, Garrity E, Reed A, et al. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction, part I: Definition and grading-A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2017;36(10):1097-103.
11. Diamond JM, Arcasoy S, Kennedy CC, Eberlein M, Singer JP, Patterson GM, et al. Report of the International Society for Heart and Lung Transplantation Working Group on Primary Lung Graft Dysfunction, part II: Epidemiology, risk factors, and outcomes-A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2017;36(10):1104-13.
12. Fischer S, Bohn D, Rycus P, Pierre AF, de Perrot M, Waddell TK, et al. Extracorporeal membrane oxygenation for primary graft dysfunction after lung transplantation: analysis of the Extracorporeal Life Support Organization (ELSO) registry. J Heart Lung Transplant. 2007;26(5):472-7.
13. Wigfield CH, Lindsey JD, Steffens TG, Edwards NM, Love RB. Early institution of extracorporeal membrane oxygenation for primary graft dysfunction after lung transplantation improves outcome. J Heart Lung Transplant. 2007;26(4):331-8.
14. Kim SY, Jeong SJ, Lee JG, Park MS, Paik HC, Na S, et al. Critical Care after Lung Transplantation. Acute Crit Care. 2018;33(4):206-15.
15. Kachulis B, Mitrev L, Jordan D. Intraoperative anesthetic management of lung transplantation patients. Best Pract Res Clin Anaesthesiol. 2017;31(2):261-72.
16. Castillo M. Anesthetic management for lung transplantation. Curr Opin Anaesthesiol. 2011;24(1):32-6.
17. Lazaro MT, Ussetti P, Merino JL. Atrial fibrillation, atrial flutter, or both after pulmonary transplantation. Chest. 2005;127(4): 1461-2.
18. Gelzinis TA. An Update on Postoperative Analgesia Following Lung Transplantation. J Cardiothorac Vasc Anesth. 2018;32(6): 2662-4.
19. Yusen RD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Dobbels F, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-first adult lung and heart-lung transplant report—2014; focus theme: retransplantation. J Heart Lung Transplant. 2014;33(10): 1009-24.
20. Remund KF, Best M, Egan JJ. Infections relevant to lung transplantation. Proc Am Thorac Soc. 2009;6(1):94-100.
21. McDermott JK, Girgis RE. Individualizing immunosuppression in lung transplantation. Glob Cardiol Sci Pract. 2018(1):5.

SECTION

4

Nephrology/Acid Base/Fluid Electrolyte

CHAPTER 27

Fluid Administration in Emergency Department: Do's and Don'ts

Debasis Pradhan, Prakash Deb, Prithwis Bhattacharyya

INTRODUCTION

Majority of the patients in the emergency department (ED) receive intravenous (IV) fluid as a part of treatment.[1] Indications for fluid therapy vary from hemodynamic optimization to administration of various medications. Conditions which need fluid resuscitation include but are not limited to trauma, sepsis, loss from gastrointestinal tract, complications of diabetes such as diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS), hyponatremia, rhabdomyolysis, and burn injury.[2] With the ongoing debate as to which fluid is better for resuscitation, majority of evidence come from studies on critically ill patients managed in intensive care units. Sepsis has remained the most common etiology for which the resuscitation is initiated in two-thirds of the patients in ED.[1] The dos and don'ts of fluid therapy needs to be discussed under the following subheadings:

- Who needs fluid and why (patient and purpose)
- Type of fluid
- Rate and volume of administration
- Objectives and limits for safety (PATROL approach and an extension of TROL approach[3]).

There is sufficient evidence to suggest that early fluid resuscitation has a survival advantage in a variety of emergency patients by improving organ perfusion. However, the role of fluid overload has also been linked to the development of organ dysfunction in acutely sick patients.

QUICK LOOK AT THE BASIC PHYSIOLOGICAL CONSIDERATIONS WHILE GIVING FLUID

During emergency, fluid administration would prevent and/or reverse the consequences of organ dysfunction by improving oxygen delivery (DO_2) which is the product of cardiac output (CO) and arterial oxygen content (CaO_2) which is also dependent on oxygen saturation (SaO_2), hemoglobin (Hb%), and arterial oxygen tension (PaO_2).

Oxygen delivery = Cardiac output × arterial oxygen content

i.e., $DO_2 = CO \times CaO_2$

i.e., $DO_2 = CO \times [(1.31 \times Hb \times SaO_2 \times 0.01) + (0.0225 \times PaO_2)]$

Not all patients will show improvement of stroke volume and cardiac output secondary to fluid administration. Preload increase will cause increase in stroke volume in the steeper part of Frank–Starling curve **(Fig. 1)**, however after reaching the flat part no/little augmentation in stroke volume would be observed against a fluid challenge. Static parameters such as central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) are also dependent on ventricular compliance which keeps fluctuating in different clinical conditions and at different times in the same patient. It is difficult to predict a patient's place in the curve, especially in cases with a quickly changing hemodynamics. Dynamic parameters, as compared to static ones, are better guidance of optimum fluid therapy. Trauma, burn, shock and sepsis patients, who are poor fluid responders, especially with abnormal ventricular compliance, will show more fluid burden following initial resuscitation and the administered fluid would be a source of additional insult to vascular endothelium.

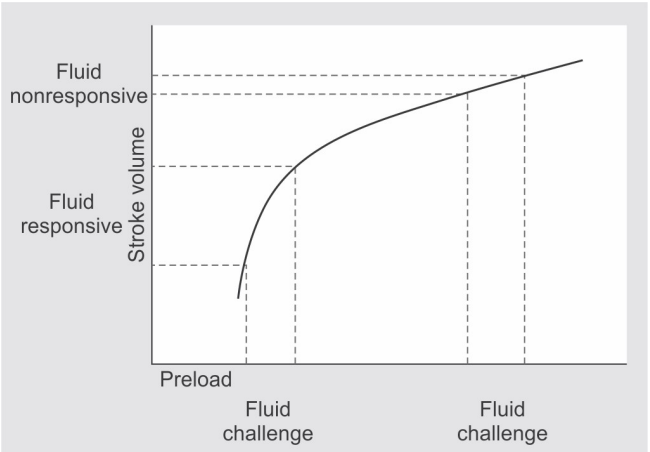


Fig. 1: Frank–Starling curve.

Presence of glycocalyx layer on vascular endothelium has greatly challenged the standard Starling law. Glycocalyx layer which is composed of glycosaminoglycan (GAGs), proteins, enzymes, growth factors, and adhesion molecules contribute to the fluid balance by holding 2% of plasma volume under normal circumstances. The role of colloid osmotic pressure exerted by the adsorbed albumin in the glycocalyx layer and the role of lymphatic absorption is now well known. Any breach in this layer by trauma, sepsis, burn, any inflammation, or overzealous fluid administration may lead to interstitial fluid accumulation and organ dysfunction.

Patient and Purpose

Maintenance fluid is indicated for patients not eating or drinking, postresuscitation and in specific clinical situations which include but not limited to patients with ongoing loss from gastrointestinal tract, endocrine emergencies such as DKA and HHS, electrolyte imbalances like hypo/hypernatremia, and burn injury.

Fluid administration during hemodynamic optimization in various types of shock or emergency conditions are done to attain the set targets. In an emergency set up, a brief and quick history along with a basic clinical assessment can guide us in fluid management with minimal insults. For example, in penetrating or blunt trauma, a permissive hypotension is recommended, whereas in traumatic brain injury (TBI), higher mean arterial pressure (MAP) >80 mm Hg is a standard practice. The role of commencement of fluid resuscitation in trauma patients from prehospital location and continuing in ED has been found to decrease mortality. However, aggressive fluid resuscitation has been known to cause clot dislodgement, hypothermia, imbalances of electrolytes and acid–base status, dilutional coagulopathy, compartment syndrome, etc., leading to further escalation of bleed and organ dysfunction in trauma patients. Bolus fluid administration in conditions such as sepsis, burn, trauma, DKA, HHS, and hypernatremia are done as per respective guidelines.

Once clear about the need for fluid administration in a particular patient, it is essential to find whether he/she would respond to it. Fluid responsiveness (FR) should be assessed for further bolus administration as <50% of the hemodynamically unstable patients are not responsive to fluid especially those with sepsis. **Table 1** enumerates various methods of checking fluid responsiveness with their pros and cons. Despite the lack of survival benefit of fluid responsiveness assessment and practical difficulty in many of the ED patients, it is worthwhile to assess FR. Positive FR does not always guarantee no harm from administration of fluid bolus. So, fluid administration needs an ongoing holistic and clinical context-specific approach rather than relying on a single test or assessment done only once. Nonetheless most of the ED patients do not fulfil the prerequisite for FR test.

Type of Fluid

Table 2 enumerates different types of crystalloids and colloids available at present. Current literature supports the avoidance of colloids as the bolus and maintenance therapy. There is no "one ideal fluid" which can fit into all resuscitative patients. The choice of appropriate fluid depends on the case scenario, composition of fluid, and the initial goals of resuscitation. A balanced salt solution is better than normal saline (NS), although there is no consistent proven benefit over Hartmann's solution or lactated Ringer or Ringer's acetate. Chloride rich solutions incite a vasoconstrictive response leading to increased incidence of acute kidney injury. High chloride delivery stimulates macula densa of juxtaglomerular apparatus leading to renal vasoconstriction.[4-10] However, conditions such as DKA, hyponatremia, and brain injury warrant NS use over other fluids. Hypotonic saline is not recommended for resuscitation, as they are mostly used for intracellular dehydration, providing substrate (dextrose) for maintenance and less likely to stay in intravascular compartment for a long time.

Though it's a matter of debate and requires individual judgment from case to case, crystalloids have largely replaced the "colloid resuscitation" in emergency department especially in critically ill, sepsis patients. Many trials have been done in last decade to find out the most appropriate fluid for resuscitation but the controversy and researches are still on.

In *severe sepsis patients*, hydroxyethyl starch (HES) 6% when compared with NS 0.9% was neither found to increase the need for renal replacement therapy (RRT) and other adverse effects, nor the mortality (CRYSTMAS Trial). 6S trial was also done on severe sepsis patients, found resuscitation with 6% HES increases 90 days mortality in addition to the increased need of RRT and risk of bleeding. On the other hand, CHEST trial showed an increased incidence of RRT in patients receiving HES but not mortality. Similar finding was reported in BaSES trial where need for RRT and other adverse events were more in sepsis patients treated with HES. In a randomized controlled trial (CRISTAL), *hypovolemic shock* patients receiving colloids had less 90 days mortality compared to the patient receiving crystalloids for resuscitation in addition to less ventilator days, less vasopressor requirements. Also, colloid group had less need for RRT though statistically not significant. SAFE trial found no survival benefit of 4% albumin with NS and moreover albumin is not recommended for *TBI*.

The benefits seen with the use of HES is not greater than the adverse effects seen in severe sepsis patients and therefore the use of HES in this group of patient is not advisable. The same is not applicable for other nonseptic indications such as trauma, hypovolemic shock, burn, and intraoperative fluid intervention, but there is no clear data on the safe upper limit of the quantity of colloids and the type. Meybohm et al.

TABLE 1: Dynamic tests for fluid responsiveness.

Type of test	*Prerequisites*	*Challenge*	*End point*	*Limitations if any*
Passive leg raising	• Direct measurement of cardiac output • Spontaneously breathing/ ventilated • Normal intra-abdominal and intracranial pressure • No contraindications for raising legs above 45° while torso being supine	• Autotransfusion from legs (250–500 mL) • Torso moved to supine, both legs raised 45° for 1 minute	10% or more increase in CO or SV	• Trauma or burn to inferior extremities or pelvis • Need direct measurement of CO/SV • Raised ICP/IAP
Mini fluid challenge	Both spontaneously breathing and mechanically ventilated	• Crystalloid 4 mL/kg or 100–250 mL over 1 minute • Colloid, 100–150 mL over 1 minute	10% or more increase in CO or SV	Direct and precise monitoring of CO/SV
Conventional fluid challenge	Both spontaneously breathing and mechanically ventilated	Crystalloid 500 mL	10% or more increase in CO or SV	Direct and precise monitoring of CO/SV
IVC collapsibility	Mechanically ventilated Tidal volume of min 8 mL/kg	Not required	• 12–46% in mechanically ventilated • 13–50% with spontaneous breathing	• Wide range of cut off value • Not a reliable • Needs correlation with other parameters
End-expiratory occlusion test	Mechanically ventilated	Occlusion at the end of expiration for 15 seconds	10% or more increase in CO or SV	Uninterrupted respiratory hold for 15 seconds
Pulse pressure variation (PPV) and stroke volume variation (SVV)	Invalid in following situations: • Spontaneously breathing • Cardiac arrhythmia • Valvular heart disease (especially aortic) • Cardiogenic shock (poor IV function) • Severe peripheral vascular disease • Tidal volume at least 8 mL/kg	Not required	Target SVV <10% and PPV <12%	• Need an arterial line and device to measure PPV/SVV • Prerequisites
Tidal volume challenge	Patients in Shock who are mechanically ventilated with low tidal volume (not spontaneously breathing)	Change in PPV with change in VT from 6 mL/kg to 8 mL/kg of PBW is noted and recorded	ΔPPV 6–8 by >3.5% indicates fluid responsiveness (high accuracy)	Unreliable in patients with raised intra-abdominal pressure, open thorax, those who are spontaneously breathing

(CO: cardiac output; IVC: inferior vena cava; SV: stroke volume; PWB: predicted body weight)

Sources:

1. Monnet X, Rienzo M, Osman D, Anguel N, Richard C, Pinsky MR, et al. Passive leg raising predicts fluid responsiveness in the critically ill. Crit Care Med. 2006;34(5):1402-7.
2. Aya HD, Rhodes A, Chis Ster I, Fletcher N, Grounds RM, Cecconi M. Hemodynamic effect of different doses of fluids for a fluid challenge: a quasi-randomized controlled study. Crit Care Med. 2017;45(2):e161-8.
3. Biais M, De Courson H, Lanchon R, Pereira B, Bardonneau G, Griton M, et al. Mini-fluid challenge of 100 mL of crystalloid predicts fluid responsiveness in the operating room. Anesthesiology. 2017;127(3):450-6.
4. Mukhtar A, Awad M, Elayashy M, Hussein A, Obayah G, El Adawy A, et al. Validity of mini-fluid challenge for predicting fluid responsiveness following liver transplantation. BMC Anesthesiol. 2019;19(1):1-6.
5. Das SK, Choupoo NS, Pradhan D, Saikia P, Monnet X. Diagnostic accuracy of inferior vena caval respiratory variation in detecting fluid unresponsiveness: a systematic review and meta-analysis. Eur J Anaesthesiol. 2018;35(11):831-9.
6. Monnet X, Osman D, Ridel C, Lamia B, Richard C, Teboul JL. Predicting volume responsiveness by using the end-expiratory occlusion in mechanically ventilated intensive care unit patients. Crit Care Med. 2009;37(3):951-6.
7. Michard F, Boussat S, Chemla D, Anguel N, Mercat A, Lecarpentier Y, et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. Am J Respir Crit Care Med. 2000;162(1):134-8.
8. Myatra S, Monnet X, Teboul JL. Use of 'tidal volume challenge' to improve the reliability of pulse pressure variation. Crit Care. 2017; 21(1):60.

TABLE 2: Common intravenous (IV) fluids available for use.

	Crystalloids						*Colloids*				
Composition	***Plasma***	***0.9% NaCl***	***Hartmann's***	***Lactated Ringer's***	***Plasma-lyte 148***	***Sterofundin***	***Gelofusine***	***Albumin 4%***	***Albumin 20%***	***Voluven (HES 6%, 130/0.4)***	***Dextran 70***
Ph	7.35–7.45	4.5–7.0	5.0–7.0	6.0–7.5	4.0–8.0	5–5.9		6.7–7.3	6.7–7.3	4.0–5.5	
Sodium (mmol/L)	135–145	154	131	130	140	140	154	140	130	154	154
Potassium (mmol/L)	3.5–5.0	0	5.0	4	5	4					
Chloride (mmol/L)	96–106	154	111	109	98	127	120	128	77	154	154
Calcium (mmol/L)	2.2–2.6	0	2	1.4	0	2.5					
Magnesium (mmol/L)	0.8–1.2	0	1	0	1.5	1					
Bicarbonate (mmol/L)	22–28	0	0	0	0	0					
Lactate (mmol/L)	1–2	0	29	0	0	0					
Acetate (mmol/L)	0	0	0	0	27	24					
Gluconate (mmol/L)	0	0	0	0	23	0					
Maleate (mmol/L)	0	0	0	0	0	5					
Osmolality (mOsm/L)	275–295	308	278	273	294	287	274	260		308	
Colloid content							Gelatin 40 g/L	Albumin 40 g/L	Albumin 200 g/L	HES 60 g/L	Dextran 60 g/L
Effective SID (mEq/L)	40	0		28			34	12		0	

(HES: hydroxyethyl starch; SID: strong ion difference)
(*Source*: Colloids vs. crystalloids as resuscitation fluids. [online] Available from: https://derangedphysiology.com/main/required-reading/electrolytes-and-fluids/Chapter%20225/colloids-vs-crystalloids-resuscitation-fluids. [Last accessed February 2022].

emphasized on the formation of an algorithm for the use of HES which is indication specific and sounds logical.

Polygeline and gelatin are increasingly being used in developing world in initial trauma resuscitation or hypovolemic shock due to their low cost, ability to reduce the crystalloid requirement, and longer stay in intravascular compartment. Compared to HES, gelatin is less likely to impact the kidney function though the higher rates of anaphylactic reactions are reported with gelatin.

Rate and Volume

Rate of fluid administration should be kept on the slower side whenever feasible while trying to achieve and maintain the hemodynamic parameters appropriate for the clinical condition. Higher flow rates are more harmful until and unless volume replenishment is life-saving.[4]

In acute situations, an initial fluid bolus of 500–1,000 mL is usually administered in patients showing signs of hypoperfusion provided the patient is not in overt cardiac failure, pulmonary edema. If history and clinical findings show a clear-cut scenario such as trauma, sepsis, and burn, initial fluid administration should be based on protocols along with an ongoing evaluation for fluid responsiveness and assessment of response. For example in case of septic shock patient presenting in ED would be ideally resuscitated with initial crystalloids of 500–1000 mL over 20–30 minutes. Vasopressors are added to achieve targets once a resuscitation of 30 mL/kg of fluid is done in 3 hours.

TABLE 3: Objectives of fluid administration for hemodynamic optimization.

Assessments	*Targets*
Mean arterial pressure	≥65 mm Hg, higher in case of known hypertensives
Urine output	≥0.5 mL/kg/hour
Well perfused end organ	• Warm extremities • Capillary refill time <3 seconds • Improved level of consciousness • Resolution of tachycardia • Improved lactate clearance • Increasing $ScVO_2$ >70%
Dynamic index	SVV <10% PPV <12%

(PPV: pulse pressure variation; SVV: stroke volume variation)

Rate of fluid administration should include the fluid required for maintenance in addition to the ongoing loss. The Holliday Segar formula of 4-2-1 is good enough to calculate maintenance rate.[1]

Objectives of Fluid Administration

Objectives of fluid administration in ED patients should include clinical as well as objective parameters. Rather than sticking to a single parameter, one should customize it to the clinical scenario, hospital protocol, and ongoing patient response. **Table 3** narrates objectives and assessments which may help us optimizing hemodynamics in acute settings. Chasing the targets during resuscitation always leads to fluid overload and there is clear evidence of fluid overload leading to poor outcome in ED patients. An optimum balance needs to be maintained between adequate organ perfusion and demerits of fluid overload. Negative effects of fluid overload include prolonged mechanical ventilation and ICU stay,[11] poor outcome of intra-abdominal hypertension and abdominal compartment syndrome,[12,13] increased need of RRT, and poor renal outcome.[14,15]

Irrespective of the inciting cause, the presence of hypotension, tachycardia, oliguria, decreased capillary refill time, altered sensorium, increased lactate, base excess prompt a fluid resuscitation. Tool for assessing fluid status is a matter of ongoing debate. We have seen the role of blood pressure, central venous pressure, central venous oxygen saturation, arterial blood gas parameters to maximum oxygen delivery claiming a superiority over conventional physiological parameters; however, results of some recent trials showed no mortality benefits over the clinical assessment guided by the physiological parameters in sepsis patients.[16] Though a more accurate way of guiding fluid therapy, use of advanced hemodynamic monitoring for early fluid administration in ED is time-consuming, requires skills and expertise to interpret, sterile preparations, and expansive gadgets, which are available only in some tertiary centers in most of the developing nations.

Limits for Safety

In most of the acute patients or in emergency situations, it is always not feasible to measure the dynamic indices such as stroke volume, cardiac output, cardiac index, stroke volume variation, pulse volume variation or systemic vascular resistance to guide fluid therapy. A more detailed discussion on these advance hemodynamic monitoring is beyond the scope of the chapter. The fluid administration relies mostly on multiple clinical and ABG parameters. Use of point of care ultrasound to assess the signs of fluid overload (distended IVC, distended left ventricle, signs of pulmonary edema in terms of increasing B lines) may also help in limiting further fluid administration. At the end we are left with surrogates of cardiac output and targets of end organ perfusion to decide the safe limits of fluid administration.

REFERENCES

1. Harris T, Coats TJ, Elwan MH. Fluid Therapy in the emergency department: an expert practice review. Emerg Med J. 2018;35(8):511-5.
2. Alexander N. Fluid therapy: Beware of (AB)normal saline - choose your resuscitation fluids carefully. In: Swadron SP, Mattu A, (Eds). Avoiding Common Errors in the Emergency Department. United States: Wolters Kluwer Health. 2017. p. 93-113.
3. Vincent JL, Weil MH. Fluid challenge revisited. Crit Care Med. 2006;34(5):1333-7.
4. Zampieri FG, Machado FR, Biondi RS, Freitas FG, Veiga VC, Figueiredo RC, et al. Effect of intravenous fluid treatment with a balanced solution vs 0.9% saline solution on mortality in critically ill patients: The BaSICS Randomized Clinical Trial. JAMA. 2021;326(9):818-29.
5. Hammond NE, Taylor C, Saxena M, Liu B, Finfer S, Glass P, et al. Resuscitation fluid use in Australian and New Zealand Intensive Care Units between 2007 and 2013. Intensive Care Medicine. 2015;41(9):1611-9.
6. Semler MW, Self WH, Wanderer JP, Wang L, Byrne DW, Collins SP, et al. Balanced crystalloids versus saline in noncritically ill adults. N Engl J Med. 2018;378(9):819-28.
7. Semler MW, Self WH, Wanderer JP, Ehrenfeld JM, Wang L, Byrne DW, et al. Balanced crystalloids versus saline in critically ill adults. N Engl J Med. 2018;378(9):829-39.
8. Young P, Bailey M, Beasley R, Henderson S, Mackle D, McArthur C, et al. Effect of a buffered crystalloid solution vs. saline on acute kidney injury among patients in the Intensive Care Unit: The SPLIT randomized clinical trial. J Am Med Assoc. 2015;314(16):1701-10.
9. Shaw AD, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. Ann Surg. 2012;255(5):821-9.

10. Yunos NM, Bellomo R, Taylor DM, Judkins S, Kerr F, Sutcliffe H, et al. Renal effects of an emergency department chloride-restrictive intravenous fluid strategy in patients admitted to hospital for more than 48 hours. Emerg Med Australasia. 2017;29(6):643-9.
11. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network; Wiedemann HP, Wheeler AP, Bernard GR, Taylor Thompson B, Hayden D, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006; 354(24):2564-75.
12. Balogh Z, McKinley BA, Cocanour CS, Kozar RA, Valdivia A, Matthew Sailors R, et al. Supranormal trauma resuscitation causes more cases of abdominal compartment syndrome. Arch Surg. 2003;138(6):637-43.
13. Kirkpatrick AW, Balogh Z, Ball CG, Ahmed N, Chun R, McBeth P, et al. The secondary abdominal compartment syndrome: Iatrogenic or unavoidable? J Am Coll Surg. 2006;202(4):668-79.
14. Salahuddin N, Sammani M, Hamdan A, Joseph M, Al-Nemary Y, Alquaiz R, et al. Fluid overload is an independent risk factor for acute kidney injury in critically ill patients: Results of a cohort study. BMC Nephrol. 2017;18:45.
15. Ostermann M, Straaten HMO, Forni LG. Fluid overload and acute kidney injury: Cause or consequence? Crit Care. 2015;19:443.
16. Angus DC, Barnato AE, Bell D, Bellomo R, Chong CR, Coats TJ, et al. A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators. Intensive Care Med. 2015;41(9):1549-60.

CHAPTER 28

Changing Strategy of Fluid Management in Four Phases of Septic Shock: Principles and Practice

Carlos Sanchez, Ahsina Jahan Lopa, Pablo Santillan

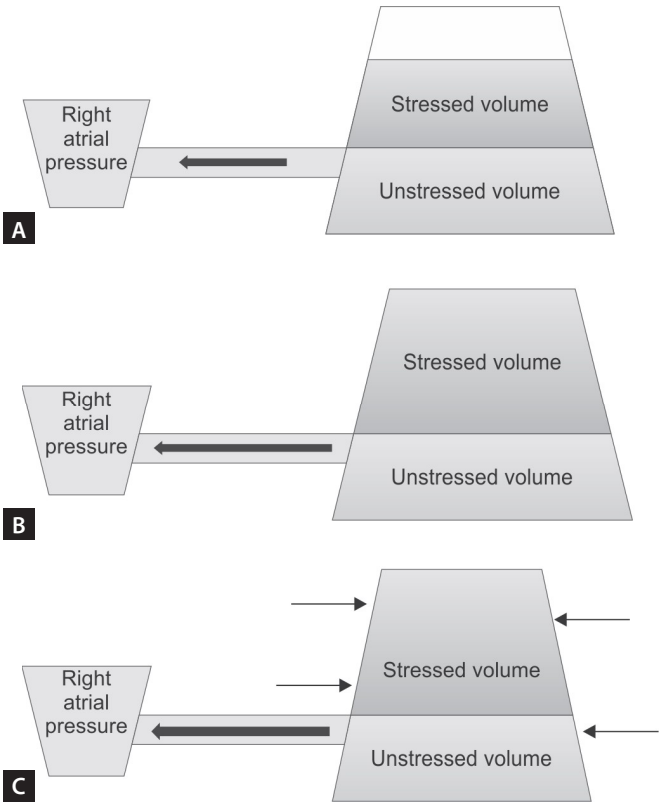
INTRODUCTION

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection secondary to inadequate perfusion.[1] Fluid therapy on patients with sepsis is key to responding to the patho-physiological mechanism of sepsis.[2]

Septic shock is a paravasoplegic state in which arterial and venous tone is affected, and the vascular smooth muscle contraction fails. This vasoplegic shock is believed to be because of increased expression of production of nitric oxide (NO) caused by inducible NO synthetase activation of KATP channels resulting in polarization changes of the muscle cell membrane, increased production of natriuretic peptides (which act synergistically with NO), and a relative lack of vasopressin.[3] Vascular dilatation results in systemic hypotension and possible hypoperfusion. Unstressed blood volume increases because of the venodilation, most in the splanchnic and cutaneous vascular beds, it could decrease preload and cardiac output.[4,5] As approximately 70% of the blood volume is within the venous system, venous blood volume changes affect the venous return more.[5] Based on this pathophysiological basis, it seems that there is no justification for administering fluids in the management of these patients, but rather vasopressors, since what there is, is a loss of vascular tone; however, intravenous fluids still seem to have an essential role in the management of septic shock.

To understand the mechanics of fluid resuscitation, we have to know that venous volume can be divided into unstressed and stressed volumes. The unstressed volume is the basal amount of blood; this volume does not affect intravascular pressure. Stressed volume refers to the volume that actively affects the venous pressure and the vascular wall stress and, consequently, the venous return. Therefore, early hemodynamic resuscitation management in sepsis recuperates the unstressed volume lost by vasodilation and endothelial damage.[2] The following resuscitation is filling the stressed volume affecting cardiac output. Filling the stressed volume is critical in resuscitation because an underload would affect tissue perfusion by an insufficient cardiac output, and an overload would cause a fluid leak and general edema[2,6,7] **(Figs. 1A to C)**.

As is known, in pediatric populations, the percentage of fluid accumulation is calculated by dividing the accumulated fluid balance in liters by the initial bodyweight of the patient and multiplying it by 100%. Fluid overload at any time during patient management is interpreted as a value of 10% of the positive fluid balance; this condition worsens the prognosis and increases mortality.[9-11]



Figs. 1A to C: Schematic venous return model. (A) Stressed volume responsible for mean systemic pressure; (B) Fluid bolus could augment venous return (preload); (C) Vasopressors could augment venous return (preload).[8]

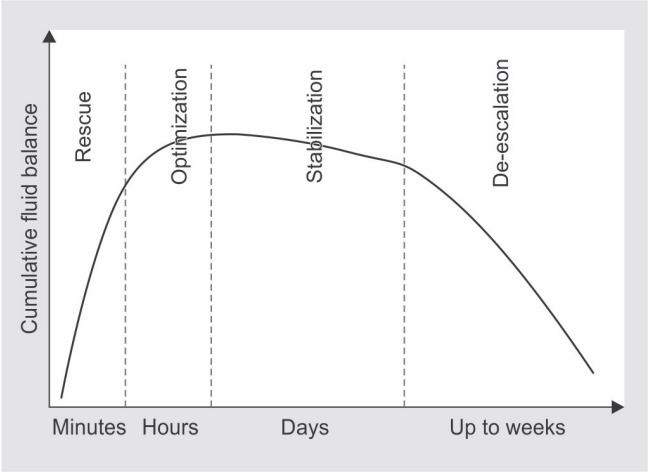


Fig. 2: Four phases of intravenous fluid therapy: Rescue, optimization, stabilization, and de-escalation.

BOX 1: Fluid terminology.

- *Fluid bolus*: A rapid infusion to correct hypotensive shock. It typically includes the infusion of at least 500 mL over a maximum of 15 minutes
- *Fluid challenge*: 100–200 mL over 5–10 minutes with a reassessment to optimize tissue perfusion
- *Fluid infusion*: Continuous delivery of intravenous (IV) fluids maintain homeostasis, replace losses, or prevent organ injury (e.g., prehydration before operation or contrast nephropathy)
- *Maintenance*: Fluid administration to provide fluids for patients who cannot meet their needs by oral route. This should be titrated to patient need and context and should include the replacement of ongoing losses. In a patient without ongoing losses, this should probably be no >1–2 mL/kg/h
- *Daily fluid balance*: Daily sum of all intakes and outputs
- *Cumulative fluid balance*: The total fluid accumulation over a set period of time
- *Fluid overload*: Cumulative fluid balance expressed as a proportion of baseline body weight. A value of 10% is associated with adverse outcomes

Current evidence has shown us that, as with other medications, the adverse effects of intravenous fluids depend on the type, dose of the fluid administered, and the patient's overall clinical condition when they are administered. This leads us to understand that, like any other medication, intravenous fluids have specific indications and contraindications without forgetting that they manage their pharmacokinetics and pharmacodynamics.[12-14]

In 2014, Hoste et al.[10] presented a conceptual model, "Four phases of intravenous fluid therapy," in which they seek to show that fluid therapy in patients with septic shock is not a constant and uniform process but rather a dynamic one that must take into account various elements. When administering fluids to a patient, the most important are: (1) comorbidities of the patient and (2) moment of fluid resuscitation in which the patient is. Thus, more personalized attention can be provided according to whether the patient could benefit from the administration of intravenous fluids and, if so, at what time and what amount?

Four phases of intravenous fluid therapy: Rescue, optimization, stabilization, and de-escalation (ROS-D) as proposed by Vincent and De Backer[15] or rescue, optimization, stabilization, and evacuation as proposed by Malbrain et al.[16] **(Fig. 2)**.

FIRST PHASE: RESUSCITATION/RESCUE

In this phase, the first water management of the patient is carried out, and it is the phase in which many times the greatest amount of intravenous fluids is administered since it is the moment when the patient is most affected by hemodynamics, such as macro-micro, the risk of mortality is high if not appropriately managed and the main strategy is the fluid bolus **(Box 1)**.

The Frank–Starling hemodynamic model explains how as the end-diastolic volume of the left ventricle (LV) increases (preload), the systolic volume (SV) of the LV increases until the optimal point of venous return is reached. The one that the SV experiences few variations.[17] This optimal preload point is related to the maximum degree of overlap of the actin-myosin filaments in the myocardial fiber. The administration of IV fluids will only improve SV if the following conditions are met: (1) that the fluid bolus increases the mean circulatory filling pressure more than it increases the CVP, which increases the gradient for venous return (preload) and (2) that both ventricles function adequately within the ascending branch of the Frank–Starling curve, that is, a possible response to increased preload.[18,19]

The Surviving Sepsis Campaign (SSC) and The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock agree on the administration of 30 mL/kg as an initial measure on any patient diagnosed with sepsis.[6,20] However, the SSC recommends that the 30 mL/kg be administered within a "1-hour bundle," but the Japanese Guideline keeps recommending an administration on a 3-hour range. This disagreement has become relevant over the last few years because of the surging literature criticizing the fluid overload-induced if the fluid therapy is too aggressive and the "one-size-fits-all" measure that contradicts the current biomedical practices that suggest a more personalized practice.[21] It has been demonstrated by a retrospective study in the New York State Department of Health that the time to completion of the fluid bolus was not associated with in-hospital mortality.[22]

Hopefully, several studies found that fluid-restrictive therapy is possible and will not affect the patient outcome.[7,23] It even seems not to affect the dose of norepinephrine used, serum lactate levels, or urinary output.[24] In 2018, the REFRESH clinical trial compared a fluid-restrictive therapy where they only administered a single 1,000 mL bolus and vasopressors to the trial group and a liberal group where they could continue administering as many liquids as the attending

clinician would consider plus the vasopressor therapy. As proposed, the local group had no damage and allowed a 30% reduction in total fluid administration in 24 hours.[23] Nevertheless, the mechanism is not precise. It is suspected to be because restrictive fluid resuscitation keeps the tissue in a low-pressure condition, avoiding harmful edema.[7]

A systematic review included 19,902 critically ill patients and compared the fluid restriction management strategy seeking to lead to a neutral or slightly negative fluid balance versus a less conservative strategy, that is, keeping the patient with a positive fluid balance for the third morning day. This review showed that the balance was lower at the end of one week; this led to lower mortality in the local group (24.7 vs. 33.2%).[25]

SECOND PHASE: OPTIMIZATION

In this phase, the patient is at a lower risk of death, but he is still a critically ill patient; he is in a state of "compensated shock," however he could still become unstable. At this point, what is sought is to administer the intravenous fluid that the patient may still need, this time with "fluid challenges," which must be monitored more closely to avoid fluid overload, seeking only to optimize cardiac function to improve tissue perfusion and thus reduce tissue hypoperfusion damage.

It is very important to distinguish between a "fluid bolus," a fluid volume of approximately 500 mL that is administered rapidly as part of rescue resuscitation and does not involve close miniature monitoring. A "fluid challenge" is a test where the effects of smaller volumes of fluids are administered more slowly and with more careful monitoring to avoid inadvertent fluid overload.

Two tools that can be used to determine which patient might respond to a fluid challenge are mentioned here.

Passive Leg Raising Test

Passive leg raising (PLR) test has the ability to predict the response to the administration of IV fluids. This test consists of changing the patient's position from semi-reclined to a position in which the legs are raised 45° from the bed, and the trunk and head are kept horizontal. This maneuver seeks to mobilize the volume of the vascular system of the lower limbs to the inferior vena cava, thereby increasing the preload, simulating the administration of fluids but without the risk of overloading the vascular system in the event of no response.[26] The passive leg elevation test is considered positive, that is, a predictor of a favorable response to the administration of IV fluids when, after approximately 90 seconds with the legs raised, there is a 10% increase in stroke volume and cardiac output.

Although the PLR is a maneuver that has been described to be guided by measuring cardiac output, it is very versatile and can be assessed in several noninvasive ways; one of them is through the variation of end-tidal carbon dioxide, Tugga Alai found that an absolute increase of $EtCO_2$ ≥2.5 mm Hg or 5% during PLR was associated with volume responsiveness.[27] Toupin et al. confirmed that the combination of $\Delta EtCO_2$ ≥2 mm Hg and a change in systolic blood pressure ≥10 mm Hg induced by PLR was predictive of fluid responsiveness in paralyzed cardiac surgery patients receiving mechanical ventilation.[28]

Burton et al. described the effects of PLR on plethysmographic oxygen saturation signal in critically ill patients as a tool to identify fluid responsiveness; if perfusion index (PI) increases by >9%, the maneuver is considered positive.[29]

End-expiratory Occlusion Test

End-expiratory occlusion test is a test of the ability to respond to IV administration of fluids; it consists of pausing end-expiratory for 15 seconds and assessing whether changes in cardiac output were present at that time. The test increases cardiac preload by stopping the cyclical impediment of venous return that occurs with each insufflation of the ventilator. An increase in the cardiac output above 5% indicates a possible favorable response to fluid administration.[30-32] If the test is performed with ultrasonography, it is better to carry out an end-inspiratory pause because the diagnostic point of changes in stroke volume is more sensitive with the precision of echocardiography.[33]

THIRD PHASE: STABILIZATION

In this phase, the patient is usually stable, so their use of IV fluids is usually only used to meet the basic hydric needs and the replacement of losses, whether physiological or pathological. In this stage, the patient is not in a state of shock; his hemodynamics are usually quite compensated. Therefore, the risk of death is lower than in the previous phases.

Fluid overload has become very relevant because it has been demonstrated that it can be even more damaging than under-load.[7,16,21] SOAP study demonstrates that the positive cumulative balance is an independent factor associated with mortality in these patients.[34] Indeed, the iatrogenic edema causes organ dysfunction in various cardiac, vascular, renal, central nervous systems, respiratory, gastrointestinal, and hepatic systems[21] **(Fig. 3)**.

"Maintenance fluids" are used mainly to cover daily needs for fluids but also for electrolytes; the final prescription of the fluid intake must take into account the other fluids and electrolytes that the patient receives, either in the dilutions of medications, nutrition, as well. Enteral as parenteral, if this contribution is sufficient to cover daily needs, it is not necessary to indicate a "maintenance hydration."

Lung ultrasound can be helpful to detect excess extravascular lung water (EVLW) and thus assess fluid tolerance. Transpulmonary thermodilution is the gold standard to measure EVLW, but this method requires specialized equipment. Traditionally, chest radiographs have been used

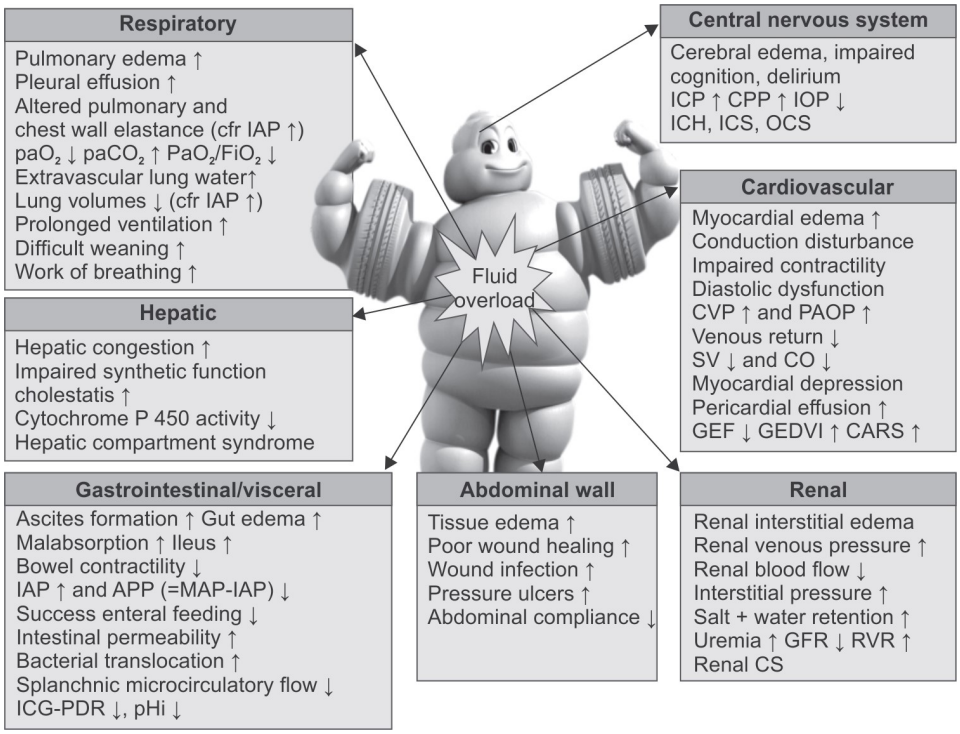


Fig. 3: Malbrain et al. description of how the various systems are affected with edema caused by excess fluids use.
(APP: abdominal perfusion pressure; CARS: compensatory anti-inflammatory response syndrome; CO: cardiac output; CPP: cerebral perfusion pressure; CS: cortical stiffness; CVP: central venous pressure; ICG-PDR: indocyanine green-plasma disappearance rate; ICH: intracerebral hemorrhage; ICP: intracranial pressure; ICS: inhaled corticosteroid; IOP: intraocular pressure; OCS: oral corticosteroid; PAOP: pulmonary artery occlusion pressure; MAP: mean arterial pressure; IAP: intra-abdominal pressure; GFR: glomerular filtration rate; GEF: global ejection fraction; GEDVI: global end-diastolic volume index; RVR: renal vascular resistance; SV: systolic volume)

to evaluate EVLW, but unfortunately, the correlation between radiographic changes and changes in EVLW is relatively poor. In comparison to both the aforementioned techniques, lung ultrasound is noninvasive, devoid of radiation, easy to learn, reproducible, and already frequently performed in many ICUs.[35] Volpicelli and colleagues measured EVLW in 32 ventilated general intensive care unit (ICU) patients with transpulmonary thermodilution and found that the absence of B-lines (A-line pattern) was associated with low levels of EVLW (10 mL/kg or less; 81% sensitivity, 91% specificity).[36] With three positive chest quadrants ("positive" defined as three or more B-lines within the quadrant), the sensitivity and specificity were 100 and 70%, respectively, for the detection of EVLW index >10 mL/kg (a value associated with pulmonary edema).[37] B-lines can give guidance about the etiology and are by no means specific for EVLW.

FOURTH PHASE: EVACUATION

This term was suggested in 2012 publications for the first time[38] and was finally coined in the literature in 2014.[10] This phase is characterized by strategies to achieve late elimination of excess fluids according to an established objective and maintain hemodynamic stability; this objective is the accumulated balance of neutral or slightly negative fluids.

Goal-directed delayed fluid elimination is based on the elimination.

Active fluid formation with diuretics to achieve a high diuretic rate would allow us to achieve our hemodynamic goal more aggressively. Another type of therapy to implement is renal replacement therapy (RRT) (ultrafiltration), either intermittent or continuous.[10,39,40]

Late conservative fluid management is a less aggressive fluid management strategy after resuscitation and maintenance to decrease and, if possible, avoid fluid overload. This conservative strategy of delayed fluid management is defined as a negative fluid balance for at least two consecutive days within the first week of stay in the ICU; this is a therapeutic objective directly related to increased survival in this group of patients.[10]

Perhaps one of the most significant risks in this phase is that the patient is taken into a negative balance so aggressively that it leads to a state of dehydration with hypotension and a worsening of the clinical condition. If it is necessary to administer to restore blood volume in this phase, the use of albumin seems to have positive effects on the integrity of the vessel wall; it facilitates the achievement of a negative fluid balance in hypoalbuminemia and is less likely to cause renal damage due to fluid overload.[41]

It is even possible to combine different therapies; in 2012, Cordemans et al. proposed PAL-treatment, which consisted

of a series of measures to be implemented in patients with acute lung injury and increased intra-abdominal pressure to achieve a negative fluid balance a little faster in these patients. PAL-treatment combines high levels of positive end-expiratory pressure, small volume resuscitation with hyperoncotic albumin, and fluid removal with furosemide or ultrafiltration; this strategy improved clinical outcomes without compromising organ function in patients with acute lung injury due to a negative fluid balance, a reduction of extravascular lung water and intra-abdominal pressure.[38]

WHAT TYPE OF FLUID SHOULD WE USE?

Although the BaSICS trial concluded that among critically ill patients requiring fluid challenges, use of a balanced solution compared with 0.9% saline solution did not significantly reduce 90-day mortality, and the findings do not support the use of this balanced solution,[42] current Surviving Sepsis Campaign (SSC) guidelines recommend the use of balanced crystalloids against the use of normal saline (unbuffered crystalloid solution) or colloids.[6,20] Buffered solutions vary slightly in their composition but typically have a pH, chloride concentration, and overall osmolality closer to human plasma than saline solutions.[2] The recommendation against the use of saline for resuscitation in sepsis is a discussed issue that seems to have finally concluded. In 2015, the SPLIT trial compared 0.9% saline versus Plasma-Lyte 148 (PL-148) (a buffered crystalloid) on a heterogeneous population of ICU patients. Even though saline was associated with hyperchloremia and metabolic acidosis, there was no difference in the outcome.[43] In 2017, the SALT pilot trial compared between 0.9 saline and balanced crystalloids (lactated Ringer's solution or Plasma-Lyte A), found no difference in the outcomes. They only acknowledged that patients exposed to larger volumes of saline appeared to experience more major adverse kidney events.[44] The main issue with these studies is that they included a heterogeneous population and not only sepsis patients. Finally, the SMART trial published in 2019 compared the two solutions on 1,641 patients admitted to the ICU diagnosed with sepsis. This trial demonstrated that balanced solutions were associated with reduced 30-day hospital mortality, major kidney events, increased ventilation, vasopressor, and RRT-free days.[45] The proposed mechanism by which balanced crystalloids may result in better outcomes than saline is not entirely understood, but it is suspected of the hyperchloremia and acidosis caused by saline, causing vasoconstriction and inflammation of renal vasculature.[45]

There are three important categories of colloids available: Albumin, hydroxyethyl starch (HES), and gelatin. This substance should act as uncritically active fluids that should counter the capillary leak and increase the inward flux of fluids toward the vasculature. Still, in sepsis conditions, the loss of the endothelial glycocalyx layer should allow uncritically active molecules to equilibrate themselves between physiological spaces.[2] Nonetheless, we should not generalize between colloids. Also, albumin is recommended only in patients who have already received an essential volume of crystalloids, and it is not recommended to use it as standard initial treatment.[6,20] Accordingly, ALBIOS, the largest trial to the date studying the use of albumin in septic patients, reported a decreased mortality only in the subgroup of septic shock patients with hypoalbuminemia.[46] Contrarily, the use of HES is strongly contraindicated.[6,20]

SPECIAL SCENARIO: PREGNANCY

The Society for Maternal-Fetal Medicine gave an approach to managing sepsis in pregnant or puerperal patients.[47] The SSC recommends initial intravenous fluid resuscitation at a rate of 30 mL/kg.[6] This recommendation is modified to 20 mL/kg by the Royal College of Obstetricians and Gynaecologists[48,49] due to an increased risk of pulmonary edema in pregnancy caused by decreased colloid oncotic pressure. PLR may not be helpful in patients carrying a third-trimester pregnancy because the uterus may compress the inferior vena cava, and venous blood from the lower limb would not return to the cardiac cavities. In these cases, it is recommended to administer a small bolus of fluid (250–500 mL) to evaluate any changes in cardiac output.[47]

REFERENCES

1. Singer M, Deutschman C, Seymour C, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-10.
2. Best MW, Jabaley CS. Fluid management in septic shock: a review of physiology, goal-directed therapy, fluid dose, and selection. Curr Anesthesiol Rep. 2019:9(2):15157.
3. Landry DW, Oliver JA. Pathogenesis of vasodilatory shock. N Engl J Med. 2001;345(8):588-95.
4. Gelman S. Venous function and central venous pressure: a physiologic story. Anesthesiol. 2008;108(4):735-48.
5. Peters J, MackGW, Lister G. The importance of the peripheral circulation in critical illnesses. Intensive Care Med. 2001; 27(9):1446-58.
6. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith C, French C, et al. Surviving sepsis campaign: international guidelines for the management of sepsis and septic shock 2021. Intensive Care Med. 2021;47(11):1181-247.
7. Jiang S, Wu M, Lu X, Zhong Y, Kang X, Song Y, et al. Is restrictive fluid resuscitation beneficial not only for hemorrhagic shock but also for septic shock?: A meta-analysis. Medicine. 2021;100(12);e25143.
8. Spiegel R. Stressed vs. unstressed volume and its relevance to critical care practitioners. Clin Exp Emerg Med. 2016;3(1):52-4.
9. O'Connor ME, Prowle JR. Fluid overload. Crit Care Clin. 2015;31(4):803-21.
10. Hoste EA, Maitland K, Brudney CS, Mehta R, Vincent JL, Yates D, et al. Four phases of intravenous fluid therapy: a conceptual model. Br J Anaesth. 2014;113(5):740-7.

11. Vaara ST, Korhonen AM, Kaukonen KM, Nisula S, Inkinen O, Hoppu S, et al. Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study. Crit Care. 2012;16(5): R197.
12. Myburgh JA, Mythen MG. Resuscitation fluids. N Engl J Med. 2013;369(13):1243-51.
13. SAFE Study Investigators 1; Australian and New Zealand Intensive Care Society Clinical Trials Group; Australian Red Cross Blood Service; George Institute for International Health; Myburgh J, Cooper DJ, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med. 2007;357(9):874-84.
14. Reinhart K, Perner A, Sprung CL, Jaeschke R, Schortgen F, Johan Groeneveld AB, et al. Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. Intensive Care Med. 2012;38(3):368-83.
15. Vincent JL, De Backer D. Circulatory shock. N Engl J Med. 2013;369(18):1726-34.
16. Malbrain MLNG, Van Regenmortel N, Saugel B, De Tavernier B, Van Gaal PJ, Joannes-Boyau O, et al. Principles of fluid management and stewardship in septic shock: it is time to consider the four Ds and the four phases of fluid therapy. Ann Intensive Care. 2018;8(1):1-16.
17. Starling EH. The Linacre Lecture on the Law of the Heart, Given at Cambridge, 1915. London: Longmans; 1918. p. 27.
18. Marik PE. The physiology of volume resuscitation. Curr Anesthesiol Rep. 2014;4:353-9.
19. Cecconi M, Aya HD, Geisen M, Ebm C, Fletcher N, Michael Grounds R, et al. Changes in the mean systemic filling pressure during a fluid challenge in postsurgical intensive care patients. Intensive Care Med. 2013;39(7):1299-305.
20. Egi M, Ogura H, Yatabe T, Atagi K, Inoue S, Iba T, et al. The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020 (J-SSCG 2020). Acute Med Surg. 2021;8(1).
21. Marik P, Byrne L, van. Haren, F. Fluid resuscitation in sepsis: the great 30 mL per kg hoax. J Thorac Dis. 2020;12(Suppl 1): S37-47.
22. Seymour C, Rosengart M. (2015). Septic shock: advances in diagnosis and treatment. JAMA. 2015;314(7):708-17.
23. Macdonald S, Keijzers G, Taylor D, Kinnear F, Arendts G, Fatovich DM, Restricted fluid resuscitation in suspected sepsis-associated hypotension (REFRESH): a pilot randomised controlled trial. Intensive Care Med. 2018;44(12): 2070-8.
24. Hjortrup PB, Haase N, Bundgaard H, Thomsen SL, Winding R, Pettilä V, et al; Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. Intensive Care Med. 2016;42:1695-705.
25. Malbrain ML, Marik PE, Witters I, Cordemans C, Kirkpatrick AW, Roberts DJ, et al. Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. Anaesthesiol Intensive Ther. 2014;46(5):361-80.
26. Monnet X, Teboul JL. Passive leg raising: five rules, not a drop of fluid! Crit Care. 2015;19(1):18.
27. Taggu A. Can passive leg raising (PLR) test induced end-tidal carbon dioxide ($EtCO_2$) changes predict fluid responsiveness in mechanically ventilated patients?. Crit Care. 2015;148(4_MeetingAbstracts):310A.
28. Toupin F, Clairoux A, Deschamps A, Lebon JS, Lamarche Y, Lambert J, et al. Assessment of fluid responsiveness with end-tidal carbon dioxide using a simplified passive leg raising maneuver: a prospective observational study. Can J Anesth/J Can Anesth. 2016;63(9):1033-41.
29. Beurton A, Teboul JL, Gavelli F, Gonzalez FA, Girotto V, Galarza L, et al. The effects of passive leg raising may be detected by the plethysmographic oxygen saturation signal in critically ill patients. Crit Care. 2019;23(1):19.
30. Monnet X, Osman D, Ridel C, Lamia B, Richard C, Teboul JL. Predicting volume responsiveness by using the end-expiratory occlusion in mechanically ventilated intensive care unit patients. Crit Care Med. 2009;37(3):951-6.
31. Monnet X, Dres M, Ferre A, Le Teuff G, Jozwiak M, Bleibtreu A, et al. Prediction of fluid responsiveness by a continuous non-invasive assessment of arterial pressure in critically ill patients: comparison with four other dynamic indices. Br J Anaesth. 2012;109(3):330-8.
32. Biais M, Larghi M, Henriot J, de Courson H, Sesay M, Nouette-Gaulain K. End-expiratory occlusion test predicts fluid responsiveness in patients with protective ventilation in the operating room. Anesth Analg. 2017;125(6):1889-95.
33. Jozwiak M, Depart F, Teboul JL, Alphonsine JE, Lai C, Richard C, et al.Predicting fluid responsiveness in critically ill patients by using combined end-expiratory and end-inspiratory occlusions with echocardiography. Crit Care Med. 2017;45(11):e1131-8.
34. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et al. Sepsis occurrence in acutely ill patients investigators sepsis in European intensive care units: results of the SOAP study, Crit Care Med. 2006;34(2):344-53.
35. Anile A, Russo J, Castiglione G, Volpicelli G. A simplified lung ultrasound approach to detect increased extravascular lung water in critically ill patients. Crit Ultrasound J. 2017;13.
36. Volpicelli G, Skurzak S, Boero E, Carpinteri G, Tengattini M, Stefanone V, et al. Lung ultrasound predicts well extravascular lung water but is of limited usefulness in the prediction of wedge pressure. Anesthesiology. 2014;121(2):320-7.
37. Engelhard P, Rademacher S, Nee J, Hasper D, Engert U, Jörres A, et al. Simplified lung ultrasound protocol shows an excellent prediction of extravascular lung water in ventilated intensive care patients. Crit Care. 2015;19(1):36.
38. Cordemans C, De Laet I, Van Regenmortel N, Schoonheydt K, Dits H, Martin G, et al. Aiming for a negative fluid balance in patients with acute lung injury and increased intra-abdominal pressure: a pilot study looking at the effects of PAL-treatment. Ann Intensive Care. 2012;2(Suppl 1):S15.
39. Chen C, Kollef MH. Targeted fluid minimization following initial resuscitation in septic shock: A pilot study. Chest. 2015;148:1462-9.
40. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network; Wiedemann HP, Wheeler AP, Bernard GR, B Thompson T, Hayden D, et al; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network: Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354(24): 2564-75.

41. Vincent JL, De Backer D, Wiedermann CJ. Fluid management in sepsis: the potential beneficial effects of albumin. J Crit Care. 2016;35:161-7.
42. Zampieri FG, Machado FR, Biondi RS, Freitas FGR, Veiga VC, Figueiredo RC, et al. Effect of intravenous fluid treatment with a balanced solution vs 0.9% saline solution on mortality in critically ill patients: The BaSICS Randomized Clinical Trial. JAMA. 2021;326(9):1-12
43. Oung P, Bailey M, Beasley R, Henderson S, Mackle D, McArthur C, Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: the SPLIT Randomized Clinical Trial. JAMA. 2015;314(16):1701-10.
44. Semler M, Wanderer J, Ehrenfeld J, Stollings J, Self W, Siew E, et al. Balanced crystalloids versus saline in the intensive care unit. The SALT Randomized Trial. Am J Resp Crit Care Med. 2017;195(10):1362-72.
45. Brown R, Wang L, Coston T, Krishnan N, Casey J, Wanderer J, et al. Balanced crystalloids versus saline in sepsis. A secondary analysis of the SMART Clinical Trial. Am J Resp Crit Care Med. 2019;200(12):1487-95.
46. Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med. 2014;370(15):1412-21.
47. Plante LA, Pacheco LD, Louis JM. SMFM Consult Series #47: Sepsis during pregnancy and the puerperium. Am J Obstet Gynecol. 2019;220(4):B2-10.
48. Royal College of Obstetricians and Gynaecologists. Bacterial Sepsis in Pregnancy. Green-top Guideline No. 64a. London: RCOG; 2012.
49. Royal College of Obstetricians and Gynaecologists. Bacterial Sepsis following Pregnancy. Green-top Guideline No.64b. London: RCOG; 2012.

29

CHAPTER

Hyperchloremia Side Effects

Mahfouz Sharapi, Ahsina Jahan Lopa, Saad Mahdy

INTRODUCTION

Chloride is an anion that predominates in the extracellular fluid (ECF) compartment. It plays a crucial role in water distribution in the body, and it enters cells to maintain the anion-cation balance. Chloride is also responsible for the acid–base balance in the body, regulating body fluids, and transmission of nerve impulses. It also plays an important function in variable physiological functions such as muscular activity and immunomodulation.[1] The normal level of chloride in blood is between 96 and 106 milliequivalents per liter. When the level of chloride exceeds 106 milliequivalents, hyperchloremia exists. Chloride is regulated in the body by the kidney.

Excessive chloride in plasma is associated with a reduction of the renal blood flow (RBF) and increased interstitial edema in both the gastrointestinal tract (GIT) and the kidney.[2,3] There is clear evidence that excess chloride is associated with an increase in mortality in critically ill patients and there is an overall reduction of the recovery and survival in those who develop acute kidney dysfunction.[4,5] Hyperchloremia is a common entity in critical care settings that have been overlooked for decades and recently it got much attention since 0.9% saline is one of the most common fluids administered in hospitals. Normal saline (0.9% sodium) contains 154 mmol/L of both sodium and chloride. Balanced crystalloids such as Hartmann are solutions in which chloride anions are replaced with bicarbonate or buffers to maintain the acid–base balance. Hartmann solution contains 112 mmol/L of chloride, and it is preferred in resuscitation and associated with less incidence of hyperchloremic metabolic acidosis in comparison to saline-based solutions.[6,7]

There is a concept proposed by Canadian physiologist, Peter Stewart, in 1981 and is known as the Stewart approach, it is a quantitative approach to acid–base chemistry. This approach describes a mathematical explanation of different variables which control H^+ in different body fluids. This approach focuses on the concept that pH is not just controlled by H^+ and HCO^{3+} (Hasselbach approach), but many other variables are involved to control the acidity. Some are dependent variables such as H^+, OH^-, HCO^{3-}, CO_3^{2-}, HA (weak acid), and A– (weak anions). The independent variables include pCO_2, ATOT (total weak nonvolatile acids), and SID (strong ion difference).[8,9]

Strong cations include Na^+, K^+, Ca^{2+}, and Mg^{2+}, meanwhile strong anions include Cl^- and SO_4^{2-}. SID is the difference between both cations and anions and its normal plasma level in humans is 42 mEq/L. In normal circumstances, both positive and negative ions in a solution must be in an equilibrium state and SID = 0 (SID = 0). An increase of SID >0 means alkalosis and vice versa for acidosis. So to change the SID, there should be strong ion changes such as increase chloride levels associated with reduced SID and acidosis, a typical scenario when normal saline is used excessively where there is a relative increase in chloride compared to Na.[8,10]

In March 2011, the British Association for Parenteral and Enteral Nutrition (BAPEN) published guidance on prescribing fluid to avoid fluid or sodium overload postoperatively. These recommendations were introduced because of increasing the risk of hyperchloremic acidosis in the perioperative settings. They recommended using a balanced solution such as Hartmann solution, except if there is evidence of hypochloremia as in vomiting.[7]

Hyperchloremia can be classified by severity into two main categories: Moderate (CL 106–110 mmol/L) and severe (CL >110 mmol/L). There is a second classification according to the onset time of electrolyte imbalance and this includes hospital-acquired where hyperchloremia starts after 24 hours of admission to the health care facility.[11] There is a common confusion between hyperchloremia as an entity and hyperchloremic metabolic acidosis. Hyperchloremic metabolic acidosis has two features, there is a decrease in both blood pH and bicarbonate levels, accompanied by an increase in blood chloride levels.[12]

ETIOLOGY OF HYPERCHLOREMIA

- Excessive loss of electrolyte-free fluid results in a higher concentration of ions like chloride and sodium in the body. Examples of fluid loss may be seen in the following circumstances:
  - Sweating from exercise and fever
  - Burns
  - Inadequate water intake
  - Hypermetabolic state and diabetes insipidus
  - Diarrhea and renal tubular acidosis (loss of bicarbonate with an exchange for chloride than pure water movement).
- Hypotonic fluid loss due to loss of electrolyte fluid. In normal circumstances, water will move from low to high ionic concentrations. In this case, the water is being excreted in the urine; therefore, less water is available to dilute these areas of high ion concentration. Examples of this scenario are:
  - Diuretic use (specifically loop diuretics and aquaretics).
  - Vomiting burns and kidney failure.
- Excessive sodium chloride intake.

It can be due to dietary intake or intravenous (IV) fluid administration in hospital settings. This can lead to hypertension, edema, and cardiovascular dysfunction.[13]

SYMPTOMS OF HYPERCHLOREMIA

Hyperchloremia may not have any notable symptoms and will be detected only by laboratory testing. The causes of hyperchloremia may cause symptoms and these include the following:

- Dehydration from gastrointestinal losses and sweating.
- Hypertension and cardiovascular dysfunction, related to increased sodium chloride load.
- Kussmaul breathing can be multifactorial due to high ion concentrations, loss of fluids, or kidney failure.
- Hyperchloremic metabolic acidosis, due to severe diarrhea and kidney failure. Respiratory alkalosis due to renal dysfunction.

MECHANISM OF HYPERCHLOREMIA

Chloride level in the blood is regulated in the kidney. Reabsorption of chloride begins in the proximal tubules and approximately 60% of chloride is absorbed here. In hyperchloremic conditions, there is an increase of chloride into the interstitial fluid and consequently into the blood capillaries. As a result, the filtrate of chloride is reduced, therefore, there is a decrease in the amount of chloride that is excreted in the urine.[14] Chloride reabsorption occurs in two phases in the proximal tubule. In the first phase, reabsorption of the organic solutes (such as phosphates, amino acids, glucose, and anions), sodium ions, and hydronium ions from the filtrate fluid into the interstitial fluid occurs. In phase 2, there is a diffusion of chloride along the concentration gradient.[13] One of the possible mechanisms of hyperchloremia, the chloride transporter proteins along the nephron are reduced. Examples of these proteins include sodium-potassium-2 chloride co-transporter, chloride anion exchangers, and chloride channels. A second mechanism is a reduction of the activity of these transporters leading to a depletion in concentration gradient. This concentration gradient depletion would allow for the passive diffusion of chloride in and out the tubule.[13]

HYPERCHLOREMIA SIDE EFFECTS

Effects of Chloride on Renal Function

Several studies confirmed that hyperchloremia induces renal afferent vasoconstriction and reduced glomerular filtration. Chloride also affects renin secretion and its macula densa concentration is inversely related to renin–angiotensin–aldosterone system (RAAS) activation.[15] A recently published trial does not confirm the vasoconstriction effect on the renal blood vessels.[16]

There are a large number of studies in the literature that focus on the development of acute kidney injury (AKI) and the need for renal replacement therapy (RRT) in those patients who received a large volume of chloride-rich fluids. This area is still debatable due to the heterogenicity in most of the literature.[17]

In a good number of studies, there are no identifiable changes in the serum creatinine or incidence of AKI rate in intensive care unit (ICU) patients.[18] But in others, there is an increase in the incidence of AKI and need for RRT.[19] Meanwhile, there may be a large number of confounding factors that can affect the sensitivity analysis if these studies, so far the debate is not concluded.[20]

However, infusion of chloride-rich fluids is associated with an increased risk of AKI, this is a conclusion of a more recent meta-analysis including both randomized and nonrandomized trials.[21] In another study, there is a higher incidence of AKI in those with increased serum chloride alone independent from IV fluid administration.[22] However, there is only a minimal number of studies that focus on serum chloride alone irrelevant of fluid administration.

In conclusion, despite the number of studies focusing on the development of AKI and need for RRT in patients receiving chloride-rich infusions, the debate is far from being decided due to the large heterogeneity in the available literature.

Cardiovascular Function

Chloride-rich infusions may be associated with hemodynamic instability. This was first described in a study by Kellum and coworkers in a rodent sepsis model.[23] In this model,

hyperchloremia and acidosis lead to hypotension. This effect was supported by additional studies which showed a decrease in mean arterial blood pressure and cardiac index in rats with abdominal sepsis.[24] There is also an increase of vasopressor requirement which is volume dependent.

In preclinical models, it was shown that simple hyperchloremia may increase blood pressure and only hyperchloremia associated with acidosis contributes to the reduction of blood pressures. So, the effect of hyperchloremia on the cardiovascular system is very crucial for clinicians for the abovementioned explanation.

Inflammation and Coagulation

The systemic inflammatory markers were elevated in several animal models after administration of chloride-rich fluids. This was seen in sepsis and trauma models.[25] However, the elevated inflammatory markers may be related to sodium, not chloride, so further clarification is still required. There is also some evidence that high chloride may affect both coagulation cascade and coagulation factors.[26] In several trials and meta- analyses, there has been increased blood products administration in those given chloride-rich fluids.[21]

Chloride Effect on Gastrointestinal Function

Chloride-rich solutions produce impairment of gastric mucosa perfusion, and this subsequently may significantly cause nausea and vomiting in surgical patients, especially in old age.[26]

Mortality and Other Clinical Outcomes

There is clear evidence of increased mortality in critically ill patients in whom chloride-rich solution was used as reported by Krajewski et al. in a meta-analysis comparing high versus low chloride contents in the perioperative resuscitation.[21] However, in four other large-scale multicenter trials and a recent meta-analysis, this evidence is not confirmed.[21] Hyperchloremia was associated with increased in-hospital mortality (after 72 hours admission to ICU) or if there is a rise in Cl^- levels of >5 mmol/L.[4] There is a gradual increase in-hospital mortality with each 10 mmol/L increase of the level of chloride.[27]

CONCLUSION

Chloride is the main anion in ECF and has an important role in anion-cations balance. Hyperchloremic metabolic acidosis should be differentiated from hyperchloremia. Several possible factors lead to the development of hyperchloremia, these include excessive loss of electrolyte-free fluid as in burns, hypotonic fluid loss as in diarrhea and iatrogenic excessive sodium intake, especially in perioperative settings. Several mechanisms of action could explain why hyperchloremia develops.

Hyperchloremia itself may not have any symptoms and is occasionally detected in the laboratory, and the causes of hyperchloremia may cause symptoms such as weakness due to loss of fluids via GIT losses or high sugar levels in diabetics. Hyperchloremia does have a multitude of side effects. It can affect the renal, cardiovascular, and it is associated with overall patient mortality.

REFERENCES

1. Berend K, van Hulsteijn LH, Gans ROB. Chloride: the queen of electrolytes? Eur J Intern Med. 2012;23(3):203-11.
2. Hansen PB, Jensen BL, Skøtt O. Chloride regulates afferent arteriolar contraction in response to depolarization. Hypertension. 1998;32(6):1066-70.
3. Shah SK, Uray KS, Stewart RH, Laine GA, Cox CS. Resuscitation-induced intestinal edema and related dysfunction: State of the science. J Surg Res. 2011;166(1):120-30.
4. Neyra JA, Canepa-Escaro F, Li X, Manllo J, Adams-Huet B, Yee J, et al. Association of hyperchloremia with hospital mortality in critically ill septic patients. Crit Care Med. 2015;43(9):1938-44.
5. Bouchard J, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int. 2009;76(4):422-7.
6. Semler MW, Kellum JA. Balanced Crystalloid Solutions. Am J Respir Crit Care Med. 2019;199(8):952-60.
7. Powell-tuck J, Gosling P, Dileep N, Allison SP, Carlson GL, Lewington AJ, et al. British Consensus Guidelines on intravenous fluid therapy for adult surgical patients. Br Assoc Parenter Enter Nutr. 2011;1-50.
8. Morgan TJ. The Stewart approach—one clinician's perspective. Clin Biochem Rev. 2009;30(2):41-54.
9. Quintard H, Hubert S, Ichai C. [What is the contribution of Stewart's concept in acid-base disorders analysis?]. Ann Fr Anesth Reanim. 2007;26(5):423-33.
10. Lee YS. Clinical significance of strong ion gap: between ICU and hemodialysis patients with metabolic acidosis. Electrolyte Blood Press. 2007;5(1):1-8.
11. Lombardi G, Ferraro PM, Bargagli M, Naticchia A, D'Alonzo S, Gambaro G. Hyperchloremia and acute kidney injury: a retrospective observational cohort study on a general mixed medical-surgical not ICU-hospitalized population. Intern Emerg Med. 2020;15(2):273-80.
12. Mythen MG. Hyperchloremic acidosis: Pathophysiology and clinical impact. Transfus Altern Transfus Med. 2003; 5(s1):33-33.
13. Hall, J, Guyton A. Textbook of Medical Physiology. Amsterdam: Elsevier; 2016.
14. Nagami GT. Hyperchloremia—Why and how. Nefrologia. 2016;36(4):347-53.
15. Wilcox CS. Regulation of renal blood flow by plasma chloride. J Clin Invest. 1983;71(3):726-35.
16. Olivier P-Y, Beloncle F, Seegers V, Tabka M, Renou de La Bourdonnaye M, Mercat A, et al. Assessment of renal hemodynamic toxicity of fluid challenge with 0.9% NaCl

compared to balanced crystalloid (PlasmaLyte®) in a rat model with severe sepsis. Ann Intensive Care. 2017;7(1):66.
17. Pfortmueller CA, Uehlinger D, Haehling S Von, Schefold JC. Serum chloride levels in critical illness—the hidden story. Intensive Care Med Exp. 2018;6:10.
18. Young P, Bailey M, Beasley R, Henderson S, Mackle D, McArthur C, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: The SPLIT Randomized Clinical Trial. JAMA. 2015;314(16):1701-10.
19. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA. 2012;308(15):1566-72.
20. Yunos NM, Bellomo R, Glassford N, Sutcliffe H, Lam Q, Bailey M. Chloride-liberal vs. chloride-restrictive intravenous fluid administration and acute kidney injury: an extended analysis. Intensive Care Med. 2015;41(2):257-64.
21. Krajewski ML, Raghunathan K, Paluszkiewicz SM, Schermer CR, Shaw AD. Meta-analysis of high- versus low-chloride content in perioperative and critical care fluid resuscitation. Br J Surg. 2015;102(1):24-36.
22. Zhang Z, Xu X, Fan H, Li D, Deng H. Higher serum chloride concentrations are associated with acute kidney injury in unselected critically ill patients. BMC Nephrol. 2013;14(1):235.
23. Kellum JA, Song M, Venkataraman R. Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. Chest. 2004;125(1):243-8.
24. Orbegozo D, Su F, Santacruz C, He X, Hosokawa K, Creteur J, et al. Effects of different crystalloid solutions on hemodynamics, peripheral perfusion, and the microcirculation in experimental abdominal sepsis. Anesthesiology. 2016;125(4):744-54.
25. Soussi S, Ferry A, Chaussard M, Legrand M. Chloride toxicity in critically ill patients: What's the evidence? Anaesth Crit Care Pain Med. 2017;36(2):125-30.
26. Phillips CR, Vinecore K, Hagg DS, Sawai RS, Differding JA, Watters JM, et al. Resuscitation of haemorrhagic shock with normal saline vs. lactated Ringer's: effects on oxygenation, extravascular lung water and haemodynamics. Crit Care. 2009;13(2):R30.
27. Shaw AD, Raghunathan K, Peyerl FW, Munson SH, Paluszkiewicz SM, Schermer CR. Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. Intensive Care Med. 2014;40(12):1897-905.

CHAPTER 30

Albumin Misuse in Intensive Care Unit

Deepak Vijayan, Sree Bhushan Raju

INTRODUCTION

Albumin is a major plasma protein produced by the liver and constitutes almost half of the serum protein compartment. Normal serum albumin level is 3.5–5 g/100 mL. The half-life of albumin is approximately 21 days. Serum albumin provides up to 65–75% of the normal colloid oncotic pressure, with globulins and fibrinogen accounting for most of the rest. Apart from its role in maintaining oncotic pressure, albumin is involved in transport of many hormones, fatty acids, and drugs. It contributes to vascular endothelial integrity and modulation of acid–base homeostasis. In addition, it has anti-inflammatory and antioxidant properties which contribute to its role as a negative acute phase reactant. Serum albumin level is a prognostic marker in critically ill patients.[1]

Commercially available albumin is purified from human plasma. It can be made as 5% or 20–25% solutions. The use of 5% albumin solutions reduces the viscosity of the circulating blood and improves the microcirculation due to hemodilution, thereby increasing the cardiac output. Albumin 20% is a hyperoncotic solution which creates a volume effect of around three to four times the quantity administered, which leads to extraction of fluid from the extravascular space. In hypovolemic states, co-administration with another suitable fluid is advised. Albumin 20% is ideally suited for treating hypoalbuminemia, as the volume load remains low. Sterile water should not be used for diluting albumin, as this can result in hypotonic solution leading to hemolysis.

The use of albumin in critically ill patients is appealing because of its oncotic and nononcotic properties. However, it is frequently misused, with some reports suggesting that its use appears unindicated 90% of the time.[2] There is a lack of appropriate guidelines regarding the choice of concentration, timing, dosing, and target values. Albumin is used widely in critically ill patients especially in fluid resuscitation, but evidence is scanty. Data from the SEMICYUC study demonstrates that only 77.2% of physicians using albumin in patients without liver disease were aware of the evidence supporting its use as opposed to 82% of those treating liver disease.[3] In correcting volume deficit, 5% albumin is generally preferred.[4]

Use of albumin varies across health systems; the reasons being the prohibitive cost coupled with lack of evidence to justify its use in general intensive care unit (ICU) patients. Rarely, albumin can cause allergic reactions and theoretical risk of prion transmission exists.[5] Hence its use should be restricted to situations where its efficacy has been established. The following review will analyze the most common misuses of albumin and highlight the accepted indications and its evidence base.

Indications of albumin use in critically ill are often not well documented and when documented, not supported by evidence. It is most commonly abused in volume resuscitation, weaning off vasopressors, correction of hypoalbuminemia, and improving oxygenation in acute respiratory distress syndrome (ARDS).

ALBUMIN IN SEPSIS

Albumin is used rampantly as a resuscitative fluid in critically ill without any substantiative evidence. The surviving sepsis guidelines 2016 describes albumin as a supplementary resuscitative fluid in sepsis.[6] Its role in resuscitation of other conditions is inconclusive. Also its optimal dose, timing, and target concentration have not been described.[7]

The Saline versus Albumin Fluid Evaluation (SAFE) study[8] concluded that the safety of 4% albumin is comparable to saline in sepsis and that albumin decreased mortality in the subgroup of patients with severe sepsis. Similar results were reported by the ALBIOS (Albumin Italian Outcome Sepsis) study[9] whereas Early Albumin Resuscitation during Septic Shock (EARSS)[10] and lactated Ringer vs albumin in sepsis (RASP) studies[11] did not show any outcome difference.

The Albumin Replacement in Patients with Severe Sepsis or Septic Shock (ALBIOS) study conducted on 1,818 patients with severe sepsis or septic shock at 100 ICUs in Italy randomized the participants to either receive 300 mL of 20% albumin plus crystalloid or to receive crystalloid alone,

initially at presentation, to attain the target resuscitation goals of the early goal-directed therapy protocol. The albumin infusions were adjusted to maintain serum albumin ≥30 g/L over the next 28 days, and crystalloid solutions were given when considered clinically indicated by the attending physician. No overall differences in 28-day or 90-day mortality rates between the groups could be observed. Post-hoc analysis of the septic shock subgroup showed no difference in 28-day mortality but suggested a 90-day mortality benefit favoring albumin, an effect that lost significance when adjusted for clinically relevant variables.

An ongoing phase IIIb interventional clinical trial, The ARISS study [Clinicaltrials.gov (NCT03869385)], aims to answer some of the queries in this respect. The study involves administration of albumin within 6–24 hours after the onset of septic shock and also aims at maintaining a serum albumin concentration of at least 30 g/L for 28 days after the onset of septic shock while observing for a possible reduction in 90-day all-cause mortality in these patients, when compared to volume replacement therapy without albumin.

In summary, albumin used either as a resuscitation agent or to normalize albumin levels in septic patients has not been shown to provide a benefit in mortality, new organ failure, or duration of mechanical ventilation. Furthermore, the hemodynamic benefits should be interpreted with caution because they are not associated with beneficial outcomes. There are no randomized control trials (RCTs) comparing the effect of different concentrations of albumin on resuscitation of septic patients.

TRAUMA

Crystalloids and colloids are widely used for resuscitation and the ideal choice is a matter of debate. Isotonic or hypertonic fluids are used in resuscitation. Albumin remains intravascular longer, rapidly achieves plasma volume, and achieves similar goals quickly with lesser volume than crystalloids but is expensive and does not have any survival benefit. Hence, crystalloids are preferred in the initial resuscitation of trauma patients.[12]

The 2019 European guidelines on management of major bleeding and coagulopathy following trauma recommends use of isotonic fluids and balanced salt solution in hemorrhagic shock. The Colloid versus Crystalloid in Critically Ill (CRISTAL)[13] trial also did not find any mortality benefit for albumin in the resuscitation of hemorrhagic shock.

Traumatic Brain Injury

Patients with traumatic brain injury (TBI) are resuscitated with fluids to optimize hemodynamics. The SAFE TBI study[14] has shown that use of albumin as a resuscitation fluid in TBI increases mortality. The probable mechanism seems to be an increase in intracranial pressure (ICP).

Burns

Albumin is often misused in resuscitation of moderate-to-severe burns primarily because of the presumed role in reducing edema due to its oncotic properties. There is a paucity of data supporting the evidence of albumin in burn resuscitation. According to American Burns Association guidelines, crystalloids are the fluids of choice for initial burns resuscitation in the first 24 hours. Ringer's lactate (RL) is preferred because it approximates intravascular solute content. However, as a rescue therapy where large amount of fluids are required to maintain organ function, albumin can be considered.

A meta-analysis by Navickis et al.[15] demonstrated reduced mortality and incidence of abdominal compartment syndrome (ACS) following albumin as a resuscitative fluid in burns. Cartotto et al. suggested colloid rescue for those whose fluid requirement exceeded the Parkland formula by 1.5 times or 6 mL/kg/% body surface area (BSA). One-third of fluid was given as albumin and two-third as RL. This formula has shown to decrease fluid requirement without increase in mortality.[16]

Acute Respiratory Distress Syndrome

A few small clinical studies have shown improvement in oxygenation with use of albumin along with furosemide in ARDS; however, poor sample size and study designs limit their utility. A meta-analysis by Uhlig et al.[17] showed that albumin improved oxygenation but not mortality in ARDS. Additional trials are needed to further define the role of albumin in ARDS and cannot be recommended at this stage.

As An Adjunct to Furosemide

The diuretic potential of furosemide is diminished in hypoalbuminemia and hence infusion of hyperoncotic albumin prior to administration of furosemide might seem rational. Concurrent use of albumin may increase furosemide-induced diuresis in hypo-oncotic patients with acute respiratory distress syndrome/acute lung injury and cirrhosis-induced ascites, although not in all critically ill patients. The effect of this strategy on patient-centered clinical outcomes is unclear. Evidence from two small trials by Martin et al. and Oczkowski et al. has shown that intravenous albumin administration along with diuretics has improved oxygenation in patients with acute lung injury but did not improve mortality.[18,19] However these findings cannot be generalized due to the small sample size and limited data on outcome. A recent meta-analysis has addressed this issue but the evidence is inconclusive and at present this practice cannot be recommended.

ALBUMIN IN HYPOALBUMINEMIA

Hypoalbuminemia (<30 g/L) in critically ill patients is associated with poor outcome. It is unclear whether the negative impact of hypoalbuminemia on outcome is due to a cause effect relation or whether it only serves as a marker

of more severe disease. Observations regarding the adverse outcomes of hypoalbuminemia clubbed with new insight into the vascular barrier function have led to increasing interest in albumin supplementation. A meta-analysis by Vincent et al.[20] of nine prospective randomized controlled trials (RCTs) on correcting hypoalbuminemia in critically ill has suggested that an albumin level >30 g/L decreased the complication rates.

A Cochrane review by Roberts et al.[21] demonstrated no mortality benefit with albumin supplementation in patients with hypoalbuminemia. This is supported by a single-center open-label study by Dubois et al.,[22] reporting that albumin supplementation improves organ dysfunction, but does not provide any survival advantage. The administration of large amounts of albumin supplements for the correction of prolonged hypoalbuminemia in major burns had no significant benefits on mortality. More RCTs are required to analyze the role of albumin infusion and optimal target values in hypoalbuminemia. Presently albumin infusion as a supplement to correct hypoalbuminemia cannot be recommended.

ALBUMIN USE IN CARDIAC SURGERY

Hypotension following cardiac surgery is common and multifactorial. Because of its oncotic properties, less volume of albumin is required when compared to crystalloid for restoring circulating plasma volume. However, in spite of its wide clinical usage, there is a lack of high-quality evidence to support the use of albumin in cardiac surgical patients.

A large study by Sedrakyan et al.[23] demonstrated a lower all-cause mortality with albumin use in patients who underwent coronary artery bypass graft (CABG), although the study had many limitations. A single center study by Matebele et al.[24] with 2,594 patients reported higher illness severity, more complications, and higher healthcare costs with no increased mortality with use of albumin in cardiac surgery patients. Various studies on the use of albumin in cardiac surgical patients have shown conflicting results including the risk of renal dysfunction. In patients with hypoalbuminemia undergoing off pump CABG, albumin might offer some protection from acute kidney injury (AKI).

NEPHROTIC SYNDROME

Various clinical trials to treat edema in patients with nephrotic syndrome using albumin and furosemide have been published. Due to variation in selection criteria, design, and clinical end points, a definitive recommendation cannot be made. Combination therapy may be considered in those with resistance to diuretics.[25]

ABDOMINAL COMPARTMENT SYNDROME

Secondary ACS is usually the result of large volume resuscitation with crystalloids. A study by O'Mara et al.[26] showed that the risk of ACS is more when crystalloids alone are used for resuscitation compared to a combination of colloid and crystalloid combination. The World Society for Abdominal Compartment Syndrome (WSACS) in their guidelines states that no recommendation can be made for or against albumin in ACS due to lack of evidence.

HEPATORENAL SYNDROME

Systemic vasoconstrictor therapy combined with albumin, a plasma volume expander, has been considered as the first-line treatment for hepatorenal syndrome (HRS). However in a recent randomized controlled trial including patients with decompensated cirrhosis, repeated daily infusion of intravenous albumin targeting a serum level >3 g/dL did not improve renal function compared to standard care, while it did increase the incidence of pulmonary edema and fluid overload.[27] The CONFIRM trial investigating the efficacy of terlipressin in HRS, where albumin was coadministered in 83% of the patients, the incidence of respiratory failure was significantly higher in the treatment arm.[28] However, the current EASL guidelines favor the use of albumin in HRS.

COST-EFFECTIVENESS OF ALBUMIN

Albumin remains the costliest resuscitative fluid. If albumin could reduce morbidity and mortality even minimally, then it can be considered as a cost-effective therapy. Guidet et al.[29] based on the presumption of 4.6% reduction in mortality in SAFE study in the group which received albumin infusion, estimated that 513 lives were saved and concluded it as a cost-effective intervention. A study by Farrugia et al.[30] on cost-effectiveness of albumin also led to a similar conclusion.

CONCLUSION

Albumin has an important role in specific situations in the critically ill population. The approved indications are as adjunct to large volume paracentesis, spontaneous bacterial peritonitis, treatment of hepatorenal syndrome, as a replacement fluid for plasmapheresis, and in ovarian hyperstimulation syndrome. Other potential beneficial function of albumin, apart from osmotic properties, had resulted in attempts to use it for other indications as well. RCTs are lacking to support the evidence for use of albumin in such conditions. Albumin is largely misused in India with many patients admitted with hypoalbuminemia receiving daily infusion without definite indications or benefits. It places an increased burden on the cost of care with added risk of potential adverse events including increasing mortality and morbidity. More RCTs are required to substantiate its use out of the current approved indications.

REFERENCES

1. Lyu PF, Hockenberry JM, Gaydos LM, Howard DH, Buchman TG, Murphy DJ. Impact of a sequential intervention on albumin utilization in critical care. Crit Care Med. 2016;44(7):1307-13.

2. China L, Freemantle N, Forrest E, Kallis Y, Ryder SD, Wright G, et al. Albumin infusion beyond standard indication hope or hype? N Engl J Med. 2021;384:808-17.
3. Monteil E, Quintana-Diaz M, Garcia de Lorenzo A, Gasero BG (SEMICYUC). Results of the survey on albumin use in clinical practise in intensive care units. Med Intensiva. 2014;38(7):403-12.
4. Liumbruno G, Bennardello F, Lattanzio A, Piccoli P, Rossettias G. Italian Society of Transfusion Medicine and Immunohaematology (SIMTI) working party recommendations for the use of albumin and immunoglobulins. Blood Transfus. 2009;7(3):216-34.
5. Xu J-Y, Chen Q-H, Xie J-F, Pan C, Liu S-Q, Huang L-W, et al. Comparison of the effects of albumin and crystalloid on mortality in adult patients with severe sepsis and septic shock: a meta-analysis of randomized clinical trials. Critical Care. 2014;18(6):702.
6. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43(3):304-77.
7. Bracht H, Georgieff M, Matejovic M, Radermacher P. Human serum albumin as a resuscitation fluid: less SAFE than presumed? Crit Care Med. 2011;39(6):1584-5.
8. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, et al. SAFE study investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350(22):2247-56.
9. Caironi, P, Tognoni, G, Masson, S, Fumagalli R, Pesenti A, Romero M, et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med. 2014;370(15):1412-21.
10. Charpentier J, Mira J-P, Group ES. Efficacy and tolerance of hyperoncotic albumin administration in septic shock patients: the EARSS study. Intensive Care Med. 2011;37(1 Suppl 1):S115-438.
11. Park C, Osawa E, Almeida J, Nakamura R, Duayer I, Fukushima J, et al. Lactated Ringer Versus Albumin in Early Sepsis Therapy (RASP) study: preliminary data of a randomized controlled trial. Crit Care. 2015;19(Suppl 1):P355.
12. Ramesh GH, Uma JC, Farhath S. Fluid resuscitation in trauma: what are the best strategies and fluids? Int J Emerg Med. 2019;12:38.
13. Annane D, Siami S, Jaber S, Martin C, Elatrous S, Declere AD, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. JAMA. 2013;310(17):1809-17.
14. The SAFE Study Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group; Australian Red Cross Blood Service; George Institute for International Health; Myburgh J, Cooper DJ, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med. 2007;357(9):874-84.
15. Navickis JR, Greenhalgh DG, Wilkes MM. Albumin in burn shock resuscitation: A meta-analysis of controlled clinical studies. J Burn Care Res. 2016;37(3):e268-78.
16. Cartotto R, Callum J. A review of the use of human albumin in burn patients. J Burn Care Res. 2012;33(6):702-17.
17. Uhlig C, Silva PL, Deckert S, Schmitt J, de Abreu MG. Albumin versus crystalloid solutions in patients with the acute respiratory distress syndrome: a systematic review and meta-analysis. Crit Care. 2014;18(1):R10.
18. Martin, GS, Moss, M, Wheeler, AP, Mealer M, Morris JA, Bernard GR. A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. Crit Care Med. 2005;33(8):1681-7.
19. Oczkowski, SJW, Klotz, L, Mazzetti, I, Alshamsi F, Chen ML, Foster G, et al. Furosemide and Albumin for Diuresis of Edema (FADE): a parallel-group, blinded, pilot randomized controlled trial. J Crit Care. 2018;48:462-7.
20. Vincent J-L, Russell JA, Jacob M, Martin G, Guidet B, Wernerman J, et al. Albumin administration in the acutely ill: what is new and where next? Crit Care. 2014;18(4):231.
21. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. BMJ. 1998;317(7153): 235-40.
22. Dubois, M-J, Orellana-Jimenez, C, Melot, C, De Backer D, Berre J, Leeman M, et al. Albumin administration improves organ function in critically ill hypoalbuminemic patients: a prospective, randomized, controlled, pilot study. Crit Care Med. 2006;34(10):2536-540.
23. Sedrakyan A, Gondek K, Paltiel D, Elefteriades J. Volume expansion with albumin decreases mortality after coronary artery bypass graft surgery. Chest. 2003;123(6):1853-7.
24. Matebele MP, Ramanan M, Thompson K, Cornmell G, Naidoo RV, Shekar K. Albumin use after cardiac surgery. Crit Care Explor. 2020;2(7):e0164.
25. Melia D, Post B. Human albumin solutions in Intensive care: A review. J Intensive Care Soc. 2021;22(3):248-54.
26. O'Mara MS, Slater H, Goldfarb IW, Caushaj PF. A prospective, randomized evaluation of intra-abdominal pressures with crystalloid and colloid resuscitation in burn patients. J Trauma. 2005;58(5):1011-8.
27. China L, Freemantle N, Forrest E, Kallis Y, Ryder SD, Wright G, et al. A randomized trial of albumin infusions in hospitalized patients with cirrhosis. N Engl J Med. 2021;384(9):808–17.
28. Wong F, Pappas SC, Curry MP, Reddy KR, Rubin RA, Porayko MK, et al. Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. N Engl J Med. 2021;384(9):818–28.
29. Guidet BR, Ghout I, Ropers J, Aegerter P. Economic model of albumin infusion in septic shock: The EMAISS study. Acta Anaesthesiol Scand. 2020;64(6):781-8.
30. Farrugia A, Bansal M, Caraceni P. Use of albumin in spontaneous bacterial peritonitis is cost-effective. Crit Care. 2015;19(Suppl 1):P353.

CHAPTER

31

Precision Mathematics in Fluid Electrolytes in Intensive Care Unit

Sanjay N Pandya, Rajendra P Mathur

INTRODUCTION

Fluid and electrolyte disorders are common in intensive care unit (ICU) patients, and their balance is a challenging area of critical care medicine. Various mathematical calculations and formulas not only help in the diagnosis but also serve as a valuable tool in the proper management of these disorders.

HYPONATREMIA

When serum sodium is found to be low (<135 mEq/L) on a laboratory test, it suggests the diagnosis of hyponatremia. For the diagnostic approach and proper treatment of hyponatremia, different calculations and formulas are used.

Calculations and Formulas for the Diagnostic Approach to Hyponatremia

Serum osmolality and fractional excretion of sodium (FENa) help in establishing the etiology of hyponatremia.

Measured and Calculated Serum Osmolality

The first and very crucial step in the diagnostic approach to hyponatremia is to determine serum osmolality which helps to establish the etiology of hyponatremia. In true hyponatremia, the plasma osmolality is low.

Osmolality vs. osmolarity: The ratio of solutes and water in plasma determines the plasma osmolality or osmolarity, and sodium concentration is the main determinant.

Osmolality is a measurement of the concentration of the dissolved solutes per weight (number of osmoles of a solute per kg of the solvent; mOsm/kg). Osmolarity measures the concentration of dissolved solutes per volume (number of dissolved solute particles per 1L of solvent; mOsm/L).

As 1 kg and 1 L of water are equal, both values are the same when solutes are dissolved in water. However, the value of osmolality (mOsm/kg) is more accurate than osmolarity because the temperature can affect the volume of solvent and, therefore, can affect the value of osmolarity (mOsm/L).

Measured and calculated serum osmolality: Plasma osmolality is measured by using a freezing point depression osmometer.

- Serum osmolality is calculated by using the value of sodium, glucose, and urea in the equation.

Plasma osmolality = (2 × Na) + [Glucose (mg/dL)/18] + [blood urea nitrogen (BUN) (mg/dL)/2.8]

The BUN or blood urea nitrogen is the measured value of blood urea divided by 2.2.

$$BUN = BUL/2.2$$

Measured Serum Osmolality

Measurement of plasma osmolality by osmometer helps to establish the diagnosis of true, hypotonic hyponatremia and exclude pseudohyponatremia or hypertonic hyponatremia.

In true hyponatremia, the plasma osmolality is low, and this is divided into hypervolemic, hypovolemic, and euvolemic based on the volume status.

When a facility to measure osmolality is not available, investigations such as random blood sugar, serum triglyceride, and serum protein are helpful to establish the etiological diagnosis. Mechanism of development and calculations for correcting the serum sodium value in hyper and isotonic hyponatremia (hyperglycemia, hypertriglyceridemia, and hyperproteinemia) is summarized below.

Hyperglycemia: Hyperglycemia is the most common cause of hyperosmolar or hypertonic hyponatremia. Hyperglycemia increases serum osmolality, which shifts water from the intracellular to the extracellular compartment, reducing serum sodium levels. Thus, in hyperglycemia, total body water remains the same, but the shift of water from intracellular fluid (ICF) to extracellular fluid (ECF) leads to a fall in sodium, which is known as translocational hyponatremia.

For every 100 mg/dL increase in glucose above 100 mg/dL, the serum sodium falls by approximately 1.6 mEq/L. In severe hyperglycemia, when serum glucose is above 400 mg/dL, the serum sodium falls by about 2.4 mEq/L for every 100 mg/dL rise in serum glucose.[1]

Pseudohyponatremia: The most common cause of pseudohyponatremia (isotonic hyponatremia) is hyperproteinemia, and the next common cause is hypertriglyceridemia (when serum triglyceride is >1,500 mg/dL).

As such, pseudohyponatremia is a laboratory artifact that occurs when sodium is measured by the less accurate methods such as indirect ion-specific electrode (ISE) or flame photometry. Hypertriglyceridemia and hyperproteinemia increase the nonaqueous portion of the serum, and as a result, the aqueous portion of plasma decreases. Abovementioned old methods measure sodium from whole serum (both aqueous and expanded nonaqueous portion), with resultant falsely low serum sodium concentrations.

In hypertriglyceridemia, 1,000 mg/dL increase in serum triglyceride concentration (above 100 mg/dL) leads to about 2 mEq/L fall in serum sodium.[2] In hyperproteinemia (multiple myeloma), 1 g/dL increase in serum protein (above 8 g/dL) leads to about 4 mEq/L fall in serum sodium.

With the widespread availability and use of the more precise method of sodium measurement, such as ISE potentiometry, pseudohyponatremia is now uncommon.

Calculated Serum Osmolality

The simplest and best formula to calculate plasma osmolality is the equation:

$$\text{Posm} = (2 \times \text{Na}) + [\text{Glucose (mg/dL)}/18] + [\text{BUN (mg/dL)}/2.8]$$

Calculated and measured osmolality are generally similar if osmotically active solutes other than sodium, urea, and glucose are absent. But calculated serum osmolality is not routinely used to confirm hypo-osmolality and approach hyponatremia because, in the presence of other osmotically active solutes (e.g., ethylene glycol, propylene glycol, ethanol, and methanol) in the plasma, calculated osmolality does not match with the measured osmolality.

Calculated serum osmolality is used to calculate the osmolar gap.

Osmolar gap = Measured osmolality – Calculated osmolality

Normal osmol gap is <10 mOsm/kg.

A high osmol gap (>10 mOsm/kg) suggests the presence of osmotically active solutes not measured routinely in plasma, such as ethylene glycol, propylene glycol, ethanol, methanol, isopropanol (isopropyl alcohol), or acetone in the plasma. Thus, a high osmolar gap helps in the diagnosis of suspected toxic alcohols ingestion.

The measured plasma osmolality may also be elevated by substances given therapeutically like mannitol, glycerol, dextrans, or starches.

FENa: FENa is a calculation and not a test based on the values of sodium and creatinine of blood and urine spot samples collected simultaneously. In hyponatremia, FENa provides a more reliable clue about volume status than the urine sodium alone. The formula to calculate the FENa is:

$$\text{FENa} = \frac{\text{UNa} \times \text{PCr}}{\text{UCr} \times \text{PNa}} \times 100$$

(U_{Na} = urine sodium, P_{Cr} = plasma creatinine, P_{Na} = plasma sodium, U_{Cr} = urine creatinine).

FENa <0.5% suggests hypovolemic hyponatremia of nonrenal origin and FENa >0.5% suggests euvolemic hyponatremia or volume depletion due to diuretics.[3]

Fractional Excretion of Uric Acid

Fractional excretion of uric acid (FEUA) is consist and accurate method to differentiate hyponatremia due to cerebral/renal salt wasting and syndrome of inappropriate antidiuretic hormone secretion (SIADH).[4] FEUA are high (>10) in both SIADH and cerebral salt wasting (CSW). But after correction of hyponatremia, FEUA returns to baseline (<10) in SIADH, but in cerebral/renal salt wasting, it continues to remain elevated (>10).[4]

Fractional excretion of uric acid also helps to differentiate hyponatremia due to diuretic (furosemide) therapy and SIADH.[5] Hyponatremia secondary to SIADH is generally associated with a serum uric acid level <4 mg/dL with an increase of FEUA. These findings are dependent on a decrease in tubular reabsorption of urate in SIADH. In contrast, the sodium depleted patients due to diuretics FEUA is low.

Calculations and Formulas in Planning for the Therapy of Hyponatremia

Various formulas are used to calculate the volume of different IV fluids to be administered and their mode of administration.

Formula to Calculate Sodium Deficit

$$\text{Sodium requirement} = (\text{Desired Na} - \text{Actual Na}) \times \text{Total body water}$$

$$\text{Total body water (L)} = \text{Body weight} \times 0.6 \text{ in adult man}$$

$$= \text{Body weight} \times 0.5 \text{ in adult women}$$

This formula is not preferred in treating hyponatremia because it cannot accurately predict changes in serum sodium and need frequent sodium monitoring.[6]

Adrogué–Madias Formula

This method is commonly used to calculate how much the serum sodium concentration will rise when 1 L of various intravenous (IV) fluids is given.[7]

$$\text{Change in serum Na} = \frac{(\text{infusate Na} - \text{Current Na})}{\text{Total body water} + 1}$$

Example: In a 60 kg hypovolemic man with serum sodium 117 mEq/L, how much sodium 1 L of normal saline will raise?

Normal saline contains 154 mEq/L sodium and total body water will be 60 × 0.6 = 36 L. So, rise in Na = (154 – 117)/(36 + 1) = 1 mEq/L.

In hypokalemic patients receiving potassium-containing IV fluids, modified formula is used because rise in serum potassium also causes increase in serum sodium.

$$\text{Change in serum Na} = \frac{(\text{infusate Na} + \text{infusate K}) - \text{Current Na})}{\text{Total body water} + 1}$$

The sodium and potassium content of routinely used IV solutions are summarized in **Table 1**.

Calculated volume of IV fluid is administered as an infusion and rate of infusion is determined by the symptoms of patients, volume status, and goal to raise serum sodium.

Formula to Calculate the Requirement of 3% Saline

A simple and rapid method to calculate the need for hypertonic saline in hyponatremia: Administration of 1 mL/kg of 3% NaCl = Rise in serum Na by 1 mEq/L.

For treatment of hyponatremia, which formula is ideal in the calculation?

Equations used for calculation in the treatment of hyponatremia provide just rough guidelines to predict the change in serum sodium. As none of the methods can consider ongoing losses, free water intake, urine output, changing composition of urine, and insensible water losses, rather than relying on calculations, we should monitor serum electrolytes closely in all patients.[8] Furthermore, as the volume status of the body may vary in different clinical disorders, calculation of total body water will not be accurate, and therefore values derived based on the same will not be reliable.[9]

Rapid intermittent bolus (RIB) versus slow continuous infusion (SCI) of hypertonic saline:

Current literature supports the use of rapid intermittent bolus of 3% NaCl because

- Both American Expert Panel Recommendations and European Clinical Practice Guidelines recommend administering 3% NaCl in bolus form to rapidly raise serum sodium in acute symptomatic hyponatremia (e.g., patients with impending herniation, active seizures, delirium, or impaired consciousness).[10,11] 100 mL bolus of 3% NaCl is infused over 10 minutes and maybe repeated twice (with a total dose of 300 mL) if neurological symptoms fail to improve, as per American Expert Panel Recommendations.[10] 150 mL bolus of 3% NaCl is infused over 20 minutes and may be repeated for one time (with a total dose of 300 mL) if necessary, as per European Clinical Practice Guidelines.[11]
- 3% NaCl bolus is a user-friendly method which effectively raises serum sodium within minutes rather than hours (i.e., faster initial rise of Na than continuous infusion) with the quicker restoration of symptoms, and therefore is both physiological and logical.[12-14]
- Lower incidence of therapeutic relowering treatment with 3% NaCl bolus compared to slow continuous infusion.[13]

HYPERNATREMIA

The fluid deficit is the most common cause of hypernatremia. Various formulas are used to calculate the amount of administered fluid to correct it are summarized below.[7]

- Calculation of the total electrolyte free water deficit provides information about the volume of fluid required to restore the increased sodium concentration to normal (140 mEq/L) in hypernatremia.

$$\text{Total electrolyte free water deficit} = \text{Total TBW} \times \frac{\text{Serum Na} - 140}{140}$$

Example: In a 60 kg man with serum sodium 170 mEq/L, how much is the total water deficit?

Total water deficit = 60 × 0.6 × [(170 – 140)/140] = 7,714 mL

- Calculation of the electrolyte free water required to reduce the actual high serum sodium level to desired lower concentration over 24 hours in patients with hypernatremia.

$$\text{Volume of electrolyte free water required} = \text{Total TBW} \times \frac{\text{Serum Na} - \text{Desired Na}}{140}$$

Example: In a 60 kg dehydrated man with serum sodium 170 mEq/L, how much water should be infused to lower serum sodium to 160 mEq/L?

Water requirement = 60 × 0.6 × [(170 – 160)/140] = 2,571. So, replacement of 2,571 mL of water may reduce serum sodium by 10 mEq/L.

- Adrogué–Madias formula calculates the expected reduction in serum sodium concentration in hypernatremia after administration of 1 L of IV fluid.

$$\text{Change in serum Na} = \frac{(\text{infusate Na} - \text{Current Na})}{\text{Total body water} + 1}$$

TABLE 1: Sodium and potassium content of intravenous (IV) solutions.

IV solutions	*7.5%/8.4% $NaHCO_3$*	*3%-NaCl*	*NS DNS*	*Plasma-lyte*	*Ringer's lactate*	*0.45% NaCl*	*Isolyte-M*	*Isolyte-P*
Sodium mEq/L	893.0/1000.0	513.0	154.0	140.0	130.0	77.0	40.0	25.0
Potassium mEq/L	0	0	0	5.0	4.0	0	35.0	20.0

(NS: normal saline; DNS: dextrose normal saline; IV: intravenous)

Example: In a 60 kg hypovolemic man with serum sodium 170 mEq/L, how much sodium 1 liter of 5% dextrose will lower?

5% dextrose contains 0 mEq/L sodium and total body water will be 60 × 0.6 = 36 L. So, fall in Na = (0 – 170)/(36 + 1) = 4.59 mEq/L

- The formula used to calculate the rough estimate of volume of fluid to be administered
  - 3–4 mL × bodyweight × (desired reduction in serum sodium in mEq/L)

  After calculating water deficit, always add the volume of ongoing water losses via the gastrointestinal (GI) tract, loss of electrolyte-free water in the urine, and insensible losses to estimate the total volume of fluid required to restore sodium concentration.
- In patients with polyuria, the proportion of electrolyte free water clearance (EFWC) in urine can be calculated by the following equation:

  EFWC = Urine volume × {1 – [(Urine Na + Urine K)/Serum Na]}

Although these equations provide reasonable accuracy to predict change in serum sodium over shorter time periods (2–4 hours), it fails when used to calculate changes over a longer period. Therefore, the most reliable approach is to monitor the serum sodium frequently.[15-17]

HYPOKALEMIA AND HYPERKALEMIA

In the diagnostic approach to patients with potassium disturbances, the calculation of transtubular potassium gradient (TTKG) measures the renal potassium secretion by the cortical collecting duct and reflects the activity of aldosterone.

TTKG = (Urine K/Serum K) × (Serum osmolality/Urine osmolality)

- The normal value of TTKG is 8–9, which reflects the normal renal conservation of potassium.
- In hypokalemia, due to renal potassium wasting, the value of TTKG will be >7, and TTKG <3 suggests that the kidney is not wasting potassium and potassium loss is extrarenal.
- In hyperkalemia, TTKG should be >10, the low value of TTKG (<7) may indicate hypoaldosteronism (mineralocorticoid deficiency).

As the results of this test are not accurate in patients with urine osmolality lower than the serum osmolality or urine sodium is <25 mEq/L, current literature recommends against the use of this test in dyskalemia.[18]

HYPOCALCEMIA

In patients with hypocalcemia, hypoalbuminemia reduces total calcium concentration without affecting the ionized calcium concentration. Each 1 g/dL fall in the serum albumin concentration will reduce the total calcium concentration by approximately 0.8 mg/dL (0.2 mmol/L). In patients with hypoalbuminemia, corrected calcium concentration can be calculated using the following equation:

Corrected calcium = Measured total calcium (mg/dL) + [0.8 × (4.0 – Patient's albumin (g/dL)]

Example: Serum total calcium 8.0 mg/dL, serum albumin 2 g/dL.

Corrected calcium = 8.0 + [0.8 × (4.0 – 2.0)]
= 8.0 + 1.6

Corrected calcium = 9.6 mg/dL

Current literature discourages the use of corrected calcium in practice because this formula overestimates ionized calcium in patients with hypoalbuminemia, with resultant inadequate treatment of hypocalcemia.[19] When in a dilemma, measure ionized calcium to avoid confusion and the potential risk of withholding appropriate treatment.[20]

CONCLUSION

Various formulae increase the accuracy of diagnosis and therapy in different electrolyte disorders. In hyponatremia, when a facility to measure serum osmolality is not available, the corrected value of serum sodium in patients with hyperglycemia, hypertriglyceridemia, and hyperproteinemia helps to exclude hypertonic and pseudohyponatremia hyponatremia. Formulae provide an estimate of the volume of different IV fluids to be administered to raise sodium in hyponatremia, but are not a substitute for frequent monitoring in the fine regulation of therapy. While applying these formulae as a guide to therapy, one should take into account the ongoing fluid losses that may be highly variable among the patients in ICU. In patients with hypocalcemia with hypoalbuminemia, the measurement of ionized calcium is recommended rather than the corrected value of total calcium.

REFERENCES

1. Hillier TA, Abbott RD, Barrett EJ. Hyponatremia: evaluating the correction factor for hyperglycemia. Am J Med. 1999;106(4):399-403.
2. Weisberg LS. Pseudohyponatremia: A reappraisal. Am J Med. 1989;86(3)315-8.
3. Steiner RW. Interpreting the fractional excretion of sodium. Am J Med. 1984;77(4):699-702.
4. Rudolph A, Gantioque R. Differentiating between SIADH and CSW using fractional excretion of uric acid and phosphate: A narrative review. Neurosci Med. 2018;9(2):53-62.
5. Bassi V, Fattoruso O. The role of fractional excretion of uric acid in the differential diagnosis of hypotonic hyponatraemia in patients with diuretic therapy. Cureus. 2020;12(4): e7762.
6. Sahay M, Sahay R. Hyponatremia: A practical approach. Indian J Endocr Metab. 2014;18(6):760-71.
7. Adrogué HJ, Madias NE. Hyponatremia. N Engl J Med. 2000;342(21):1581-9.
8. Sterns RH. Formulas for fixing serum sodium: curb your enthusiasm. Clin Kidney J. 2016;9(4):527-9.

9. Tzamaloukas AH, Malhotra D, Rosen BH, Raj DSC, Murata GH, Shapiro JI. Principles of management of severe hyponatremia. J Am Heart Assoc. 2013;2(1):e005199.
10. Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013;126(10 Suppl 1):S1-42.
11. Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, et al. Hyponatraemia Guideline Development Group. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Eur J Endocrinol. 2014;170(3):G1-47.
12. Garrahy A, Dineen R, Hannon AM, et al. Continuous versus bolus infusion of hypertonic saline in the treatment of symptomatic hyponatremia caused by SIAD. J Clin Endocrinol Metab. 2019;104(9):3595-602.
13. Baek SH, Jo YH, Ahn S, Medina-Liabres K, Oh YK, Lee JB, et al. Risk of overcorrection in rapid intermittent bolus vs slow continuous infusion therapies of hypertonic saline for patients with symptomatic hyponatremia: The SALSA Randomized Clinical Trial. JAMA Intern Med. 2021;181(1):81-92.
14. Rondon-Berrios H, Sterns RH. Hypertonic saline for hyponatremia: Meeting goals and avoiding harm. Am J Kidney Dis. 2021:S0272-6386(21)00838-6.
15. Lindner G, Schwarz C, Kneidinger N, Kramer L, Oberbauer R, Druml W. Can we really predict the change in serum sodium levels? An analysis of currently proposed formulae in hypernatremic patients. Nephrol Dial Transplant. 2008;23(11):3501-8.
16. Hanna RM, Yang WT, Lopez EA, Riad JN, Wilson J. The utility and accuracy of four equations in predicting sodium levels in dysnatremic patients. Clin Kidney J. 2016;9(4):530-9.
17. Hanna RM, Wilson J, Kurtz I. The clinical utility and accuracy of four equations predicting delta serum Na+ over shorter timeframes (2-4 hours). The accuracy of delta Na+ modeling equations revisited over shorter time periods. Proceedings of UCLA Health. 2019;23.
18. Halperin ML. Assessing the renal response in patients with potassium disorders: a shift in emphasis from the TTKG to the urine K^+/creatinine ratio. Afr J Nephrol. 2017;20(1):22-4.
19. Steen O, Clase C, Don-Wauchope A. Corrected calcium formula in routine clinical use does not accurately reflect ionized calcium in hospital patients. Can J Gen Int Med. 2016;11(3):14-21.
20. Kenny CM, Murphy CE, Boyce DS, Ashley DM, Jahanmir J. Things we do for no reason™: Calculating a "Corrected Calcium" level. J Hosp Med. 2021;16(8):499-501.

CHAPTER

32

Delaying Renal Replacement Therapy in Acute Kidney Injury: How Long?

Rajeev A Annigeri, Dedeepiya V Devaprasad

INTRODUCTION

Acute kidney injury (AKI) is seen in 30–60% of critically ill patients[1] and about a quarter of patients with AKI require renal replacement therapy (RRT). AKI in critically ill patients is associated with high mortality, especially when RRT is needed. In addition, severe AKI may lead to chronic kidney disease (CKD) and end-stage kidney disease in the long term.[2] There is wide variability in dialysis practice patterns across the globe, including the optimal timing of initiation of RRT and a lack of consensus guidelines in several aspects of RRT in AKI accounts for some of this variability.

TIMING OF RENAL REPLACEMENT THERAPY INITIATION IN ACUTE KIDNEY INJURY, EARLY VERSUS DELAYED

It is generally accepted that RRT should be initiated for life-threatening uremic complications of AKI such as uremic encephalopathy, bleeding, severe hyperkalemia (> 6 mEq/L with ECG changes), metabolic acidosis (pH < 7.1), pulmonary edema, which do not respond to medical treatment. However, there is no consensus on the timing to initiate RRT in situations wherein there are no urgent indications. The proponents of early initiation of RRT in AKI suppose that such a strategy would prevent uremic complications, removes cytokines in sepsis, thereby improve outcomes. On the other hand, early initiation of RRT would increase the risk of catheter-insertion-related complications, catheter-related bloodstream infections (CRBSIs), and thrombosis, RRT-induced hypotension and electrolyte imbalance, may remove constituents which may be helpful in healing and repair of kidneys and may increase the cost due to unnecessary RRT.

DEFINING EARLY AND LATE INITIATION OF RENAL REPLACEMENT THERAPY IN ACUTE KIDNEY INJURY

Several studies in the last two decades have focused on the timing of RRT in ICU and the approaches have been generally categorized as early and delayed initiation of RRT. However, there is considerable diversity, in defining the timing of initiation of RRT as early and delayed in the published literature. Several parameters have been used, such as blood urea nitrogen (BUN) and serum creatinine (SCr),[3,4] temporal relation to the duration of admission to ICU,[3] time since diagnosis of AKI, and more recently AKI stages as defined by SCr and urine output criteria such as RIFLE[5] and KDIGO.[6-9]

COMPARISON OF STUDIES ON EARLY VERSUS LATE INITIATION OF RENAL REPLACEMENT THERAPY IN ACUTE KIDNEY INJURY

Till recently, the information on RRT initiation was derived largely from observational studies, which suggested that early initiation of RRT in AKI may improve survival.[10] In the last decade, several major randomized controlled trials (RCTs) have compared the early versus delayed RRT initiation in AKI. The study design and the major results of these studies are summarized in **Table 1**.

The first large study published from India in 2013, compared early versus late in the initiation of RRT based on BUN and SCr concentration. The results showed no difference in-hospital mortality. However, there was a criticism of the study that the study population did not represent the current pattern of patients admitted to ICU. The shock was present in only 25% of patients and the mean SOFA score was low at 8, indicating that many patients were not very sick.[4] This study included many patients with AKI due to acute gastroenteritis, tropical infections such as malaria, leptospirosis, and Dengue, which generally have a good prognosis. This notion is supported by the observed mortality which was low in both groups **(Table 1)**.

The next important study was the ELAIN trial, wherein CRRT was initiated for predominantly postsurgical patients at AKI stage-2 in the early RRT group and within 12 hours of AKI stage-3 in the delayed group. The study showed a significant reduction in 90-day mortality, an unusually

TABLE 1: Summary of RCTs on the timing of RRT initiation in AKI.

	Jamale et al.[4]	*ELAIN*[5]	*AKIKI-1*[7]	*IDEAL-ICU*[5]	*STARRT-AKI*[8]	*AKIKI-2*[9]
No. of centers	***1***	***1***	***31***	***29***	***>135***	***39***
Study populations	Mixed	Surgical	Mixed	Sepsis-associated AKI	Mixed	Mixed
No. of patients	208	231	620	488	2,866	278
Early RRT	BUN > 70 mg/dL, SCr > 7 mg/dL	KDIGO stage-2	KDIGO stage-3	KDIGO stage-3	KDIGO stage-2 or 3	KDIGO stage-3 with BUN > 112 mg/dL or oliguria > 72 hours
Delayed RRT	Urgent indications	KDIGO stage-3	BUN > 112 or oligoanuria of 72 hours	48 hours later or for urgent indications	Persistent AKI 72 hours after randomization or urgent indications	BUN > 140 mg/dL or urgent indications
Primary outcome	Hospital mortality	90-day mortality	60-day mortality	90-day mortality	90-day mortality	60-day mortality
Mortality	20.5% (E), 12.2% (D), p = NS	39% (E), 55% (D), p = 0.03	48.5% (E), 49.7% (D), p = NS	58% (E), 54% (D), p = NS	43.9% (E), 43.7% (D), p = NS	44% (E), 55% (D), p = 0.07
RRT initiation	100% vs. 83%	100% vs. 91%	98% vs. 51%	97% vs. 62%	97% vs. 62%	100% vs. 78%
Conclusions	Early initiation based on BUN and SCr is not beneficial	Early initiation of CRRT in surgical patients improved survival, reduced RRT duration and hospital stay	Early initiation of RRT has no survival benefit, may increase the risk of CRBSI	Early initiation of RRT has no benefits	Early initiation of RRT is associated with delayed renal recovery and RRT-related complications	More-delayed initiation of RRT is potentially harmful

(AKI: acute kidney injury; BUN: blood urea nitrogen; CRBSI: catheter-related bloodstream infection; CRRT: continuous renal replacement therapy; D: delayed; E: early; RCTs: randomized controlled trials; RRT: renal replacement therapy; SCr: serum creatinine)

large benefit considering that the vast majority (91%) in the delayed group also received RRT.[6] The major criticism of this study is that it is from a single center and 75% of the patient population at baseline had refractory fluid overload, some with pulmonary edema, which is a standard indication for initiation of RRT. Delaying RRT in patients who have a standard indication for RRT may have influenced the poor outcome in the delayed RRT group.

Artificial Kidney Initiation in Kidney Injury 1 (AKIKI-1) study was published at the same time as the ELAIN study, which randomized patients with AKI stage-3 to early or delayed initiation of RRT and found that no difference in 60-day mortality between the groups. In addition, delayed strategy with close monitoring of patients enabled avoidance of RRT in 50% of cases.[7] There was an increased incidence of dialysis-related complications such as CRBSI in the early RRT group.

The IDEAL-ICU trial specifically studied the impact of early versus delayed RRT in sepsis-associated AKI, wherein removal of cytokines by dialysis may have a beneficial effect but found no mortality difference between the two groups.[5]

The STARRT-AKI the largest among all RCTs was published in 2020. The study found no difference in mortality between the early and delayed RRT groups and reported that early RRT increased the risk of dialysis-related complications and delayed renal recovery.[8] The sub-group analysis of patients for sepsis, the severity of critical illness, and surgical patients showed no difference in the 90-day mortality between the two approaches to RRT initiation. This study firmly established the delayed initiation of RRT as the preferred strategy in AKI.

The analysis of these RCTs indicates that the strategy to delay RRT in AKI stage-3 allows a significant number of patients (up to 50%) to avoid RRT without an increased risk of mortality.[5,7,8] On the contrary, early initiation of RRT is associated with an increased risk of dialysis-related complications and delayed renal recovery.[7,8] Recent meta-analyses of studies concluded that in the absence of urgent indications, the timing of initiation of RRT does not affect survival. The delayed strategy with close patient monitoring may reduce the use of RRT, thereby reducing the cost of hospitalization.[11,12]

How long we can delay renal replacement therapy in acute kidney injury?

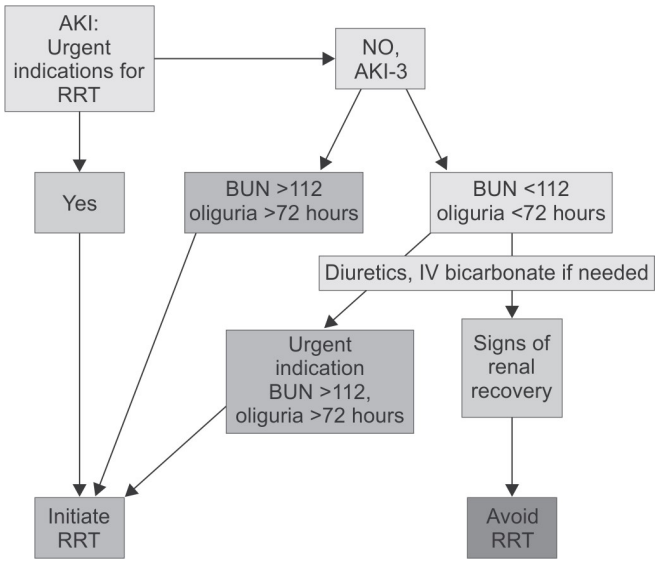
Though most of the recent studies support delaying RRT in AKI in the absence of urgent indications, there is no consensus on the threshold beyond which delaying RRT would be harmful. Recently published AKIKI-2 trial

sought to address this issue and concluded that delaying RRT beyond BUN 112 mg/dL or oliguria >72 hours in AKI stage-3 did not reduce RRT-free days and on the contrary is associated with increased risk of 60-day mortality (hazard ratio 1.65, $p = 0.02$).[9] However, the criteria chosen for more-delayed initiation of RRT in this study is questioned, since the study used BUN >140 mg/dL to initiate RRT in this group and ignored the duration of oligoanuria.

A few studies suggest that delayed RRT for too long in AKI stage-3 may have adverse outcomes. FINNAKI, a Finnish study of 239 patients of AKI showed that RRT initiated based on one or more conventional indications had higher 90-day mortality compared to no urgent indication at the time of RRT initiation [odds ratio (OR) = 2.05, 95% confidence interval (CI): 1.03–4.09].[13] In addition, in the AKIKI-1 study, the patients in the delayed RRT group, who ultimately received RRT had significantly higher mortality compared to the early RRT group (61.8% vs. 48.5%, $p < 0.001$), indicating that delaying RRT too late till conventional indication appear may be too late.[7] Hence, the clinicians should decide to initiate RRT on an individual basis in patients with AKI stage-3 with no urgent indication. While under close observation in AKI stage-3, clinicians should take into consideration in addition to BUN and SCr concentration, several other factors such as age, comorbidities, degree of acute illness, changing trends in acid-base balance, fluid balance, and intrinsic kidney capacity to decide to initiate RRT.

We propose an algorithm based on the current evidence to guide the timing of RRT initiation in AKI is shown in **Flowchart 1**.

Flowchart 1: Algorithm to guide the timing of initiation of RRT in AKI.



(AKI: acute kidney injury; BUN: blood urea nitrogen; RRT: renal replacement therapy)

BIOMARKERS TO GUIDE INITIATION OF RENAL REPLACEMENT THERAPY

Biomarkers to guide RRT initiation are an attractive approach in AKI stage-3 but are not explored sufficiently. Srisawat et al. reported that initiation of RRT based on high plasma neutrophil gelatinase-associated lipocalin (NGAL) (>400 ng/mL) did not show improved 28-day mortality.[14] Klein et al. recently reviewed the literature and concluded that though several biomarkers showed a reasonable prediction of RRT need, the strength of current evidence does not support their use to guide a decision to initiate RRT.[15]

CONCLUSION

Current evidence supports the practice of delaying RRT in AKI stage-3 till an indication to initiate dialysis urgently to treat uremic complication appear. However, in the absence of any specific standard indication to initiate dialysis, one should consider RRT in stage-3 AKI, when BUN is >112 mg/dL or when there is prolonged oliguria of 3 days or more.

REFERENCES

1. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 2015;41(8):1411-23.
2. Chawla LS, Kimmel PL. Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. Kidney Int. 2012;82(5):516-24.
3. Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, et al. Timing of renal replacement therapy and clinical outcomes in critically ill patients with severe acute kidney injury. J Crit Care. 2009;24(1):129-40.
4. Jamale TE, Hase NK, Kulkarni M, Pradeep KJ, Keskar V, Jawale S, et al. Earlier-start versus usual-start dialysis in patients with community-acquired acute kidney injury: a randomized controlled trial. Am J Kidney Dis. 2013;62(6):1116-21.
5. Barbar SD, Clere-Jehl R, Bourredjem A, Hernu R, Montini F, Bruyère R, et al. Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis. N Engl J Med. 2018;379(15):1431-42.
6. Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstädt H, et al. Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. JAMA. 2016;315(20):2190-9.
7. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, et al. Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. N Engl J Med. 2016;375(2):122-33.
8. STARRT-AKI Investigators; Canadian Critical Care Trials Group; Australian and New Zealand Intensive Care Society Clinical Trials Group; United Kingdom Critical Care Research Group; Canadian Nephrology Trials Network, et al. Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury. N Engl J Med. 2020;383(3):240-51.

9. Gaudry S, Hajage D, Martin-Lefevre L, Lebbah S, Louis G, Moschietto S, et al. Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): a multicentre, open-label, randomised, controlled trial. Lancet. 2021;397(10281):1293-300.
10. Seabra VF, Balk EM, Liangos O, Sosa MA, Cendoroglo M, Jaber BL. Timing of renal replacement therapy initiation in acute renal failure: a meta-analysis. Am J Kidney Dis. 2008;52(2):272-84.
11. Gaudry S, Hajage D, Benichou N, Chaïbi K, Barbar S, Zarbock A, et al. Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials. Lancet. 2020;395(10235): 1506-15.
12. Li X, Liu C, Mao Z, Li Q, Zhou F. Timing of renal replacement therapy initiation for acute kidney injury in critically ill patients: a systematic review of randomized clinical trials with meta-analysis and trial sequential analysis. Crit Care. 2021;25(1):15.
13. Vaara ST, Reinikainen M, Wald R, Bagshaw SM, Pettilä V; FINNAKI Study Group. Timing of RRT based on the presence of conventional indications. Clin J Am Soc Nephrol. 2014;9(9):1577-85.
14. Srisawat N, Laoveeravat P, Limphunudom P, Lumlertgul N, Peerapornratana S, Tiranathanagul K, et al. The effect of early renal replacement therapy guided by plasma neutrophil gelatinase associated lipocalin on outcome of acute kidney injury: A feasibility study. J Crit Care. 2018;43:36-41.
15. Klein SJ, Brandtner AK, Lehner GF, Ulmer H, Bagshaw SM, Wiedermann CJ, et al. Biomarkers for prediction of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. Intensive Care Med. 2018;44(3): 323-36.

CHAPTER 33

Continuous Urine Output Monitoring

Ramesh Venkataraman, Meghena Mathew

INTRODUCTION

This chapter aims to address the role of monitoring of continuous urine output in intensive care unit (ICU). Monitoring is a very crucial aspect of ICU management. Most of the ICU patients are on multiple monitoring devices that assist in the optimization of physiological parameters and titration of care. Both oxygenation and perfusion are key elements of monitoring and most of the devices are aimed at the same. The intention to monitor these parameters is to enable early identification of any derangements that pave the way for quick response and prevention of progression of organ failure. Urine output as a marker of perfusion of kidneys is usually monitored with indwelling catheters, but still manually estimated and recorded. Urine output although insensitive and nonspecific as a marker of renal perfusion has been used to define and hence identify acute kidney injury (AKI) in the ICU. Recent work has attempted to evaluate the utility of continuous urine output monitoring (rather than hourly) in early identification and prevention of AKI.

URINE OUTPUT MONITORING AS PREDICTOR OF ACUTE KIDNEY INJURY

One of the key reasons to monitor urine output is to reduce the incidence of AKI. AKI is a frequent complication in ICU, which affects nearly 60% of critically ill patients and is associated with significantly increased length of stay, increased costs, and 40–80% mortality rate.[1,2] Despite the growing awareness about AKI, it is increasingly associated with poor patient outcomes.[3]

All the major AKI guidelines (RIFLE, AKIN, and KDIGO criteria) have included urine output along with serum creatinine for diagnosing AKI. Serum creatinine is easily measured and is a single value at a particular point of time, whereas urine output measurement over time is a dynamic parameter. Much of the earlier studies that had looked into serum creatinine as a biomarker of AKI prediction, had excluded urine output in view of challenges in accurate collection, monitoring, and documentation. However, serum creatinine can often be diluted in patients with fluid overload and may underestimate the severity of AKI in moribund patients with poor muscle mass. Diagnosing AKI with serum creatinine alone seems to miss 20% of patients with AKI and can result in misclassification.[4] However, urine output seems to be an earlier predictor of AKI with much better sensitivity and specificity.[5,6] A single-center study by Kellum et al. had looked into the outcomes of AKI when the criteria for AKI was met with serum creatinine or urine output alone as well as in combination. The morbidity and mortality had almost doubled when AKI was met by both criteria together than either criterion alone.[4] Another single-center prospective observational study looked at monitoring both urine output and serum creatinine (hourly urine output and serum creatinine being monitored every 12–24 hours). The incidence of AKI increased from 24% based on serum creatinine criteria to 52% based on combined urine output and serum creatinine criteria.[5] Although serum creatinine and urine output have been given equal weightage in all the definitions, it seems that presence of oliguria, increases the chances of identifying AKI and portends a severe disease. Brief periods of oliguria can also predict AKI. Along with urine output monitoring, the intensity of monitoring also appears to affect outcomes. In a single-center retrospective cohort study, an intensive urine output monitoring (hourly recordings with no gaps > 3 hours) for first 48 hours after admission was compared with intensive creatinine monitoring (daily monitoring for 3 calendar days).[7] Intense urine output monitoring was associated with increased detection of moderate to severe AKI, reduced fluid overload and 30-day mortality in patients with AKI as compared to the intensive creatinine monitoring group. Intensive urine output monitoring plausibly may facilitate early recognition of AKI and prompt aggressive management with judicious use of fluids and vasopressors. Understanding the importance of detection of oliguria, a prospective observational study that had compared intensive manual and automated urine output monitoring demonstrated significant amount

of missing data (39%) when urine output was documented manually as compared to automated devices (8.6%).[8] There was also significant delay and overestimation of urine output if recording was done manually and showed that automated urine output monitoring was more accurate.

In critically ill patients, increasing awareness, concern, and education about catheter-associated urinary tract infections (CAUTIs) have appropriately led to more stringent use of indwelling urinary catheters. However, in patients at risk of AKI or in those having early AKI, the risk versus benefit of an indwelling urinary catheter need to be carefully evaluated each day in the ICU.

CONTINUOUS URINE OUTPUT MONITORING AND RENAL REPLACEMENT THERAPY

Renal replacement therapy (RRT) is the treatment of choice once AKI sets in and homeostatic derangements are refractory to medical therapy. However, the optimal timing of initiation of RRT is still debatable and has been an area of growing interest among both nephrologists and intensivists.[9] The balance of benefits of early correction of azotemia, salt and electrolyte imbalances, and prevention of fluid overload should be weighed against the risks of exposing patients to unnecessary dialysis and the associated risks including hemodynamic instability and infections. Multiple studies have evaluated different predictors of RRT initiation and have found urine output to have a strong predictive value. Low urine output in the 24 hours period prior to initiation of RRT was associated with lower survival.[10,11] When compared to other biomarkers such as blood urea nitrogen or serum creatinine, urine output was shown to improve mortality when used as decisive criteria for initiating RRT.[12] Urine output response to a standardized dose of furosemide [furosemide stress test (FST)] was studied and found to be good predictor for progression of AKI and need for RRT. Furosemide stress test is a diuretic challenge test, with 1 mg/kg of furosemide in patients who are diuretic naive and 1.5 mg/kg in patients with prior exposure to loop diuretic. A multicenter prospective observational study revealed that the urine flow rate following diuretic challenge, if <200 mL over the first 2 hours, predicts progression to stage III AKI or RRT initiation with a sensitivity of 73.9% and specificity of 90%.[13]

The kidney disease: Improving global outcomes (KDIGO) 2012 guidelines lack specific recommendations for RRT discontinuation. A recent meta-analysis published in 2020 looked at multiple variables for predicting weaning of RRT. Many studies included in the meta-analysis, although observational in nature, had urine output as the most evaluated variable along with other biomarkers such as serum creatinine, cystatin, and other biomarkers. The pooled analysis showed that urine output had a sensitivity of 66.2% and specificity of 73.6% to predict successful RRT discontinuation. However, absolute cutoff of urine output threshold could not be determined due to heterogeneity between the studies.[14]

DEVICES USED FOR CONTINUOUS URINE OUTPUT MONITORING IN ICU

As mentioned earlier, common physiological parameters such as heart rate, blood pressure, and saturation are sensed continuously and automatically monitored with sophisticated bedside devices. They record data on a continuous fashion and are not prone to human error. These devices generally also come with alarms that can alert the physician and staff taking care of the patient regarding any fluctuation from pre-established range, set by the caregivers. Often these monitors synchronize data with electronic charts negating the need for manual entry. This offloads a huge work burden from the bedside staff.

Traditionally, urine output is monitored with Foley's catheter which is introduced into the urinary bladder and has the other end connected to a graduated collection chamber, which is connected to a plastic bag. The urine output in this graduated chamber is measured hourly and documented. The chamber has a valve which when opened helps in discarding urine into the plastic bag. Monitoring urine output can get very challenging in a busy ICU as the entire process of monitoring and recording urine output is manually done and is very prone to human error. To overcome these issues, there are many innovative automatic urine flow meter devices available which are more precise and accurate. Most of which not only help in reducing the error, but also help in having a continuous data. These devices, however, are still not widely available and are expensive. These devices are based on varied working principles. Some of the devices combine a mechanical system, optical technology, and an algorithm to accurately measure urine flow. Most of the devices now come with the additional merits of liaising with electronic medical record system. In the current situation of COVID-19 pandemic, such zero-contact monitoring device may play a key role in minimizing patient contact and can reduce a significant burden on nursing care.

CONTINUOUS MONITORING OF URINE OUTPUT FOR FLUID BALANCE AND FOR PREVENTION OF CONTRAST-INDUCED NEPHROPATHY

Avoidance of fluid overload in a critically ill patient has been proven to prevent AKI and shown to have improved morbidity and mortality. Fluid overload, in recent times, has been associated with higher incidence of AKI.[15] Continuous urine output monitoring can help detect development of positive balance and alert the physician very early for appropriate actions to be initiated.

Continuous urine output monitoring has also been studied for the prevention of contrast-induced AKI (CI-AKI). One of the first few promising studies (PRINCE study) had demonstrated that forced diuresis along with intravenous fluid hydration to targeted urine output provided a moderate protective effect against CI-AKI.[16] The study revealed that urine flow rates above 150 mL/hour showed 50% reduction in rates of AKI. But this came with the risk of fluid overload and variable effect of diuretic resulting in volume depletion. In addition, the achievement of the target urine flow rate of 150 mL/hour was challenging. To overcome this, a device was developed, namely the RenalGuard system which enabled continuous monitoring of urine output following diuretics and automated administration of intravenous saline based on the urine output to avoid under-/overhydration and mitigate the side effects of diuretics. The automated urine output monitoring device used had a collection bag that was attached to Foley's catheter, and the bag was being placed on a digital scale. The device titrated the intravenous hydration based on the urine output changes. The first randomized control trial (MYTHOS) evaluated RenalGuard in patients undergoing percutaneous coronary intervention in patients with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 and compared RenalGuard with standard intravenous hydration.[17] It was demonstrated that patients with RenalGuard (automated continuous urine output monitoring) had much lower rates of CI-AKI and also had demonstrated significant reduction in hospital complications such as dialysis, pulmonary edema, shock, arrhythmias, and death.

RenalGuard system was evaluated in many other single-center and multicenter trials involving coronary procedures with contrast and was clearly shown to be associated with lesser incidence of CI-AKI.[18] RenalGuard system (continuous automated urine output monitoring) also decreased major adverse cardiac and cerebrovascular events at 1 year in patients who underwent contrast procedures. In 2014, European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) in their recommendations had incorporated the role of furosemide with matched hydration with targeted urine flow rate in moderate to severe chronic kidney disease undergoing contrast procedures. Thus, continuous urine output monitoring with automated system appears to be promising and may very soon be the standard of care in prevention of CI-AKI.

URINE OUTPUT AS GOAL FOR RESUSCITATION

Maintaining tissue perfusion is an essential component of sepsis management. Sepsis is a common cause of AKI in ICU and intravenous fluid administration is an essential part of management. Hemodynamic targets following resuscitation are indicators of macrocirculation. Urine output monitoring is an indicator of renal perfusion and hence forms part of goals of sepsis resuscitation. Certain other common conditions in an ICU where urine output is closely monitored and is part of recommendations in management include burns, pancreatitis, and postsurgical patients, most commonly post cardiopulmonary bypass surgery. AKI can occur in as high as 30% of patients undergoing cardiac surgery due to multiple predisposing factors.[19] The mortality sweeps up as high as 60% in case of AKI following cardiac surgery as compared to overall mortality of 2–8% after cardiac surgery.[20] Placement of urinary catheters and monitoring urine output during intraoperative period is a key intervention done during most cardiac surgeries. Further, use of continuous automated urine output monitoring will definitely help in prevention of postoperative AKI.

CONCLUSION

To conclude, urine output seems to be an easy bedside variable with significant utility in the ICU. Continuous monitoring of urine output could lead to early detection and faster action to physiologic derangements and make management of critically ill patients efficient and effective. It is real time, accurate, can enable early detection of kidney injury, expedite treatment actions, and avoid progression to AKI and possibly help in deciding initiation and liberation of RRT in advanced AKI. It also minimizes patient contact with reduced handling of urine bags and decreases workload of nursing staff. Automated continuous monitor is more accurate and has clearly proved its mettle in prevention of CI-AKI and possibly needs more studies to understand its role in intraoperative periods.

Conflict of interest: The authors declare that they have no conflict of interest.

REFERENCES

1. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol. 2005;16:3365-70.
2. Hoste EA, Kellum JA. Acute kidney injury: epidemiology and diagnostic criteria. Curr Opin Crit Care. 2006;12:531-7.
3. Hoste EA, Kellum JA. RIFLE criteria provide robust assessment of kidney dysfunction and correlate with hospital mortality. Crit Care Med. 2006;34:2016-7.
4. Kellum JA, Sileanu FE, Murugan R, Lucko N, Shaw AD, Clermont G. Classifying AKI by urine output versus serum creatinine level. J Am Soc Nephrol. 2015;26:2231-8.
5. Macedo E, Malhotra R, Bouchard J, Wynn SK, Mehta RL. Oliguria is an early predictor of higher mortality in critically ill patients. Kidney Int. 2011;80:760-7.
6. Macedo E, Malhotra R, Claure-Del Granado R, Fedullo P, Mehta RL. Defining urine output criterion for acute kidney injury in critically ill patients. Nephrol Dial Transplant. 2011;26:509-15.
7. Jin K, Murugan R, Sileanu FE, Foldes E, Priyanka P, Clermont G, et al. Intensive monitoring of urine output is associated with

increased detection of acute kidney injury and improved outcomes. Chest. 2017;152(5):972-9.
8. Minor J, Smith A, Deutsch F, Kellum JA. Automated versus manual urine output monitoring in the intensive care unit. Sci Rep. 2021;11(1):17429.
9. Section 5: Dialysis Interventions for Treatment of AKI. Kidney Int Suppl (2011). 2012;2(1):89-115.
10. Pérez-Fernández X, Sabater-Riera J, Sileanu FE, Vázquez-Reverón J, Ballús-Noguera J, Cárdenas-Campos P, et al. Clinical variables associated with poor outcome from sepsis-associated acute kidney injury and the relationship with timing of initiation of renal replacement therapy. J Crit Care. 2017;40:154-60.
11. Lee JH, Kim HK, Bae EH, Kim SW, Ma SK. Biomarkers Predicting Survival of Sepsis Patients Treated with Continuous Renal Replacement Therapy. Chonnam Med J. 2017;53:64-8.
12. Sugahara S, Suzuki H. Early start on continuous hemodialysis therapy improves survival rate in patients with acute renal failure following coronary bypass surgery. Hemodial Int. 2004;8(4):320-5.
13. Rewa OG, Bagshaw SM, Wang X, Wald R, Smith O, Shapiro J, et al. The furosemide stress test for prediction of worsening acute kidney injury in critically ill patients: A multicenter, prospective, observational study. J Crit Care. 2019;52: 109-14.
14. Katulka RJ, Al Saadon A, Sebastianski M, Featherstone R, Vandermeer B, Silver SA, et al. Determining the optimal time for liberation from renal replacement therapy in critically ill patients: a systematic review and meta-analysis (DOnE RRT). Crit Care. 2020;24(1):50.
15. Ding X, Cheng Z, Qian Q. Intravenous fluids and acute kidney injury. Blood Purif. 2017;43:163-72.
16. Stevens MA, McCullough PA, Tobin KJ, Speck JP, Westveer DC, Guido-Allen DA, et al. A prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy: results of the P.R.I.N.C.E. Study. Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation. J Am Coll Cardiol. 1999;33:403-11.
17. Marenzi G, Ferrari C, Marana I, Assanelli E, De Metrio M, Teruzzi G, et al. Prevention of contrast nephropathy by furosemide with matched hydration: the MYTHOS (Induced Diuresis With Matched Hydration Compared to Standard Hydration for Contrast Induced Nephropathy Prevention) trial. JACC Cardiovasc Interv. 2012;5(1):90-7.
18. Putzu A, Boscolo Berto M, Belletti A, Pasotti E, Cassina T, Moccetti T, et al. Prevention of contrast-induced acute kidney injury by furosemide with matched hydration in patients undergoing interventional procedures: a systematic review and meta-analysis of randomized trials. J Am Coll Cardiol Interv. 2017;10:355-63.
19. O'Neal JB, Shaw AD, Billings FT. Acute kidney injury following cardiac surgery: current understanding and future directions. Crit Care. 2016;20:187-201.
20. Huen S, Parikh CR. Predicting acute kidney injury following cardiac surgery: a systematic review. Ann Thorac Surg. 2012;93:337-47.

SECTION 5

Neurocritical Care

CHAPTER 34

Analgosedation in Neurosurgical Intensive Care Unit

Quirino Piacevoli, Ahsina Jahan Lopa

INTRODUCTION

In critical care, fewer drugs and careful selection of drugs for analgesia and sedation are critically important to patient outcomes. The concept of "analgosedation" is to assess the patient's comfort, treat pain first, and judiciously use sedative hypnotics if necessary to control anxiety and agitation.

If we consider the critically ill patients and the population analysis we have:

- Postsurgical patients with length of stay shorter with controlled and protected awakening. For these patients, it is useful to maintain sedation with the same drugs of total intravenous anesthesia (TIVA).
- Medical and postsurgical patients with longer length of stay with greater control of the acute phase, recovery and mobilization.

The current definition of sedation in intensive care unit (ICU) is—agitation is violent motion and strong or tumultuous emotion. This simple definition has the merit of encompassing both physical and emotional distress: Under this characterization, both the nonsedated paralyzed patient and the comatose patient can be considered agitated. (Consensus Conference Madrid 30, 1,97-123,2002-CCM). Agitation is also defined as excessive, purposeless cognitivity, and motor activity or restlessness, usually associated with a state of anxiety. Both anxiety and agitation are frequently encountered in the neurosurgical ICU and are associated with adverse outcomes. The etiological factors contributing to agitation are hypoxemia, hypercapnia, hypotension, anemia, uremia and renal failure, metabolic acidosis, coma, pain, and brain injury. Sedation of agitated critically ill patients should be started after providing adequate analgesia and treating reversible physiological causes.

PHYSIOPATHOLOGY OF ANALGOSEDATION

Clinicians need to plan an "ideal" goal of sedation for each patient. Generally, a state of quiet, sleepy patients requiring stimulus to be awaken without distress and excessive movements is considered an adequate level of sedation.[1,2]

Adequate analgesia and sedation depend not only on pharmacologic and nonpharmacologic treatment, but also on environmental factors.

Over-sedation is correlated with increased length of ventilation and ICU stay and with incidence of delirium. Under-sedation is correlated with patient's discomfort and adverse events related to the risk of devices removal.

Which is the best pharmacologic treatment ensuring adequate analgesia and sedation in patients in neurosurgical ICU?

First of all, the suppression of the noxious stimulus is required to attain hemodynamic stability and for mortality and morbidity reduction.

We know that stress can induce immunosuppression and many sequelae such as increase of catecholamine and of corticosteroids, increase of infections and metastases, and ischemia. On the contrary, we have decrease of phagocytosis and anticorpal production activity.

Efforts by the Society of Critical Care Medicine aim to optimize pain management while reducing delirium and long-term adverse consequences of ICU admission.[3] This quality improvement and knowledge transition initiative known as "ICU liberation" sets its foundation on "bundling" several elements that show more expedited mechanical ventilation weaning and encourage early mobility.

The goals of analgosedation are: Patient contort, control of pain, anxiolysis and amnesia, blunting autonomic responses, facilitating nursing care and management, patient safety, reduced oxygen consumption, ventilator synchrony, avoidance of muscle relaxants, avoiding post-traumatic stress, and normal sleep patterns (Michael Ramsay).

The sedation in neurosurgical ICU needs defining and monitoring.

Unfortunately, the evaluation of the sedation level (objective or subjective) is infrequent in an ICU, therefore, we are not sure of the result: suspended life or extending death? (Petty TL Chest 1998; 114:360).

TABLE 1: Ramsay sedation scale.

	Score	*Definition*
Awake	1	Anxious/agitated or restless or both
	2	Cooperative, oriented and calm
	3	Responds to commands only
Asleep	4	A brisk response to a light glabellar tap or loud auditory stimulus
	5	A sluggish response to a light glabellar tap or loud auditory stimulus
	6	No response to a light glabellar tap or loud auditory stimulus

ANALGOSEDATION IN NEUROSURGICAL ICU: SCALES AND TOOLS TO MONITOR AGITATION

The ideal scale or tool should be simple to apply, yet able to describe clear graded changes among levels to allow titration of intervention depending on the conditions of the patient. The scales can be considered subjectively, the tools objectively. The most well-known are: Ramsay Sedation Scale **(Table 1)**, Riker Sedation Agitation Scale, Motor Activity Assessment Scale, and Brussels Sedation Scale, all using electroencephalography (EEG), auditory evoked potential (AEP), and bispectral index (BIS).

ANALGOSEDATION IN NEUROSURGICAL ICU: HISTORY

This technique started in 1984 with a deep sedation and neuromuscular blockade of the patients benzodiazepines (BZD) and opioids.

In the following years we have a progressive reduction of neuromuscular blockade and sedation and in 2001 sedation with arousing patient with new drugs (propofol, midazolam, opioids, and alpha 2-agonists).

We can still say today sedation is most prevailing rather than analgesia and unfortunately neuromuscular blockade is still widely used.

Recommendations for sedation by panels of experts are:

- Midazolam or diazepam for rapid sedation (C)
- Propofol is the preferred sedative when rapid awakening is important (B)
- Midazolam is recommended for short term use only (A)
- Lorazepam is recommended for sedation of most patients (B)
- Titration of the sedative dose to a defined end point (B)
- The use of sedation guidelines or a protocol
- Reassess, Reassess, Reassess.

Our action must be to move from sedation to analgosedation in order to reduce trauma response.

Analgosedation in Neurosurgical ICU: Neuromuscular Blocking Agents

The use of the neuromuscular blocking agents is not recommended for the following targets: Improving mechanical ventilation and invasive techniques during the use of the new hypnotic and analgesic drugs, with evidence of damages.

On the contrary, neuromuscular blocking agents can be used in severe respiratory failure (acute respiratory distress syndrome), severe head injury, controlled hypothermia, tetanus–seizures (?), and invasive procedures.

Analgosedation in Neurosurgical ICU: Importance

The ICU is the "Dominium" of the long-lasting infusions. It is clear that the choice of analgesic modality influences most bundle elements. For example, several pharmacological elements indicated for analgesia may also confound respiratory drive, mechanical ventilation weaning, development of delirium, and ability to mobilize early.

Use of intravenous (IV) opioids is considered first-line management of non-neuropathic pain. The effects of opioids can be divided into two categories: (1) central—analgesia, euphoria, decreased respiratory rate, and mitosis; and (2) peripheral—pruritus, urinary retention, flushing, altered gut motility, decreased blood pressure, and heart rate.

REMIFENTANIL PHARMACOKINETICS: THE "FORGIVING" DRUG

Remifentanil is a synthetic opioid, characterized by quick onset and similarly rapid offset, the latter being a result of its large clearance by plasma and tissue esterases, minor tissutal accumulus, small distribution volume, low molecular dimension (md, 413 Daltons), pKa (fast dissociation constant) (7.07) < physiologic pH, nonionization, good lipophilia, easy blood-brain-barrier (bbb) crossing, and rapid onset.[1] These characteristics make remifentanil ideally suited for target-controlled infusions (TCI). Consequently, Dr Minto developed a pharmacokinetic model which allows its administration via a TCI infusion (target infusion control) system. In 2003, Dr Mertens demonstrated that the pharmacokinetic parameter set described by Minto resulted in significant median over prediction of the measured plasmatic remifentanil concentration by 15% with an inaccuracy of 20%. The conclusion from his study was that remifentanil can be administered by TCI with acceptable bias and inaccuracy. In the same year, Dr Hoymork concluded his study showing that TCI for propofol and remifentanil gives large variations in measured serum values, with a significant median over prediction of 25%. Despite huge variations in measured concentrations of propofol and remifentanil, almost all patients in his study experienced uneventful anesthesia. In spite of these studies, so far, the cerebral concentrations of the drug have never been verified in vivo. Even though we are well aware of the fact that the effect site as described in the pharmacokinetic mode cannot be directly measured within the brain being a virtual compartment with

no capacity by definition, we succeeded for the first time in measuring this concentration in patients directly in the cerebral extracellular fluid.

ANALGOSEDATION IN AN ICU: TOWARD A THERAPEUTIC SEDATION?

We can use the propofol therapeutic effects for these purposes: Decreasing cerebral metabolic rate and intracranial cerebral pressure (ICP), decreasing airways resistance in patients with reactive airways diseases, possessing antiseizure activity, and suppressing EEG activity. It also significantly reduces: The production of proinflammatory cytokines, tumor necrosis factor (TNF), interleukin-6 (IL-6), and IL-10. In addition, we have attenuating endotoxin-induced increases in cytokines and pulmonary neutrophil infiltration, reducing oxygen radical production and inhibiting lipid peroxidation, and attenuating ischemia-reperfusion injury that may also be considered a selective nitric oxide synthase (NOS) inhibitor. (CCM 30 (4): 949-52 2020).

Modulated Analgosedation (I)

Circadian rhythm of urinary 6-sulfatoxymelatonin (MT6s) excretion is abolished in sedated critically ill patients with severe sepsis. Melatonin has been shown to activate monocytes to enhance natural killer cell activity and cytokine production to inhibit apoptosis and to antagonize stress-induced immunosuppression.[4] Potent antioxidant properties of melatonin have been reported.

Considering this immunomodulatory and antioxidative role of melatonin, abnormalities of melatonin secretion might be of particular relevance. (CCM 30 (3), 536-40, 2012).

Modulated Analgosedation (II)

The regular circadian rhythm of melatonin secretion is closely related to the normal cyclic change between daytime activity and sleep during night.

The use of our sedation protocol allows us to modulate the analgesic/hypnotic relationship favoring the normal cyclic change.

Further studies are required to investigate whether therapeutic administration of supraphysiologic doses of melatonin confers any additional benefits in these patients. (CCM 30 (3), 536-40, 2020).

CONCLUSIONS: PART (I) AND PART (II)

Part (I)

- Therapeutic plan and goal of analgesia should be established for each patient to ensure consistent analgesic therapy (start with analgesia).
- Objective or at least subjective evaluation of sedation should be done. Regular assessment and response to therapy should be systematically documented.
- Choice of analgesic and hypnotic drugs on the basis of their pharmacokinetic and pharmacodynamic properties.

Part (I)

- Consider the possibility of application of modulate analgosedation.
- In the future, the choice of sedative will probably be based on the nonsedative therapeutic actions of the agents.[5]
- Reassess, reassess, reassess—why wasting a long time if it is possible to use a "forgiving" drug?

REFERENCES

1. Piacevoli Q, Del Gaudio A, Mincolelli G, Tonti MP, Wouters G, Mastronardi P. No correlation between remifentanil blood, cerebrospinal fluid and cerebral extracellular fluid levels and TCI prediction: a pharmacokinetic study. Minerva Anestesiol. 2015;81(3):305-11.
2. Barnes-Daly MA, Phillips G, Ely EW. Improving hospital survival and reducing brain dysfunction at seven California Community Hospitals: implementing PAD guidelines via the ABCDEF bundle in 6,064 patients. Crit Care Med. 2017;45:171-8.
3. Slutsky AS, Ranieri VM. Mechanical ventilation: lessons from the ARDSNet trial. Respir Res. 2000;1:73-7.
4. Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342: 1301-8.
5. Shehabi Y, Bellomo R, Mehta S, Riker R, Takala J. Intensive care sedation: the past, present and the future. Crit Care. 2013;17:322.

CHAPTER 35

Delirium in the Intensive Care Unit

Luis A Vázquez Zubillaga, Gerald Marín García, William Rodríguez-Cintrón, Gloria Rodríguez-Vega

DEFINITION

Delirium is a neuropsychiatric complication commonly encountered in the intensive care unit (ICU). It has been found with an incidence that ranges from 5 to 92%.[1] Delirium is consistently associated with morbidity determinants such as longer ICU length of stay, increased mechanical ventilation days, and long-term cognitive dysfunction.[2,3]

RISK FACTORS

Delirium triggers in the ICU can be divided into two groups: baseline and hospital-related.[4] The former are those intrinsic to the patient's characteristics and comorbidities that can seldom be corrected. Hospital-related factors are associated with the patient's underlying disease and management. Measures to prevent and treat delirium focus on altering the latter, as the hospital-related risk factors are usually modifiable.[5] The delirium development threshold is inversely related to a patient's susceptibility. It might only take a minor insult for a highly vulnerable patient to develop delirium.[5]

Pain is one of the most common and preventable delirium triggers. Pain is not only an etiology, but it also leads to agitation, promoting interventions that further enhance delirium development. The pain must be appropriately assessed and managed in the process of delirium prevention. The DOLOREA study found that ICU patients evaluated adequately for pain were less likely to receive delirium-promoting drugs such as benzodiazepines and more likely to receive analgesic medications.[6]

Immobility has been associated with delirium development in observational cohort studies. Early mobilization research has assessed the relationship between early physical rehabilitation and delirium.[7] The findings suggest that early mobility might play an essential part in reducing the delirium duration among intensive care patients.

ASSESSMENT

Elderly hospitalized patients that develop delirium end up with higher mortality and admission to long-term care.[8] Therefore, it is imperative to adequately assess delirium throughout the entire hospital stay for proper patient care. There are various objective scoring tools to complete this evaluation, and the chosen instrument will depend on the patient's population, needs, and goals.[8]

One of these tools is the Delirium Triage Screen (DTS). The DTS was designed to be the first step of a two-step delirium diagnostic method. It rapidly rules out delirium in <30 seconds. It consists of assessing the level of consciousness via the Richmond Agitation Sedation Scale (RASS) and inattention. The DTS is positive if the RASS is other than 0 (alert and calm) or the patient commits more than one error spelling the word "lunch" backward. If positive, a confirmatory second tool must rule in delirium. If negative, due to its >95% sensitivity, no additional testing is needed. Therefore, it effectively reduces the number of formal delirium assessments.

Several more specific tools can be used as confirmatory tests. These include the Brief Confusion Assessment Method (bCAM), the Confusion Assessment Method (CAM), the three-dimensional (3D)-CAM, and the 4 A's test (4AT). The bCAM is a delirium assessment that can be performed in under 3 minutes. It is a simplified CAM-ICU designed to improve sensitivity for delirium diagnosis in noncritically ill patients in demanding clinical areas such as the "emergency department". It uses objective testing to determine the presence of altered mental status, inattention, altered level of consciousness, and disorganized thinking. For delirium to be present, the patient must have altered mental status and inattention with either one of the latter characteristics. The bCAM is highly specific when performed by physicians and nonphysicians, ruling in >95% of patients with delirium.[9]

The CAM is the most extensively studied and used delirium assessment instrument. As is the case with the bCAM, for the CAM to diagnose delirium, the patient must have altered mental status, inattentiveness, and either disorganized thinking or RASS other than zero. A recent meta-analysis evaluated the effectiveness of bedside delirium diagnostic tools demonstrated that CAM had a sensitivity and specificity of 86% and 93%, respectively.[8] The major drawback for the CAM is that it might be time-consuming, and it takes approximately double the time of the bCAM. This disadvantage is offset because the nursing staff can repeatedly perform the test with adequate reliability. The high specificity and reliability lead to a broader and continuous delirium diagnostic tool that can be performed several times throughout the day.

The 3D-CAM is a 3-minute delirium assessment that is also based upon the original CAM algorithm. It uses both clinical and objective variables to determine the presence of delirium. As is the case with the CAM, a patient must be inattentive and altered with either of the other two clinical features to be 3D-CAM positive. Despite some modifications to the CAM tool, the 3D-CAM's sensitivity and specificity are maintained above 90% in the elderly population.[10]

The 4AT is a brief delirium and cognitive impairment assessment tool that can be used outside the ICU. It is easy to perform as it takes <2 minutes to complete. The 4AT is not based upon the CAM algorithm and assigns a score to four delirium or cognitive impairment clinical characteristics. This tool uses alertness without using the RASS, three questions that measure cognition, attention, and acute mental changes. After grading each variable, a score of 0 makes delirium or cognitive impairment unlikely, 1–3 makes cognitive impairment possible, or >4, makes both scenarios possible. Bellelli et al. validated this tool in the elderly inpatient population with a sensitivity and specificity of 90% and 84%, respectively.[11] This score is very versatile and has been validated in acute stroke and culturally diverse elderly populations.

PREVENTION AND TREATMENT

Delirium risk factors vary in the ICU patients, and thus an individualized prevention and treatment strategy should be sought. Nonetheless, three risk factors are consistently present because of clinical practice habits in most ICUs. These are *sedatives, immobility, and sleep disruption*. Therefore, these serve as important targets for delirium prevention and treatment.[5]

Sedative administration is common among patients receiving mechanical ventilation.[12] It is imperative to emphasize two critical components of sedation management that can improve cognitive function. The first is performing coordinated daily spontaneous awakening and spontaneous breathing trials. The second one is avoiding the administration of benzodiazepines.

Daily sedation interruption combined with spontaneous breathing trials has demonstrated improvement in clinical variables associated with improved survival. The 2008 landmark study and the Awakening and Breathing Controlled (ABC) trial confirmed that their Wake Up and Breathe protocol resulted in a decreased number of days patients had acute brain dysfunction.[13]

Randomized trials have demonstrated faster awakening times and fewer mechanical ventilation days among ICU patients sedated with alternative agents other than benzodiazepines. However, only three studies have explicitly measured delirium as a clinical variable.[14,15] The MENDS (Maximizing the Efficacy of Targeted Sedation and Reducing Neurologic Dysfunction) trial randomized mechanically ventilated ICU patients to sedation with lorazepam versus dexmedetomidine for up to 5 days. It found that patients in the dexmedetomidine group had a median of 4 more days alive and delirium-free.[14,15] A second trial compared dexmedetomidine with midazolam. In the SEDCOM (Safety and Efficacy or Dexmedetomidine Compared with Midazolam) study, patients sedated with midazolam had 23% higher delirium rates.[14,15]

The ABCDEF bundle is one of the optimal methods to avoid delirium. The ABCDEF bundle combines several interventions that enhance patient care. These include awakening and breathing coordination for liberation from sedation and mechanical ventilation, choosing sedatives that are less likely to increase the risk of delirium, optimizing analgesia, consistent delirium assessment, prevention, treatment, early mobility, and family involvement in inpatient care. The ABCDEF bundle demonstrated improvement in multiple outcomes, including preventing and reducing delirium in the ICU. In addition to potential positive effects on delirium, individual components of the ABCDEF bundle are associated with numerous outcomes, including fewer mechanical ventilation days, shorter ICU, and hospital length of stay, improved functional outcomes, and mortality.[16]

CONCLUSION

Delirium is one of the most common complications in the ICU, and it is associated with worse outcomes. The intensivist must address modifiable risk factors to help prevent and reduce the duration of this deadly syndrome. These include sedation management, deliriogenic medications, immobility, and sleep disruption. Multiple objective tools are available for the adequate assessment and diagnosis and delirium. The ABCDEF acronym is a bundled approach that clinicians can implement for ICU patients to prevent the adverse outcomes associated with delirium and critical illness.

REFERENCES

1. Spronk PE, Riekerk B, Hofhuis J, Rommes JH. Occurrence of delirium is severely underestimated in the ICU during daily care. Intensive Care Med. 2009;35(7):1276-80.
2. Lin SM, Liu CY, Wang CH, Lin HC, Huang CD, Huang PY, et al. The impact of delirium on the survival of mechanically ventilated patients. Crit Care Med. 2004;32(11):2254-9.
3. Ely EW, Gautam S, Margolin R, Francis J, May L, Speroff T, et al. The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med. 2001;27(12):1892-900.
4. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. JAMA. 1996;275(11):852-7.
5. Brummel NE. Preventing delirium in the ICU. Crit Care Clin. 2013;29(1):51-65.
6. Payen JF, Bosson JL, Chanques G, Mantz J, Labarere J. Pain assessment is associated with decreased duration of mechanical ventilation in the intensive care unit: a post Hoc analysis of the DOLOREA study. Anesthesiology. 2009;111(6):1308-16.
7. Needham DM, Korupolu R, Zanni JM, Pradhan P, Colantuoni E, Palmer JB, et al. Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project. Arch Phys Med Rehabil. 2010;91(4):536-42.
8. Wong CL, MD, Holroyd-Leduc J, Simel DL, Straus SE. Does this patient have delirium? value of bedside instruments. JAMA. 2010;304(7):779-86.
9. Hustey FM, Meldon SW. The prevalence and documentation of impaired mental status in elderly emergency department patients. Ann Emerg Med. 2002;39:248-53.
10. Marcantonio ER, Ngo LH, O'Connor M, Jones RN, Crane PK, Metzger ED, et al. 3D-CAM: derivation and validation of a 3-minute diagnostic interview for CAM-defined delirium: a cross-sectional diagnostic test study. Ann Intern Med. 2014;161(8):554-61.
11. Bellelli G, Morandi A, Davis DH, Mazzola P, Turco R, Gentile S, et al. Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalized older people. Age Ageing. 2014;43(4):496-502.
12. Patel RP, Gambrell M, Speroff T, Scott TA, Pun BT, Okahashi J, et al. delirium and sedation in the intensive care unit: survey of behaviors and attitudes of 1384 healthcare professionals. Crit Care Med. 2009;37(3):825-32.
13. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomized controlled trial. Lancet. 2008;371(9607):126-34.
14. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al.; SEDCOM (Safety and Efficacy of Dexmedetomidine Compared with Midazolam) Study Group. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA. 2009;301(5):489-99.
15. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA. 2007;298(22):2644-53.
16. Morandi A, Brummel NE, Ely EW. Review Sedation, delirium, and mechanical ventilation: the 'ABCDE' approach. Curr Opin Crit Care. 2011;17(1):43-9.

CHAPTER 36

Point-of-care Electroencephalography

Barkha Bindu, Harsh Sapra

INTRODUCTION

Patients with acute brain injury present with varying degrees of mental status changes. Inflammation, edema, and ischemia are the most common factors that precipitate secondary brain injury. A major hindrance to early detection of neurological deterioration in these patients is their unresponsive or sedated state that limits a complete neurological examination. Commonly used clinical assessment scales such as the Glasgow Coma Scale (GCS)[1] and Coma Recovery Scale-R (CRS-R)[2] are subjective. They assess patient responses without giving consideration to several other variables.[3] Such scales can misdiagnose certain patients because consciousness can exist even without behavioral signs. Multimodality monitoring (MMM) encompasses various tools to monitor various cerebral parameters such as cerebral blood flow, cerebral metabolism, and cerebral oxygenation. MMM is done with the aim of detecting changes in critical parameters such as intracranial pressure, cerebral perfusion pressure, cerebral blood flow, brain tissue oxygenation, cerebral metabolism, and electrocortical activity.

ELECTROENCEPHALOGRAPHY

Electroencephalography provides information about cerebral electrical activity. It helps to detect seizures, more importantly, nonconvulsive. EEG also helps in the diagnosis and prognostication of conditions such as encephalopathy, hypoxic and traumatic brain injuries, seizure disorders, and coma. Important therapeutic indications for EEG monitoring in ICU include determination of depth of anesthesia in pharmacologically induced coma and determination of nonconvulsive status epilepticus cessation by antiepileptic medications.

Nonconvulsive seizures occur in 4–30%[4] of patients sustaining brain injury [i.e., traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), intracranial hemorrhage (ICH), hypoxic ischemic encephalopathy (HIE) etc.]. Regardless of the etiology, nonconvulsive seizures are associated with increased morbidity and mortality.[5-7] Continuous EEG monitoring for at least 48 hours can detect seizures with >90% sensitivity in these patients.

The use of continuous electroencephalography (cEEG) in critically ill patients has been endorsed by the American Clinical Neurophysiological Society and European Society of Intensive Care Medicine.[8,9] Current MMM guidelines recommend EEG in all patients with acute brain injury, unexplained altered consciousness, during therapeutic hypothermia and within 24 hours of rewarming, and in patients with convulsive status epilepticus whose seizures do not stop within 60 minutes after medication.[10]

Basics of Electroencephalography

Standard EEG recording typically uses 21 electrodes. International 10–20 system is used for placement of electrodes on the scalp.[11] The details of the 10–20 system of electrode application can be understood from any standard neurology textbook. Electrodes are grouped into five transverse planes and five sagittal planes. Odd numbers denote left and even numbers denote right side of the head. Leads are named according to their respective anatomical locations (Fp = frontopolar, F = frontal, C = central, P = parietal, T = temporal, O = occipital). These electrodes actually detect voltage of electrical activity of the brain. What is displayed for visual assessment is the voltage difference between two leads. "Montages" compare different voltages on the scalp and therefore, help in localizing the site of any abnormal activity. "Bipolar" or "double banana" montage is the most commonly used montage by interpreters. Interpreters often switch between different montages in a single EEG for better analysis.

The EEG records electrical activity generated by neurons in the form of potential differences between various electrodes. In a healthy adult, normal cerebral electrical activity is of 20–100 mV. The EEG is digitized, amplified, filtered (to reduce noise), and displayed as waveforms of varying morphologies and frequencies. EEG waveforms are divided into different types based on their morphologies and frequencies **(Table 1)**.

TABLE 1: Electroencephalography (EEG) waveforms.

Wave	*Location*	*Frequency (Hz)*
γ	Somatosensory cortex	>30
β	Frontal	13–30
α	Occipital	8–13
θ	Diffuse	4–8
δ	Diffuse	<4

POINT-OF-CARE ELECTROENCEPHALOGRAPHY

Electroencephalography is a commonly ordered investigation in neuro ICUs, but not always understood by the ordering physicians. EEG tracings can only be intermittently reviewed by neurophysiologists. This apart, conventional scalp EEG has several limitations in an ICU setting. Poor signal-to-noise ratio, poor electrode contact with scalp, interference from other electrical devices, etc., are some of the factors that hamper proper interpretation of scalp EEG. These limitations of conventional EEG have led to the development of EEG headsets that can be comfortably applied and interpreted even by nonepileptologists.

Quantitative electroencephalography (qEEG), in essence, is a visually simplified, time-compressed display that summarizes various parameters of the raw EEG such as frequency, amplitude, power, and rhythmicity. qEEG is actually the data obtained from processing several hours of raw EEG, using compressed spectral array. Interpreters are therefore able to screen huge amounts of data much more efficiently and do not need to review the entire raw EEG tracing.[12] Most widely studied modalities of qEEG are color density spectral array (CDSA) and amplitude integrated electroencephalography (aEEG). The main advantage of qEEG is that it saves time during interpretation. The sensitivity of quantitative displays is reported to be around 65–90%. Changes noted on quantitative EEG should always be cross-checked and confirmed using the raw EEG tracing before making any changes in treatment.

Several EEG headsets are available at present. MindWave Mobile (NeuroSky Inc., USA) and Yband (Ybrain, Korea) can measure very few (only one or two) channels. The Emotiv EPOC (Emotiv, USA) is similar, and needs conductive gel injection for use. The Stat X24 mobile EEG system (Advanced Brain Monitoring Inc., USA) can measure up to 24 channels, but needs gel injection and application of headset is also difficult. The HD-72 High Density Dry Headset (Cognionics Inc., USA) can measure up to 72 channels, but it also needs assistance for application. The DSI 10/20 (Quasar, USA) is easy to apply, but after donning the headset, each electrode needs to be twisted for stable contact. The Quick-20 Dry EEG Headset (Cognionics) is quick and easy to set up, but the electrodes are sharp, have high impedance, and cause pain when pressed onto the skin. The AE-120A headset from Nihon Kohden **(Fig. 1)** features 8 channels of EEG with disposable electrodes **(Fig. 2)** that optimize the speed and ease of setup. It is a telemetry EEG amplifier developed for EEG monitoring in the emergency room (ER)/ICU setting. The headset has seven fixed electrode positions. Two more optional disk electrodes (for occipital location) can be added. It transmits data using Bluetooth technology to a laptop **(Fig. 3)**, which is a major benefit in the ICU environment, given the number of devices and wires already in place.

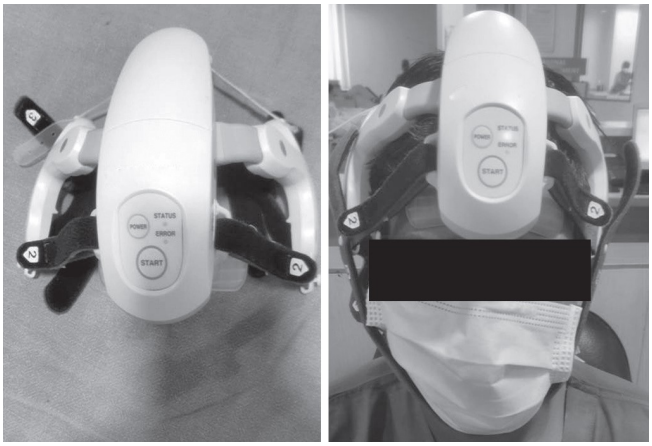


Fig. 1: AE-120A headset (Nihon Kohden).

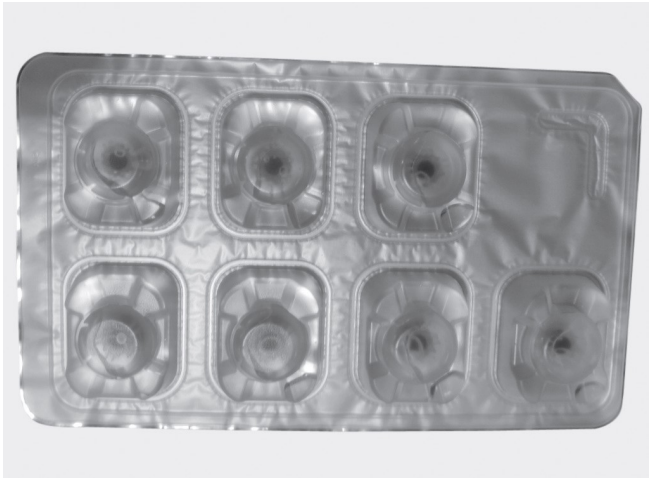


Fig. 2: Disposable electrodes used with the AE-120A headset.

Utility of Point-of-care Electroencephalography

The utility of point of care EEG can be understood from the current utility of other point of care monitors such as electrocardiogram (ECG) in the ICU. If a patient has an abnormal baseline ECG, and there are no fresh changes, no additional testing or treatment is done. However, continuous ECG monitoring in ICUs provides valuable information that can impact patient management. The same applies to point-of-care EEG monitoring.

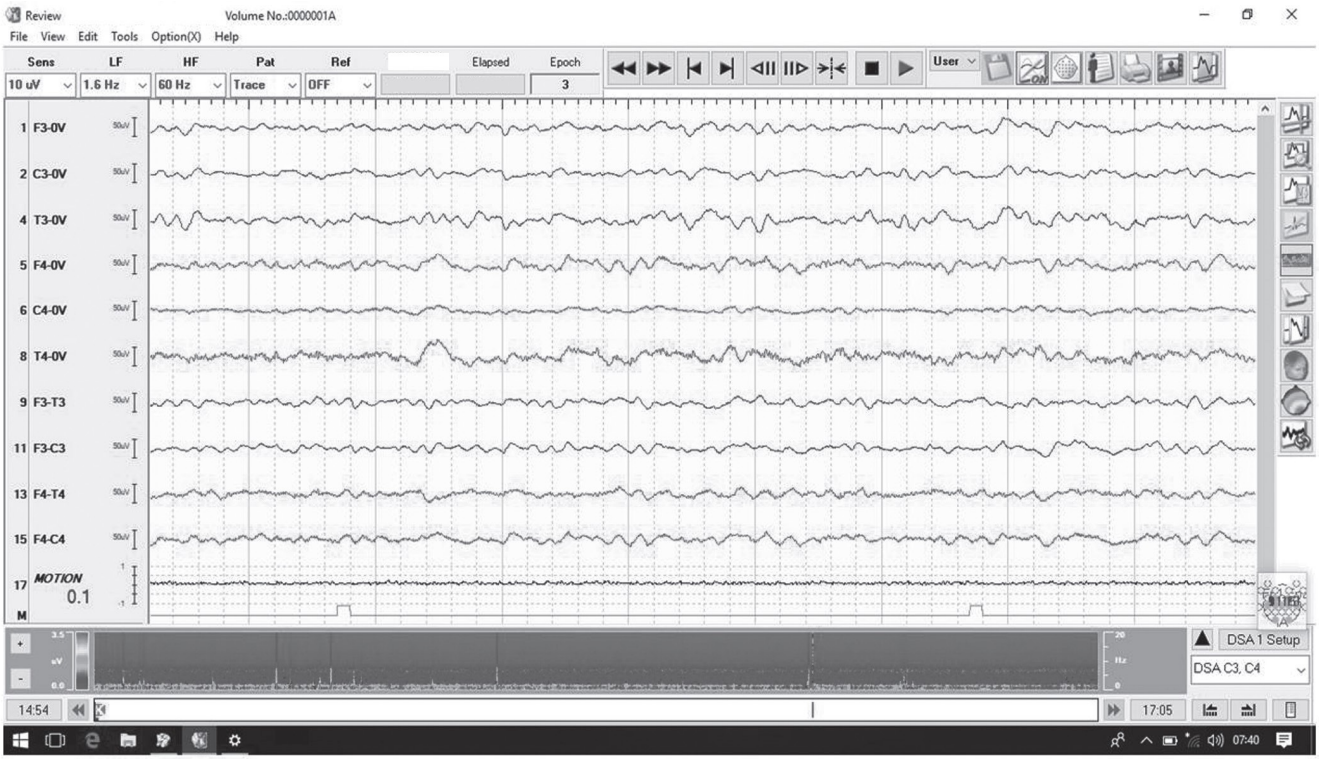


Fig. 3: EEG displayed on laptop using bluetooth technology.

A number of headsets are now available for POC EEG monitoring, as discussed above. These headsets take considerably lesser time for set up and acquisition, and use Bluetooth technology for transmission of data. The main limitation of these EEG headsets is that they have limited channels. The main advantage of these headsets is that they are quick to setup and simple to use. Studies have shown an incidence of nonconvulsive seizures of up to 16.9% using reduced-lead EEG in the ER in pediatric patients with altered mental status.[13]

Various Electroencephalography Patterns

Electroencephalography patterns that are commonly encountered in ICU include slow wave activity, triphasic waves, epileptiform patterns, and periodic discharges (PDs), suppression, and burst suppression (BS).[14] Some common terms used while interpreting and reporting EEG are discussed below.[15]

Reactivity

Change in EEG activity in response to stimulation. Change may occur in voltage or frequency, or in the form of attenuation of activity.

Periodic

Repetition of a waveform with relatively uniform morphology and duration. There is a clear interdischarge interval and the waveform recurs at approximately regular intervals.

Discharges

Waveforms lasting <0.5 seconds, irrespective of number of phases; or waveforms lasting ≥0.5 seconds with ≤3 phases.

Epileptiform

Epileptiform means "resembling epilepsy." It does not mean that the patient has clinical or subclinical seizure.

Spike

A transient and clearly distinguished from background activity. It has a pointed peak, and duration of 20–70 ms.

Sharp Waves

Similar to a spike, but with a duration of 70–200 ms. Frequent occurrence of spikes or sharp waves indicates an area of potential seizure activity. A spike or sharp wave is asymmetric, with a steeper ascending slope than descending, and either followed by a slow wave or associated with some other disruption of background activity.[15]

Polyspike

Polyspike refers to two or more spikes occurring in a row with no interdischarge interval and lasting <0.5 seconds.

Bursts

Waveforms lasting ≥0.5 seconds and having at least four phases.

Generalized

Any pattern that is bilaterally synchronous and symmetric. The field might be restricted.

Lateralized

Unilateral or bilateral, but of higher amplitude in one hemisphere than other (i.e., bilaterally asymmetric).

Bilateral Independent

Two independent and asynchronous lateralized patterns, one in each hemisphere, and both patterns occurring simultaneously.

COMMON ELECTROENCEPHALOGRAPHY PATTERNS IN NEUROCRITICAL CARE

It is important to know the most common EEG findings in critically ill patients to make effective use of this monitoring modality in ICU.

Normal (Awake) Electroencephalography

The normal awake EEG is characterized by an α rhythm (symmetrical 8–12 Hz pattern) that is best appreciated in the posterior scalp leads. It is commonly known as the "posterior dominant rhythm." This α activity is "reactive," i.e., it attenuates on eye opening or mental activity.[16] β activity is commonly seen over anterior regions of head.[11] α band frequencies may also be seen in comatose patients, but an α or posterior dominant rhythm is rarely seen in patients under effect of anesthetic drugs.[17]

Electroencephalography Artifacts

Interference from various physiological and nonphysiological sources can lead to artifacts. Electrocardiography artifacts usually occur simultaneously with QRS complexes of ECG. These ECG artifacts show a 1:1 relationship between QRS complexes and artifacts on EEG. Eye blink artifacts on EEG occur due to vertical movement of eye. These eye blink artifacts indicate that the patient is awake. Myogenic or muscle artifacts are composed of high frequency activity in frontopolar electrodes. They are commonly seen in individuals who are tense during EEG recording. They can occur during activities such as chewing also. The 60-cycle artifact occurs due to amplifier circuits. It can be eliminated by application of the 60 Hz notched filter. Certain surgically implanted devices such as pacemakers can produce electrical artifacts that contaminate the EEG. Similar electrical artifacts or "noise" is also produced by power cables located in close vicinity of patient.

Slowing

Slowing of α rhythm, either diffuse or focal, suggests encephalopathy. As encephalopathy progresses, EEG becomes increasingly slow.[17] EEG frequencies between 4 and 7 Hz are said to be moderately slow (θ band), and frequencies <4 Hz are said to be markedly slow (δ band). Pure cortical lesions do not cause slowing, but, produce a decrease in waveform amplitude.[18]

Slow waves (θ and δ activity) must be present for approximately >50% of a recording in an awake patient to be deemed pathological. Common neuropsychiatric drugs that cause diffuse slow wave activity include tricyclic antidepressants, lithium, and clozapine.[19] Other etiologies such as brain tumor, gliosis, encephalitis, infarction, subdural hematoma, and subarachnoid hemorrhage generally cause asymmetrical slowing. The presence of diffuse or severe slowing, or polymorphic delta activity (PDA, i.e., persistent and diffuse δ activity) is a nonspecific finding. PDA can occur in conditions such as sepsis, drug intoxications, hepatic failure, renal failure, hypoxia, and head trauma.[20]

Focal slowing is a more specific finding. It indicates a lesion in the underlying brain parenchyma[18] which could be abscess, hematoma, tumor, cerebral ischemia, or due to recovery from a focal seizure.[21]

Periodic Epileptiform Discharges

Periodic epileptiform discharges present as recurrent and sharp waveform abnormalities. They have an interdischarge interval ranging from 0.3 seconds to several seconds. Various types of PEDs are periodic lateralized epileptiform discharges (PLEDs), bilateral independent periodic lateralized epileptiform discharges (BIPLEDs), generalized periodic epileptiform discharges (GPEDs), stimulus-induced periodic, rhythmic or ictal discharges (SIRPIDs), and triphasic waves.

Periodic Lateralized Epileptiform Discharges

Periodic lateralized epileptiform discharges refer to PEDs that are lateralized and recur every 1–2 seconds. PLEDs may not indicate ongoing seizures, but do indicate a high risk of developing seizures.[22] They occur in the presence of an acute, destructive lesion of the underlying brain parenchyma. Common causes are acute stroke,[23] herpes encephalitis, autoimmune encephalitis, and rapidly expanding tumors. Regardless of etiology, PLEDs are usually transient and stop within days to weeks. They do not always need treatment with antiepileptic drugs (AEDs).[22,23]

Bilateral Independent Periodic Lateralized Epileptiform Discharges

These are PLEDs that are asynchronous and independent, and occur in both hemispheres. They too occur in the

presence of an acute, destructive lesion of the underlying brain parenchyma[24] and are associated with a more diffuse pathology.[25] Common causes of BIPLEDs are cerebral hypoxia, central nervous system infection, severe hypoglycemia, and herpes simplex encephalitis.[24,26] BIPLEDs are associated with a high risk of developing seizures. These patients have a worse prognosis compared to PLEDs.[24]

Generalized Periodic Epileptiform Discharges

Periodic epileptiform discharges that occur across both hemispheres, are synchronous and symmetrical are called as GPEDs. They indicate diffuse pathologies such as anoxia, Creutzfeldt–Jacob disease, HIE, drug intoxication, and end-stage Alzheimer disease.[27] GPEDs also are highly associated with seizures.

Stimulus-induced Periodic, Rhythmic or Ictal Discharges

Alerting stimuli such as suctioning, background noise, and pain can produce periodic EEG discharges or even electrographic seizures in comatose patients. This stimulus-induced pattern is called SIRPID. They are assumed to be a purely electrographic phenomenon with no clinical correlate and do not need treatment with AEDs.[28] Clinical significance of this entity is therefore uncertain.

Triphasic Waves

Earlier thought to be diagnostic of hepatic encephalopathy, triphasic waves are now known to be produced by many toxic and metabolic encephalopathies[29] like HIE and Creutzfeldt–Jakob disease.[22] They can also occur in drug overdose due to sodium valproate, baclofen, lithium, levodopa, barbiturates, and serotonergic drugs.[19] Triphasic waves are generalized, periodic, and symmetric, and occur across both hemispheres. Three phases, negative-positive-negative, are seen. Each phase is longer than the previous, and the second (positive) phase has highest voltage.[15] They are also known as "blunt spike and wave."[30] They recur at a rate of about 1 or 2 per second.

Burst Suppression

Suppression implies a low amplitude recording (<10 mV) throughout all channels. BS is characterized by alternating periods of high-voltage activity and suppressed electrical activity. When >50% of the record consists of attenuated or suppressed activity, the pattern is known as BS.[15]

It indicates diffuse cerebral dysfunction and is almost exclusively seen in deeply comatose patients.[31] It often confirms a poor prognosis. BS can be seen in patients with hypoxic injury following cardiac arrest,[32] head trauma,[17] drug intoxication with carbamazepine,[33] hypothermia, postictal suppression, brainstem hemorrhage, cerebral ischemia or edema, and end-stage status epilepticus.[34]

Burst suppression can also be caused by residual deep sedation/anesthesia. In neurocritical care units, clinicians often titrate sedatives to achieve BS. Patients with resistant status epilepticus or intractable intracranial hypertension are common examples. The patient is maximally sedated once BS is achieved and further doses of sedatives will only increase drug-related side effects with no added clinical benefit.

Electrocerebral Inactivity

Electrocerebral inactivity represents extremely suppressed EEG recording that is caused by global loss of electrical activity (<2 mV). Profound hypothermia, central nervous system (CNS) depressant drug intoxication, and severe hypotension are reversible causes of ECI and must be excluded before making a diagnosis of irreversible coma.[35]

Electrographic Seizures

Electrographic seizures are common in comatose patients and may or may not be associated with motor movements. Hence, 30-minute or 60-minute EEGs are commonly ordered to detect subtle seizures in these patients. ESz are characterized by rhythmic epileptiform discharges that evolve in frequency, morphology, and location.[36] Rare ESz may not be picked up on shorter EEGs. Continuous EEG is therefore often requested to detect nonconvulsive status epilepticus.[20]

Salzburg EEG criteria are used for diagnosing ESz.[37] They are:

- Epileptiform discharges averaging >2.5 Hz for ≥10 seconds (>25 discharges in 10 seconds)
- Any pattern with definite evolution and lasting ≥10 seconds

Focal Electrographic Seizures

Electrocerebral irritation due to localized cortical pathologies results in focal ESz. Causes include stroke, encephalitis, brain abscess, tumors, and post-traumatic gliosis.[22] Focal ESz occur over one hemisphere and are often restricted to a particular region. They can arise de novo or evolve from PLEDs.

Generalized Electrographic Seizures

Generalized ESz occur throughout the brain. Generalized ESz can be caused by focal pathologies or by idiopathic/cryptogenic epilepsy.[20]

Electrographic Status Epilepticus

Electrographic status epilepticus is defined as an ESz lasting for ≥10 minutes or for a total duration of ≥20% of any 60-minute recording.

Frontal Intermittent Rhythmic Delta Activity

Frontal intermittent rhythmic delta activity refers to sinusoidal or sawtooth waves that occur regularly and synchronously at 1.5–2.5 Hz in the frontal regions. It is associated with mild-to-moderate encephalopathy due to metabolic derangement or cerebrovascular disease.

Brief Ictal Rhythmic Discharges

Brief ictal rhythmic discharges refer to focal or generalized rhythmic activity of >4 Hz lasting 0.5–10 seconds, not consistent with a known normal pattern or benign variant and not part of BS.

Breach Effect

Breach effect refers to EEG activity detected over a skull defect. The activity here is of higher amplitude, increased sharpness and faster frequencies, compared with the rest of the brain.[15]

ELECTROENCEPHALOGRAPHY IN VARIOUS CLINICAL SITUATIONS

Given below are the EEG patterns observed in specific clinical conditions.

Effect of Drugs

Several sedative, anesthetic, and anticonvulsant medications (e.g., barbiturates, propofol, and benzodiazepines) initially increase β activity.[19] With increasing depth of anesthesia, there is progressive increase in slower frequencies.[38] With propofol, β activity decreases first followed by α activity which becomes more prominent over the anterior head regions ("anteriorization"). This is followed by emergence of slower frequencies, followed by BS and finally suppression of all cortical activity.[39]

Encephalopathy

Encephalopathy can occur due to metabolic derangement, hepatic or renal failure, toxins, and traumatic or HIE or systemic infection. EEG gives information regarding the severity of encephalopathy.[40] The earliest change seen in encephalopathy is usually "slowing," which can progress to FIRDA, triphasic waves, PDs, intermittent suppression, and BS.

Epileptiform Disorders

Patients with convulsive status epilepticus are at a high risk of ongoing subclinical seizures even after clinical seizures appear to have terminated. The diagnosis of nonconvulsive seizure (NCS) and nonconvulsive status epilepticus (NCSE) is made based on Salzburg criteria as already discussed.

Continuous electroencephalography, with or without video monitoring, monitors cerebral activity alongside patients' clinical behavior over a period of hours to weeks. In cases of refractory status epilepticus, it is also used to guide the depth of anesthesia, with BS acting as a marker of depth of anesthesia.

Subarachnoid Hemorrhage

Some recorded variables such as α/δ ratio, power, and α variability are used to detect delayed cerebral ischemia in SAH.[10,41,42] A detailed description of these entities is beyond the scope of this chapter.

Prognostication in Comatose Patients

Electroencephalography can also aid in prognostication in comatose patients, particularly after hypoxic and TBI.[43] Favorable outcomes are reported when continuous and rhythmic EEG activity is present, that is reactive to alerting stimuli.[44] Unfavorable outcomes are usually reported with discontinuous or suppressed EEG that is nonreactive, and in the presence of epileptiform discharges, GPDs, or both.[45]

CONCLUSION

Electroencephalography provides real-time and objective measure of cerebral activity in critically ill patients. Its importance is manifold higher in neurologically injured patients in whom clinical neurological examination is difficult or unreliable. EEG can detect disturbances in cerebral activity including epileptiform activity. An understanding of basics of EEG can go a long way in the diagnosis and treatment of patients. Point-of-care EEG is an upcoming neuromonitoring tool that has the capability to majorly alter the way neurocritical care is practiced.

REFERENCES

1. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet. 1974;2(7872):81-4.
2. Giacino JT. The vegetative and minimally conscious states: consensus-based criteria for establishing diagnosis and prognosis. Neurorehabilitation. 2004;19(4):293-8.
3. Reith FCM, Brennan PM, Maas AIR, Teasdale GM. Lack of standardization in the use of the Glasgow coma scale: results of international surveys. J Neurotrauma. 2016;33(1):89-94.
4. Friedman D, Claassen J, Hirsch LJ. Continuous electroencephalogram monitoring in the intensive care unit. Anesth Analg. 2009;109(2):506-23.
5. DeLorenzo RJ, Waterhouse EJ, Towne AR, Boggs JG, Ko D, DeLorenzo GA, et al. Persistent nonconvulsive status epilepticus after the control of convulsive status epilepticus. Epilepsia 1998;39(8):833-40.
6. Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch LJ. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology. 2004;62(10):1743-8.
7. Kramer AH, Jette N, Pillay N, Federico P, Zygun DA. Epileptiform activity in neurocritical care patients. Can J Neurol Sci. 2012;39(3):328-37.
8. Herman ST, Abend NS, Bleck TP, Chapman KE, Drislan FW, Emerson RG, et al. Consensus statement on continuous EEG

in critically ill adults and children, part I: indications. J Clin Neurophysiol. 2015;32(2):87-95.
9. Claassen J, Taccone FS, Horn P, Holtkamp M, Stocchetti N, Oddo M, et al. Recommendations on the use of EEG monitoring in critically ill patients: consensus statement from the neurointensive care section of the ESICM. Intensive Care Med. 2013;39(8):1337-51.
10. Roux P Le, Menon DK, Citerio G, Vespa P, Bader MK, Brophy GM, et al. Consensus summary statement of the international multidisciplinary consensus conference on multimodality monitoring in neurocritical care: a statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine. Neurocrit Care. 2014;21 suppl 2:S1-26.
11. Libenson MH (Ed). Practical Approach to Electroencephalography, 1st edition. Philadelphia: Elsevier/Saunders; 2010.
12. Haider HA, Esteller R, Hahn CD, Westover MB, Halford JJ, Lee JW, et al. Sensitivity of quantitative EEG for seizure identification in the intensive care unit. Neurology. 2016;87(9):935-44.
13. Yamaguchi H, Nagase H, Nishiyama M, Tokumoto S, Ishida Y, Tomioka K, et al. Nonconvulsive seizure detection by reduced–lead electroencephalography in children with altered mental status in the emergency department. J Pediatr. 2019;207:213-19.
14. Anderson D, Jirsch JD, Wheatley MB, Brindley PG. Electroencephalogram patterns in critical care: A primer for acute care doctors. J Int Care Soc. 2020;23(1):58-69.
15. Hirsch LJ, Fong MWK, Leitinger M, LaRoche SM, Beniczky S, Abend NS, et al. American Clinical Neurophysiology Society's standardized critical care EEG terminology: 2021 version. J Clin Neurophysiol. 2021;38(1):1-29.
16. Sewell L, Abbas A, Kane N. Introduction to interpretation of the EEG in intensive care. BJA Educ. 2019;19(3):74-82.
17. Young GB. The EEG in coma. J Clin Neurophysiol. 2000; 17(5):473-85.
18. Schaul N. Pathogenesis and significance of abnormal non-epileptiform rhythms in the EEG. J Clin Neurophysiol. 1990;7(2):229-48.
19. Blume WT. Drug effects on EEG. J Clin Neurophysiol. 2006;23(4):306-11.
20. Brenner RP. The interpretation of the EEG in stupor and coma. Neurologist. 2005;11(5): 271-84.
21. Huppertz HJ, Hof E, Klisch J, Wagner M, Lücking CH, Kristeva-Feige R. Localization of interictal delta and epileptiform EEG activity associated with focal epileptogenic brain lesions. Neuroimage. 2001;13(1):15-28.
22. Brenner RP, Schaul N. Periodic EEG patterns: classification, clinical correlation, and pathophysiology. J Clin Neurophysiol. 1990;7(2):249-67.
23. Pohlmann-Eden B, Hoch DB, Cochius JI, Chiappa KH. Periodic lateralized epileptiform discharges–a critical review. J Clin Neurophysiol. 1996;13(6):519-30.
24. Orta DSJ, Chiappa KH, Quiroz AZ, Costello DJ, Cole AJ. Prognostic implications of periodic epileptiform discharges. Arch Neurol. 2009;66(8):985-91.
25. Lawn ND, Westmoreland BF, Sharbrough FW. Multifocal periodic lateralized epileptiform discharges (PLEDs): EEG features and clinical correlations. Clin Neurophysiol. 2000;111(12):2125-9.
26. Lee JW. EEG in the ICU: what should one treat, what not? Epileptologie. 2012;29:210-7.
27. Husain AM, Mebust KA, Radtke RA. Generalized periodic epileptiform discharges: etiologies, relationship to status epilepticus, and prognosis. J Clin Neurophysiol. 1999;16(1):51-8.
28. Hirsch LJ, Claassen J, Mayer SA, Emerson RG. Stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs): a common EEG phenomenon in the critically ill. Epilepsia. 2004;45(2):109-23.
29. Fountain NB, Waldman WA. Effects of benzodiazepines on triphasic waves: implications for nonconvulsive status epilepticus. J Clin Neurophysiol. 2001;18(4):345-52.
30. Foley JM, Watson CW, Adams RD. Significance of the electroencephalographic changes in hepatic coma. Trans Am Neurol Assoc. 1950;51:161-5.
31. Amzica F. What does burst suppression really mean? Epilepsy Behav. 2015;49:234-7.
32. Zaret BS. Prognostic and neurophysiological implications of concurrent burst suppression and alpha patterns in the EEG of post-anoxic coma. Electroencephalogr Clin Neurophysiol. 1985;61(4):199-209.
33. Rubeis DA De, Young GB. Continuous EEG monitoring in a patient with massive carbamazepine overdose. J Clin Neurophysiol. 2001;18(2):166-8.
34. Niedermeyer E. The burst-suppression electroencephalogram. Am J Electroneurodiagnostic Technol. 2009;49(4):333-41.
35. Husain AM. Electroencephalographic assessment of coma. J Clin Neurophysiol. 2006;23(3):208-20.
36. Chong DJ, Hirsch LJ. Which EEG patterns warrant treatment in the critically ill? Reviewing the evidence for treatment of periodic epileptiform discharges and related patterns. J Clin Neurophysiol. 2005;22(2):79-91.
37. Leitinger M, Trinka E, Gardella E, Rohracher A, Kalss G, Qerama E, et al. Diagnostic accuracy of the Salzburg EEG criteria for non-convulsive status epilepticus: a retrospective study. Lancet Neurol. 2016;15(10):1054-62.
38. Rampil IJ. A primer for EEG signal processing in anesthesia. Anesthesiology. 1998;89(4):980-1002.
39. Purdon PL, Sampson A, Pavone KJ, Brown EN. Clinical electroencephalography for anesthesiologists: Part I: Background and basic signatures. Anesthesiology. 2015;123(4):937-60.
40. Kaplan PW. The EEG in metabolic encephalopathy and coma. J Clin Neurophysiol. 2004;21(5):307-18.
41. Roh D, Park S. Brain multimodality monitoring: updated perspectives. Curr Neurol Neurosci Rep. 2016;16(6):56.
42. Stuart RM, Waziri A, Weintraub D, Schmidt MJ, Fernandez L, Helbok R, et al. Intracortical EEG for the detection of vasospasm in patients with poor-grade subarachnoid hemorrhage. Neurocrit Care. 2010;13(3):355-8.
43. Sivaraju A, Gilmore EJ, Wira CR, Stevens A, Rampal N, Moeller JJ, et al. Prognostication of post-cardiac arrest coma: early clinical and electroencephalographic predictors of outcome. Intensive Care Med. 2015;41(7):1264-72.
44. Young GB, Wang JT, Connolly JF. Prognostic determination in anoxic-ischaemic and traumatic encephalopathies. J Clin Neurophysiol. 2004;21(5):379-90.
45. Sandroni C, Cariou A, Cavallaro F, Cronberg T, Friberg H, Hoedemaekers C, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European resuscitation council and the European society of intensive care medicine. Resuscitation. 2014;85: 1779-89.

CHAPTER 37

Curing Coma

Yash Javeri, Abhishek Shrivastava, Neeraj Yadav

INTRODUCTION

Coma has remained a huge challenge for the healthcare fraternity across the globe. The impact on populations across the world is damaging with mortality and long-term morbidity. The dilemmas, the uncertainties, and the fight between life and death make it more enigmatic. Coma has ignited passion with calculated skepticism for clinicians and researchers. In 2019, the Neurocritical Care Society (NCS) launched Curing Coma® as a campaign. Curing coma is a signature clinical, scientific, and public health effort. Being the first global public health initiative to understand the common concepts of coma as a curable disease. The final goal is to translate all efforts into treatment strategies for coma. From the patient's perspective, the disorders of consciousness (DoC) have hope for treatment.

BACKGROUND

Coma is the most severe manifestation of brain injury. Coma and DoC burden the families, healthcare systems, and public health alike globally. The condition is widely prevalent across nations with different etiology and myriad presentations. This could be the ultimate manifestation of many serious acute neurological disorders or non-neurological conditions ranging from trauma, stroke, infection, metabolic, toxic, seizure, and many other pathologies. For an intensivist, it is an ever-challenging, pervasive, intriguing, and highly unpredictable condition. The pathophysiology, course, therapies, and outcomes are all variable. Heterogeneous care adds to the burden. There are major challenges and gaps in neurological assessment, prognostic tools, and therapies for coma. Coma can herald long-lasting unconsciousness, a transient state followed by the return of consciousness, or a chronic state characterized by partial recovery of consciousness.

CURING COMA CAMPAIGN

The NCS launched the Curing Coma Campaign in 2019 addressing the humongous challenge of bettering outcomes of coma patients. An advisory council with academicians representing all stakeholders was formulated first. The council had included coma scientists, neurointensivists, neurorehabilitationists, and implementation experts to address different issues and incorporate opinions from all allied specialists.

We need to identify the cause or all the components contributing to coma. Every effort should be made to reverse the modifiable cause. Secondary brain injury prevention is pivotal. Patients with poor neurological outcomes need to be identified objectively with conviction. The same needs to be communicated and ethical principles of care be applied. The last 20 years witnessed rapid advances in coma science. Detection, pathophysiology, prediction, diagnostics, and therapeutics for promoting coma recovery made substantial progress. Advanced neuroimaging and electrophysiological techniques have elucidated biological mechanisms defining recovery of consciousness. This helped identify newer tools for diagnostics, prognostication, and therapy for coma.

SOCIETAL IMPACT

The most difficult question asked by the family is—will my patient have a purposeful recovery? This deserves a definitive and clearer answer with conviction. There have been no clear answers for the majority of coma patients. However, understandably the answer to this question decides further care process. Recovery from a coma and its prognostication is the most vital factor determining physician and family decision on further clinical course. The question of cognitive improvement remains a compelling and perplexing variable for patients, families, and care providers. Recovery from the coma, pace of recovery, degree of recovery, and functional status after recovery are questions haunting family and care providers. Uncertainty in current prognostication methods compounded by the lack of pharmacological, surgical, and rehabilitation interventions that specifically improve cognition are the most encompassing challenges. Recognizing this gap in

coma understanding and intervention, and the key importance of advancing research in this area, the NCS has launched the Curing Coma Campaign.

RECOVERY FROM COMA IS POSSIBLE

While we have learned a lot about coma, we still do not have a definitive care process for the comatose. As a clinician, we might have some understanding on the short-term recovery in hospital or nursing home facility, but what happens beyond that in domiciliary care still is largely unclear. Long-term outcomes and trajectories also need to be emphasized in the patient care plan.

For patients with DoC and their families, the search for the Holy Grail has been disappointing. Clinical research also has been largely disappointing for the therapeutics segment in coma care. These trials are often limited by small sample sizes, lack of placebo groups, and the use of heterogeneous outcome measures. Rarely do we find therapy with strong evidence to support their use in this segment. To foster and advance the development of consciousness-promoting therapies for patients with DoC, the Curing Coma Campaign convened a Coma Science Work Group to perform a gap analysis.

Neurocritical Care Society in partnership with the National Institutes of Health defined six core strategies targeting coma treatment. The meeting suggested six key strategies: (1) Defining endotype/phenotypes, (2) biomarkers, (3) proof-of-concept clinical trials, (4) neuroprognostication, (5) long-term recovery, and (6) large datasets.

THE PLAN'S THREE PILLARS

The three fundamental and overarching pillars that form the foundation are:

1. *Endotyping*—will help categorize coma/DoC in a pragmatic way
2. *Biomarkers*—evaluating current tools and their shortcomings in an understanding coma and its prognosis
3. *Proof-of-concept clinical trials*—identifying early proof-of-concept interventional studies to evaluate new treatment protocols and inform clinical trial design

Endotyping

The first and foremost recommendation is to group and understand myriad types of coma based on etiology and other confounders. Different pathophysiology and underlying mechanism of decreased consciousness could have different outcomes and different therapeutic targets. This will help care providers facilitate difficult decision-making at an earlier stage.

Initially, the term phenotype was utilized but there were major drawbacks. We understand that the physical manifestation of the different disease processes can manifest finally as DoC/coma. Such similar clinical phenotypes with diverse etiology were a major hurdle in right classification and coma prognostication. This was the basis for changing to endotyping which better reflects on the hugely variable phenotypes. To date, DoC endotypes in the acute stage have not been well classified. Better identification of DoC endotypes and their recovery trajectories early in the course of critical care management may identify better chances of cognitive recovery from those where the interventions could prove futile.

Potential Methods to Classify Different Coma Endotypes

The tiered multidimensional framework counts in for complexity of pathogenesis, disease course, proven, and future therapeutic targets amongst other variables.

Structural imaging and clinical phenotypes form the basis of Tier 1. Tier 2 adds functional measures such as electroencephalography (EEG), positron emission tomography (PET), and functional magnetic resonance imaging (MRI), categorized using the Arousal, Volition, Cognition, and Mechanisms (AVCM) score. Tier 3 depicts different dynamic variations over time with a plethora of physiologically distinct states to define recovery from coma. It also suggests therapeutic targets for DoC. Whereas Tiers 1 and 2 propose an approach for low-resource settings and state-of-the-art expertise at leading academic centers, respectively. Tier 3 is a visionary multidimensional consciousness paradigm driven by continuous incorporation of new knowledge while addressing the Curing Coma Campaign's aspirational goals.

Early recognition of different endotypes of DoC categorizes patients with different recovery trajectories, helping precise prognostication. Identification of patients amenable to interventions at specific time points will enable clinical trials of targeted treatments to accelerate emergence from the coma and improve cognitive and functional outcomes. These models also help stakeholders of patients have better clarity and set realistic goals for treatment.

Different Coma/Disorders of Consciousness Endotypes

Endotyping of coma follows an open-minded and pragmatic approach to DoC. This classification system emphasizes how the specific DoC cause affects the recovery and response to various interventions. There are four broad subcategories:

1. *DoC endotype without commensurate structural damage*: Coma with no structural injury like those because of seizure or drugs or substance consumption are commonly reversible with/without therapy or with time. These are recognized on the basis of metabolic or electrical instability. The treatment pathways are well-defined.

2. *DoC endotype with structural or functional damage that is amenable to the replacement or bypass therapy*: The subgroup includes DoC caused by damage that could potentially be replaced by surrogate brain function such as stimulant medications or brain-machine. Barring the most severe cases, hypoxic-ischemic injury and traumatic brain injury would be in this group.
3. *DoC endotype that is not amenable to the pharmacologic or anatomic replacement or repair therapy*: Essentially, this endotype will not be amenable to prevalent therapeutic strategies under underlying pathologies, such as Alzheimer disease or end-stage prion. This endotype may progress from endotypes 1 or 2 if structural, metabolic, or electrical insult remains unreversed.
4. *DoC mimics endotype*: This group includes cases in which structural damage leads to a syndrome mimicking DoC. Locked-in syndrome, severe aphasia, or abulia are classic mimics.

Biomarkers for Coma/Disorders of Consciousness (Box 1)

Multitier models for prognostication and outcome trajectory have pillars of clinical, neuroimaging, physiological, electrographic, and other biomarker data at different time points. These biomarkers and other signals need to be assessed dynamically and contextually.

Biomarkers have three major goals in the practice of DoC which are as follows:

1. Make endotypic or mechanistic diagnostic determinations
2. Follow the progression of the comatose patient, either as part of a natural disease course or as a theranostics tool
3. Develop multidimensional flexible trajectory models

BOX 1: Currently used biomarkers for disorders of consciousness (DoC).

- *Brain at rest*
- *Structural analysis*: MRI (FLAIR, high resolution T1, etc.) and head CT
- *Neuronal activity*: Spectral analysis, entropy and connectivity measures of the resting EEG
- *Functional connectivity*: EEG coherence, phase-amplitude modulations, and resting state functional MRI
- *Direct measures of brain physiology*: Metabolism (FDG PET), oxygen (partial brain tissue oxygenation and oxygen saturation), blood flow (MR or CT perfusion imaging, MR arterial spin labeling, Xenon CTP, invasive measure of rCBF), ICP/CPP, cerebral metabolites (MR spectroscopy, microdialysis), brain water content, brain temperature, and cortical spreading depolarization
- *Measures reflecting injury to the brain*: CSF and serum (NSE, S110Beta, GFAP, vimentin, myelin basic protein, inflammatory markers such as IgG electrophoresis)
- *Passive perturbation tasks*
- *Sensory stimulation-induced evoked potentials (SSEP, BAEP, MEP)*: Short versus long latency
- *Event-related potentials*: Cognitive processing involved with processing of regularities (i.e., local global paradigm), processing of ERPs-induced modulation of the autonomic nervous system
- Transcranial magnetic stimulation with high-density EEG co-registration
- Stimulus-based functional EEG or functional MRI (e.g., with language or music stimuli)
- *Active perturbation tasks*
- *Behavioral assessment*: Coma recovery scale-revised, other less comprehensive clinical scales (FOUR score, Glasgow Coma Score), and differential electromyographic response
- Task-based functional EEG or functional MRI (e.g., commanded motor acts, motor imagery, or spatial navigation)

(BAEP: brainstem auditory evoked potential; CPP: cerebral perfusion pressure; CT: computed tomography; CTP: computed tomographic perfusion; EEG: electroencephalography; ERP: event-related potential; FDG-PET: fluorodeoxyglucose positron emission tomography; FLAIR: fluid-attenuated inversion recovery; FOUR: full outline of unresponsiveness; GFAP: glial fibrillary acidic protein; ICP: intracranial pressure; MEP: motor evoked potential; MR: magnetic resonance; MRI: magnetic resonance imaging; NSE: neuron specific enolase; rCBF: regional cerebral blood flow; SSEP: somatosensory evoked potential)

Proof-of-concept Trials

Arousal and awareness are the two essential elements of consciousness. Earlier proof of concept research has tested pharmacological and electrophysiological interventions for both these elements. Most recent trials of therapies targeting reversal from a coma in patients with the structural disease have been researched for an acute or subacute phase of DoC/coma. Limited success with most trials and no definitive therapy is challenged by recent clinical and radiological data suggesting that some patients with prolonged DoC may improve with therapeutic interventions even after years of the initial insult. Noninvasive brain stimulation, brain imaging open-label trials, and behavioral interventions seem to be yielding encouraging results. Most pharmacologic trials have tested stimulant medications, particularly those that promote dopamine signaling within the brain. Despite initial encouraging results from several proof-of-concept pharmacologic and electrophysiologic trials conducted in the subacute-to-chronic setting, there have been few studies of consciousness-promoting therapies in the acute intensive care unit (ICU) setting. Next steps to developing proof-of-concept clinical trials with recent studies showing that pharmacologic and electrophysiologic stimulation therapies can reactivate brain networks in selected patients, personalized connectome mapping tools and fluid biomarkers available at the point of care are urgently needed to identify patients who may benefit from these therapies. An individualized and personalized approach to DoC endotypes may help fine-tune the neurological recovery and help some categories of patients. This may open the road to recovery with judicious interventions beyond the acute phase with more conviction and titrated outcomes.

LIMITATIONS/CHALLENGES

Real world issues of relevance, and implementation of endotypes in the clinical setting. There is lot of overlap between various endotypes which will add to confusion. Definitions are inconsistent and multiple descriptions are given to a coma syndrome. The campaign needs validation across heterogeneous clinical setups, especially in resource limited settings.

CONCLUSION

Coma/DoC remain a major challenge for the patient, family, and care providers. Accurate prognostication tools and judicious interventions remain a glimmer of hope. A rational and pragmatic system for endotyping patients with coma is developed. The lack of appropriate biomarkers and limitations in endotyping individual patients make interventional trials difficult to construct and interpret. The curing coma campaign is a first step toward framing the broad scientific resources required to fundamentally improve the understanding and treatment of DoC.

The campaign envisages that a clearer clinical pathway for prognostication and measuring responses to new interventions could pave way for individualized and definitive curative targeted treatments that are personalized to each patient. This personalized approach can be realized through rigorous clinical trial design and international collaboration, both of which will be essential for advancing the development of new therapies and ultimately improving the lives of patients with DoC.

REFERENCES

1. Provencio JJ, Hemphill JC, Claassen J, Edlow BL, Helbok R, Vespa PM, et al. The Curing Coma Campaign: Framing Initial Scientific Challenges—Proceedings of the First Curing Coma Campaign Scientific Advisory Council Meeting. Neurocritical Care. 2020;33(1):1-12.
2. Claassen J, Akbari Y, Alexander S, Bader MK, Bell K, Bleck TP, et al. Proceedings of the First Curing Coma Campaign NIH Symposium: Challenging the Future of Research for Coma and Disorders of Consciousness. Neurocrit Care. 2021;35 (Suppl 1):4-23.
3. Brogan ME, Provencio JJ. Spectrum of catastrophic brain injury: coma and related disorders of consciousness. Crit Care. 2014;29(4):679-82.
4. Edlow BL, Claassen J, Schiff ND, Greer DM. Recovery from disorders of consciousness: mechanisms, prognosis and emerging therapies. Nat Rev Neurol. 2021;17:135-56.
5. Edlow BL, Sanz LRD, Polizzotto L, Pouratian N, Rolston JD, Snider SB, et al. Therapies to restore consciousness in patients with severe brain injuries: A gap analysis and future directions. Neurocrit Care. 2021;35(Suppl 1):68-85.
6. Hocker S, Shah S, Vespa P, Provencio JJ, Calvillo E, Olson DM, et al. The future of neurocritical care research: proceedings and recommendations from the fifth neurocritical care research network conference. Neurocrit Care. 2020;32(1):311-6.
7. Kondziella D, Menon DK, Helbok R, Naccache L, Othman MH, Rass V, et al. A precision medicine framework for classifying patients with disorders of consciousness: Advanced Classification of Consciousness Endotypes (ACCESS). Neurocrit Care. 2021;35(Suppl 1):27-36.
8. Thibaut A, Schiff N, Giacino J, Laureys S, Gosseries O. Therapeutic interventions in patients with prolonged disorders of consciousness. Lancet Neurol. 2019;18(6):600-14.

38

CHAPTER

Status Epilepticus Relook

Sivakumar MN, Shankha S Sen, Bhuvna Ahuja

INTRODUCTION

Status epilepticus (SE) is an acute neurologic emergency with an estimated 30-day mortality rate as high as 21%[1] and survivors have high incidence of neurologic and cognitive deficits. It disproportionately affects younger children and elderly population. SE is caused by wide range of etiologies. Etiology also determines the severity and prognosis of the disease along with other factors such as type, duration of seizure, and the changes in electroencephalogram (EEG). Recent advancement in the understanding of etiopathogenesis and pathophysiology of SE has helped in identifying the need for early administration of antiepileptics.

DEFINITION

A seizure is defined as "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. The term 'transient' is used as demarcated in time with a clear start and finish". SE is defined as seizure activity persisting for 5 minutes or longer (particularly in the case of convulsive SE), as seizures are less likely to stop spontaneously after 5 minutes.

International League Against Epilepsy (ILAE) Task Force in 2015 has proposed a definition that encompasses all types of SE and takes into consideration current knowledge regarding the pathophysiology of SE and the need to address clinical treatment decision-making time points, as well as the conduct of epidemiologic and clinical studies. It is a conceptual definition with two operative time points t_1 and t_2 **(Table 1)** which guide us on initiation and escalation of antiseizure measures.

Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which leads to abnormally prolonged seizures (after time point t_1). It is a condition that can have long-term consequences (after time point t_2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.

CLASSIFICATION

Classification of SE should encompass conceptual scientific knowledge available regarding etiopathogenesis and should be a pragmatic empirical classification. It should facilitate clinical differentiation and communication between clinicians with common terminologies and should improve the treatment of patients. It should permit epidemiological studies of consequences and prognosis as well to aid basic research to identify natural classes which in turn will lead to basis of true scientific classification.

Status epilepticus is not a disease entity but rather a symptom with myriad etiologies. Symptoms and signs can

TABLE 1: Operational dimensions with t_1 indicating the time that emergency treatment of status epilepticus (SE) should be started and t_2 indicating the time at which long-term consequences may be expected.[2]

Type of SE	Operational dimension 1 time (t_1), when a seizure is likely to be prolonged leading to continuous seizure activity	Operational dimension 2 time (t_2), when a seizure may cause long-term consequences (including neuronal injury, neuronal death, alteration of neuronal networks, and functional deficit)
Tonic-clonic SE	5 minutes	30 minutes
Focal SE with impaired consciousness	10 minutes	>60 minutes
Absence of status epilepticus	10–15 minutes[a]	Unknown

[a]Evidence for the timeframe is currently limited and future data may lead to modifications.

be dynamic, hence, ILAE Task Force has classified SE along four axes:

1. Semiology
2. Etiology
3. Electroencephalography correlates
4. Age

Semiology

It refers to clinical presentation of SE. The two main criteria are:

1. Presence or absence of predominant motor symptoms
2. The degree of impaired consciousness

Status epilepticus can be convulsive SE with predominant motor symptoms and impaired consciousness as opposed to nonconvulsive SE where motor symptoms are usually absent **(Table 2)**.

Etiology

Status epilepticus is categorized based on the concepts put forth by the ILAE commission for classification proposal in 2010. It is based on known or unknown cause of the disease tagged along with its temporal relationship as acute, remote, progressive, etc. **(Box 1)**.

Electroencephalography Correlates

None of the ictal EEG patterns of any type of SE are specific, epileptiform discharges are considered hallmark but as SE duration prolongs EEG patterns may progress to rhythmic nonepileptiform patterns. These dynamic EEG patterns in SE are classified based on:

- *Location*: Generalized, lateralized, bilateral independent, and multifocal
- *Name of the pattern*: Periodic discharges, rhythmic delta, spike and wave/sharp, and wave subtypes
- *Morphology*: Sharpness, number of phases, absolute and relative amplitude, and polarity
- *Time-related feature*: Prevalence, frequency, duration, daily pattern duration, onset, and dynamics
- *Modulation*: Stimulus induced *versus* spontaneous
- Effect of intervention on EEG

Age (Box 2)

- Neonatal (0–30 days)
- Infancy (1 month to 2 years)
- Childhood (>2–12 years)
- Adolescence and adulthood (>12–59 years)
- Elderly (60 years and above)

TABLE 2: Axis 1: Semiological classification.[2]

With prominent motor symptoms	*Without prominent motor symptoms (i.e., nonconvulsive SE, NCSE)*
• Convulsive SE (CSE, synonym: tonic–clonic SE) – Generalized convulsive – Focal onset evolving into bilateral convulsive SE – Unknown whether focal or generalized • Myoclonic SE (prominent epileptic myoclonic jerks) – With coma – Without coma • Focal motor – Repeated focal motor seizures (Jacksonian) – Epilepsia partialis continua (EPC) – Adversive status – Oculoclonic status – Ictal paresis (i.e., focal inhibitory SE) • Tonic status • Hyperkinetic SE	• NCSE with coma (including so-called "subtle" SE) • NCSE without coma – Generalized - Typical absence status - Atypical absence status - Myoclonic absence status – Focal - Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/psychic/experiential, or auditory symptoms) - Aphasic status - With impaired consciousness – Unknown whether focal or generalized - Autonomic SE

(SE: status epilepticus)

BOX 1: Etiological classification.[2]

- Known (i.e., symptomatic)
  - Acute (e.g., stroke, intoxication, malaria, encephalitis, etc.)
  - Remote (e.g., post-traumatic, postencephalitic, poststroke, etc.)
  - Progressive [e.g., brain tumor, Lafora's disease and other progressive myoclonic epilepsy (PMEs), dementias]
  - Status epilepticus in defined electroclinical syndromes
- Unknown (i.e., cryptogenic)

BOX 2: Status epilepticus (SE) in selected electroclinical syndromes according to age.[2]

- Neonatal and infantile-onset epilepsy syndromes:
  - Tonic status (e.g., in Ohtahara syndrome or West syndrome)
  - Myoclonic status in Dravet syndrome
  - Focal status
  - Febrile SE
- Childhood and adolescence:
  - Autonomic SE in early-onset of benign childhood occipital epilepsy (Panayiotopoulos syndrome)
  - Nonconvulsive status epilepticus (NCSE) in specific childhood epilepsy syndromes and etiologies (e.g., ring chromosome 20 and other karyotype abnormalities, Angelman syndrome, epilepsy with myoclonic-atonic seizures, other childhood myoclonic encephalopathies
  - Tonic status in Lennox–Gastaut syndrome
  - Myoclonic status in progressive myoclonus epilepsies
  - Electrical status epilepticus in slow wave sleep (ESES)
  - Aphasic status in Landau–Kleffner syndrome
- Adolescence and adulthood:
  - Myoclonic status in juvenile myoclonic epilepsy
  - Absence status in juvenile absence epilepsy
  - Myoclonic status in Down syndrome
- Elderly:
  - Myoclonic status in Alzheimer's disease
  - Nonconvulsive status epilepticus in Creutzfeldt–Jakob disease
  - De novo (or relapsing) absence status of later life

Based on Response to Medications

- *Refractory SE*: Status epilepticus that persists beyond two appropriately dosed antiseizure drugs including benzodiazepines (BZDs).
- *Super-refractory status epilepticus (SRSE)*: Status epilepticus persisting beyond 24 hours of third line antiseizure drug (anaesthetic drug), or seizures that re-emerge when anesthetic drugs are withdrawn.
  An international and multidisciplinary group of experts convened on the occasion of the 6th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures in Salzburg, Austria to develop proposed consensus definitions for new onset refractory seizures (NORSE), febrile illness-elated epilepsy syndrome (FIRES), and related conditions and terms. These definitions were endorsed by the Critical Care EEG Monitoring Research Consortium.[3]
- *New onset refractory seizures*: NORSE is a clinical presentation, not a specific diagnosis, in a patient without active epilepsy or other pre-existing relevant neurological disorder, with new onset of refractory status epilepticus (RSE) without a clear acute or active structural, toxic or metabolic cause.
- *Febrile illness-related epilepsy syndrome*: FIRES is a subcategory of NORSE, applicable for all ages, which requires a prior febrile infection starting between 2 weeks and 24 hours prior to onset of RSE, with or without fever at onset of SE.

PATHOPHYSIOLOGY

Recent ILAE Task Force definition of SE recognizes that SE is defined by two pathological processes—those that lead to prolongation and those that lead to its consequences like neuronal death, neuronal injury, and alteration of neural networks. Important pathological processes that can lead to persistence of seizures are:

- Suppression or failure of seizure termination processes
- Nature of RSE
- Drug resistance and acute receptor changes
- Neuronal death and dysfunction

Suppression or Failure of Seizure Termination Processes

A host of different biologic processes have been identified to lead to seizure termination like ionic changes at synapses, neurotransmitter depletion, adenosine triphosphate (ATP) depletion, etc. Moreover, there may be proseizure processes like breach in blood-brain barrier, inflammation that led to persistence of seizures. These mechanisms are enlisted in **Table 3**. It has been observed that spatial and temporal synchronization occurs before seizure termination. Further studies of EEG changes prior to seizure termination have identified slowing of frequency of mean power and flickering. These observations lead to the concept of critical transition from ictal to postictal state leading to seizure transmission. SE can be considered as failure of this critical transition.

TABLE 3: Mechanism for persistence of seizures.

Changes leading to decreased inhibition	*Changes leading to increased excitation*
• Neurotransmitter depletion • ATP depletion • Ionic changes • Acidosis • Increased GABAergic drive • Decreased adenosine • Decreased dynorphins, galanins	• Breakdown of the blood-brain barrier • Inflammation • Increased expression of proepileptogenic peptides like substance P • Increased glutamate release

(ATP: adenosine triphosphate; GABA: γ-aminobutyric acid)

Nature of Refractory Status Epilepticus

It has been observed that longer the seizure persists, less likely for it to stop. It is because seizure activity itself can exhaust seizure inhibitory processes. Many of the times seizures can be terminated by initial therapy or with second line or anesthetic drugs. Few patients with RSE progress into SRSE wherein withdrawal of anesthetic drugs leads to reverting back to ictal state. Two main reasons why it occurs are: there may be an ongoing pathological process (infection, inflammation, and autoimmune) that drives back the brain to seizure activity. Another reason could be that the prolonged seizure activity has resulted in changes in the brain (neuronal death) that make the brain intrinsically unstable during the postictal state leading to recurrence of seizures. Understanding these pathological processes and guidance of EEG in identifying the unstable state of the brain helps in identifying potential treatment targets (immunosuppression and polytherapy) in achieving early seizure control.

Drug Resistance and Acute Receptor Changes

- Internalization of synaptic GABA (A) receptors due to activation of N-methyl-D-aspartate (NMDA) receptors leading to BZD resistance.
- Decreased efficacy of GABA-mediated inhibition due to increased intracellular chloride levels occurring as result of KCC2 (potassium chloride transporter) internalization.
- Increased NMDA receptor expression in excitatory cells, presynaptic adenosine A1 receptor, and increase in AMPA receptors without GluA2 subunit leading to increased intracellular calcium.
- Increased aberrant expression of drug transporter proteins (like P-glycoprotein) that promotes resistance to antiseizure drugs.

Neuronal Death and Dysfunction

Specific groups of cells have been particularly identified to be more vulnerable to pathological changes after prolonged seizures. Cells in hilum of hippocampus, CA3, and CA1 regions of hippocampus are particularly injured as they have increased expression of NMDA receptors which are increased during SE. Excess NMDA activation leads to accumulation of intracellular calcium. Increased intracellular calcium in turn leads to activation of several enzymes to accelerate the apoptotic pathways mediated through nonlysosomal cysteine protease activation.

Other significant enzymes activated secondary to increased intracellular calcium are Calpain 1 and 2 and inducible nitric oxide synthase (iNOS). NO at high concentrations results in deoxyribonucleic acid (DNA) injury, lipid peroxidation, and mitochondrial dysfunction. In SE, it activates ryanodine receptors leading to increased intracellular calcium stores release. Mitochondria act as main buffer for cytosolic calcium and increased mitochondrial calcium expression leads to mitochondrial membrane depolarization and energy failure ultimately leading to cell death. It also leads to excess production of reactive oxygen species (ROS) like peroxynitrites which make the mitochondrial membrane more permeable to proapoptotic proteins such as cytochrome c.

Metabolic Changes

Convulsive SE exerts a huge metabolic demand on the body. Changes in heart rate, blood pressure, respiratory rate, blood glucose, and body temperature occur to compensate the increase metabolic demands of the brain during ongoing SE. Repetitive muscle contractions during ongoing SE lead to a shift to anaerobic metabolism causing lactic acidosis. These compensatory mechanisms fail when SE prolongs >20–40 minutes leading to inadequate ventilation, worsening respiratory and metabolic acidosis, and hypoxia. Prolonged convulsive SE leads to hyperthermia and rhabdomyolysis which accelerates neuronal death especially in hippocampal cells and dentate nucleus leading to hippocampal sclerosis. Hippocampal sclerosis can in turn be a focus of seizures and epilepsy in future, producing a vicious cycle.

DIAGNOSIS

Diagnostic workup includes:

- Clinical examination
- Laboratory investigations
- Electroencephalography
- Neuroimaging
- Metabolic disorder and autoimmune workup whenever necessary

To start with a detailed history should be taken from the bystander who witnessed the seizure and a thorough clinical examination to be completed. In SE diagnostic workup and management should be done simultaneously. As etiology is an important determinant of outcome, diagnostic workup should include the evaluation for etiology.

Initial investigations should be done immediately on arrival to emergency department. This includes capillary blood sugar at bedside, complete blood counts, liver and renal functions tests, electrolytes, coagulation profile, and antiepileptic drug (AED) levels (in known case of epilepsy). Other tests are toxicology screening, arterial blood gas analysis, and electrocardiogram. Toxicology screening should be comprehensive and include drugs and toxins frequently associated with seizures. Testing for metabolic and mitochondrial disease should be done in young patients with myoclonus, intellectual disability, or unexplained neurologic signs and symptoms.

Once patient is stabilized, he should be subjected to computed tomography to look for any structural lesions or acute problems. If the history is suggestive of central nervous system (CNS) infections lumbar puncture should be done at the earliest after completion of CT brain. In case of persistent seizures or patient has not regained consciousness, urgent EEG should be ordered.

Electroencephalography

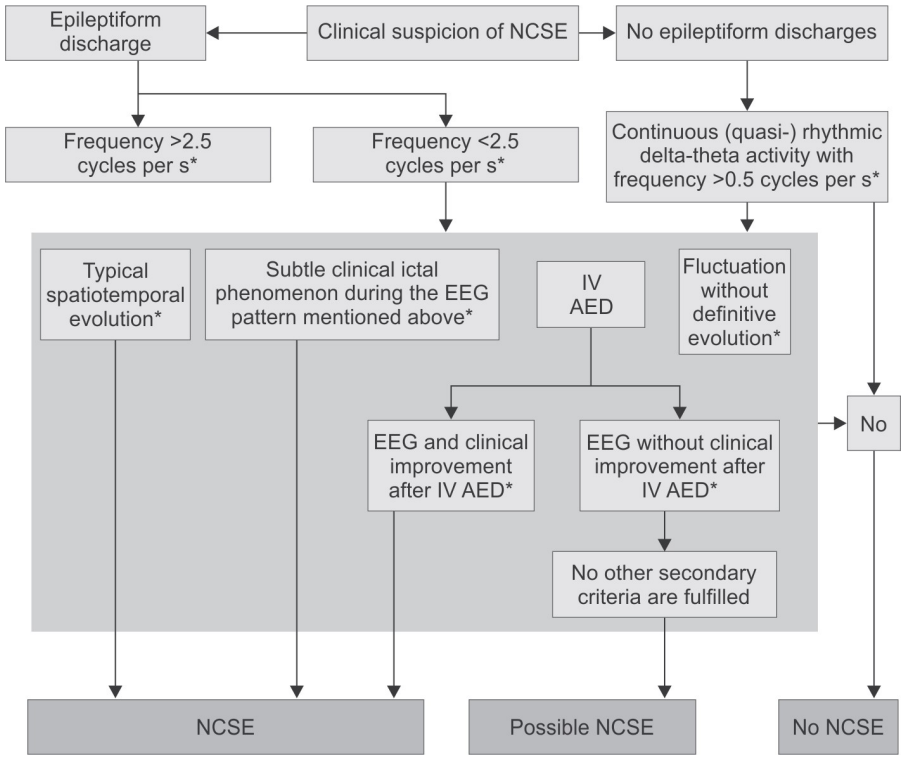
Electroencephalography is used for diagnosis and to monitor the response to treatment. EEG may be of lesser importance in diagnosis of convulsive SE, as the clinical presentation is clear and movement artifacts will obscure the EEG. However, it may be very helpful in the diagnosis of NCSE and in patient with deep coma. In a multidisciplinary and neuro-ICU, the incidence of NCSE is 8%, 13.5% respectively.[4,5]

Electroencephalography criteria to diagnose SE is frequent repetitive electrographic seizures and respective generalized or focal epileptic discharges >3 Hz. Less than 3 Hz can be considered ictal, if patients improve after BZD therapy. Patients with underlying brain pathology or who are persistently comatose following a convulsant SE are most likely to develop to NCSE. NCSE is also common in critically ill comatose patients with no prior seizures. Salzburg EEG criteria for the diagnosis of NCSE is given in **Flowchart 1**. In majority of patients, seizures are captured in EEG in the first 24 hours, in comatose it may take a longer time to be captured. EEG is also helpful to monitor the therapeutic goals and response to AED.

Autoimmune Workup

Though autoimmune etiology is uncommon, in recent times a greater number of cases have been reported. In certain specific presentations, autoimmune etiology has to be suspected and after confirmation early immune modulatory therapy has to be initiated for better outcomes. It commonly presents as NORSE and FIRES.

Flowchart 1: Salzburg electroencephalography (EEG) criteria for diagnosis of nonconvulsive status epilepticus (NCSE).



(IV AED: intravenous antiepileptic drug)

*Patients with known epileptic encephalopathy should fulfill one of the additional secondary criteria: increase in prominence or frequency of the features above when compared to baseline, and observable change in clinical state; or improvement of clinical and EEG features with IVAEDs.

In the following circumstances in patients with SE autoimmune etiology is to be suspected:

- New onset seizures presenting as SE
- Progression to RSE or SRSE
- Known history of underlying malignancy
- Lymphocytic pleocytosis in cerebrospinal fluid (CSF)
- With prior history, but abrupt onset and persistent seizures
- New psychiatric symptoms or behavioral changes

Management

Goal is for early cessation of seizure and avoid progression to refractory forms (RSE/SRSE). Adequacy of control and outcome are poor with NCSE compared to SE. Antiseizure drugs modulate the cellular pathway and produce the therapeutic effects in central nervous system. Epilepsy is precipitated by imbalance between the following pathways.

Excitatory Pathway

Occurs during hyperpolarization of action potential effects by glutamate coupled AMDA (α-amino-3-hydroxy-5-methyl-4-iso-oxazolepropionic acid) and NMDA receptors.

Inhibitory Pathway

Occurs with depolarization of membrane potential and affected by GABA (γ-aminobutyric acid) coupled to GABA-A receptor.

Antiseizure drugs act by enhancing the GABA-mediated pathway and/or inhibiting the glutamate and Na^+/Ca^+-mediated neuronal excitation.

Following are the drugs used for various forms:

- *Benzodiazepines:* Rapid control
- *Classical AEDs:* SRE
- *General anesthetics:* SRSE

Benzodiazepines: BZDs are the first-line drug and it is efficacious when given in close proximity to seizure onset. Efficacy decreases over time because of internalization of GABA receptor and upregulation of NMDA receptor.[6] Common BZDs used are midazolam, lorazepam and diazepam by oral, buccal, nasal, intravenous, intramuscular, and rectal route. However, recent meta-analysis reveals lorazepam is the preferred agent in view of longer intracranial half-life. Midazolam is better than lorazepam for out-of-hospital seizures, since it can be stored in room temperature and can be given intramuscularly.[7]

When seizures are refractory to BZD, second-line drugs have to be introduced at the earliest. Second-line AEDs have to be started with a loading dose. Phenytoin, phenobarbital, levetiracetam, lacosamide, and valproic acid are the options available. Though robust evidence in terms of efficacy between second-line AEDs is not available, American Epilepsy Society suggests valproic acid to have equal efficacy and better tolerance compared to

phenobarbital.[8] BZDs are inferior to phenobarbital or sodium valproate if seizures are refractory.

Treatment of Refractory Status Epilepticus

At this stage of SE, recommendations are to switch over to continuous infusion from intermittent boluses. Diagnosis is made when clinical or electrographic seizure persists despite adequate doses of first- and second-line drugs. In pediatric populations, incidence may vary from 10 to 40%.[9] Neurocritical care treatment society recommends to use an "urgent" control drug to which patient is not previously exposed and to follow it up with a pharmacological coma by intravenous or inhalational agents.

Drugs used in RSE for continuous infusion are midazolam, propofol, and barbiturates. Bolus of these drugs needs to be administered before starting an infusion to rapidly abort the seizures. Though case fatality and complications were similar among the above agents. Mechanical ventilation duration was prolonged in barbiturate group. Propofol should be used with caution in pediatric age group because of propofol infusion syndrome.

Ketamine, lidocaine, topiramate, perampanel, and clobazam are the other agents which are used in the management of RSE. Rapid absorption, large volume of distribution, lesser drug interactions, and safety are the advantages of clobazam. Inhalational agents such as isoflurane and desflurane can be used if RSE is refractory to intravenous agents. When using inhalational agents we should watch for hypotension, respiratory depression, and recurrence after withdrawal. Current guidelines recommend titration of propofol and barbiturates to EEG burst suppression and midazolam to seizure suppression. This should be maintained for 24–48 hours and chronic AEDs are initiated.

Alternative Treatment

Nonconvulsive status epilepticus is a heterogeneous disorder and at present there is no clear consensus on treatment options. Most of the recommendations are extrapolated from treatment of SE. Antiseizure drugs and intravenous drugs are the mainstay of treatment. Commonly used drugs are topiramate, clobazam, lacosamide, levetiracetam, and perampanel.

Treatment Modalities

Other alternative treatments modalities are:

- Recurrent transcranial magnetic stimulation
- Immunomodulation
- Induced hypothermia
- Ketogenic diet
- Vagus nerve/deep brain stimulation
- Electroconvulsive therapy

Immunotherapy has to be considered in SRSE when the usual treatment fails. CSF and serum autoantibodies screening should be done before initiation of treatment. Immunoglobulin, steroids, and plasma exchange are the options available. At present, there is no good quality data to suggest the best therapeutic option.

In recent times, ketogenic diet earlier used in pediatric population for refractory seizures is being extrapolated to adult population. Higher fat to protein and carbohydrate ratios (3:1 to 4:1) are being used to produce ketosis. Ketosis has anti-inflammatory property which is responsible for therapeutic effect. Acidosis and hyperlipidemia are the complications of ketogenic diet.

PROGNOSIS

Older age, impaired consciousness, prominent motor signs, and duration longer than 30 minutes are associated with poorer outcomes. Etiologies such as cerebrovascular accident, hypoxic encephalopathy, brain tumors, meningitis, and drug toxicity lead to higher mortality in patients with SE. Convulsive SE has got better prognosis compared to NCSE and focal or absent seizures of onset has got a higher mortality risk compared to tonic-clonic seizures or NCSE. Myoclonic SE because of underlying etiology is associated with decreased survival.

There are two prognosis scores currently available **(Table 4)**:

1. Status epileptic severity score (STESS)
2. Epidemiology-based mortality score (EMSE)

Status epileptic severity score has variables such as worst seizure type, age, stupor (or) coma, history of seizures and NCSE. Score <2 is associated with good outcomes. Addition of modified Rankin scale to STESS is called as mSTESS and is associated with better positive predictive value.[10] EMSE includes variables such as age, comorbidity, etiology, and electroencephalogram (EEG) characteristics. Both the above scoring systems will be useful in patients with few comorbidities and have to be validated in patients with more comorbidities.

TABLE 4: Prognostic scores.

Predictors of outcome in scales	
STESS score	***EMSE score***
Level of consciousness	Etiology
Worst seizure type	Duration
Age	Comorbidity
History of previous seizure	Age EEG Level of consciousness

(EEG: electroencephalography; EMSE: epidemiology-based mortality score in status epilepticus; STESS: status epileptic severity score)

Biomarkers of inflammations and neuronal damage can be used as a determinant of poor outcome. Though elevated levels of neuron-specific enolase in prolonged SE could be indicative of poor outcome it needs to be validated in larger trials. Tau protein which indicates axonal and neuronal injury is used as a diagnostic and prognostic biomarker in traumatic brain injury but yet to be validated in SE patients. Elevated serum albumin >3.5 g/L at onset of SE is a good predictor of refractoriness.

CONCLUSION

"Time is brain" is not only applicable to stroke but also for SE. Prognosis of SE worsens with increased duration of seizures. Prompt recognition and early treatment are associated with lower morbidity and mortality. Treatment protocols encompass a staged approach of different drugs during various stages of SE.

REFERENCES

1. Lu M, Faure M, Bergamasco A, Spalding W, Benitez A, Moride Y, et al. Epidemiology of status epilepticus in the United States: A systematic review. Epilepsy Behav. 2020;112:107459.
2. Trinka E, Cock H, Hesdorffer D, Rossetti A, Scheffer I, Shinnar S, et al. A definition and classification of status epilepticus—Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia. 2015;56(10):1515-23.
3. Hirsch L, Gaspard N, van Baalen A, Nabbout R, Demeret S, Loddenkemper T, et al. Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES), and related conditions. Epilepsia. 2018;59(4):739-44.
4. Towne A, Waterhouse E, Boggs J, Garnett L, Brown A, Smith J, et al. Prevalence of nonconvulsive status epilepticus in comatose patients. Neurology. 2000;54(2):340-5.
5. Laccheo I, Sonmezturk H, Bhatt A, Tomycz L, Shi Y, Ringel M, et al. Non-convulsive Status Epilepticus and Non-convulsive Seizures in Neurological ICU Patients. Neurocrit Care. 2014;22(2):202-11.
6. Brevoord J, Joosten K, Arts W, van Rooij R, de Hoog M. Status Epilepticus: Clinical Analysis of a Treatment Protocol Based on Midazolam and Phenytoin. J Child Neurol. 2005;20(6):476-81.
7. Goodkin H, Yeh J, Kapoor J. Status Epilepticus Increases the Intracellular Accumulation of GABAA Receptors. J Neurosci. 2005;25(23):5511-20.
8. Silbergleit R, Durkalski V, Lowenstein D, Pancioli A, Palesch Y, Barsan W. Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus. N Engl J Med. 2012;366(13):591-600.
9. Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, et al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr. 2016;16(1):48-61.
10. González-Cuevas M, Santamarina E, Toledo M, Quintana M, Sala J, Sueiras M, et al. A new clinical score for the prognosis of status epilepticus in adults. Eur J Neurol. 2016;23(10):1534-40.

39

CHAPTER

Postintensive Care Syndrome—An Indian Perspective

Vikas Marwah, Deepu K Peter, Shailender Kumar

INTRODUCTION

Admission to an acute care unit can be traumatizing to the patient and the consequences arising in the long term can be even more devastating.[1] The health problems that persist after a critical illness constitute postintensive care syndrome (PICS). There is no absolute definition of PICS. It is however agreed that new or worsening impairment of cognitive, psychiatric, and physical function after a critical illness constitutes PICS.[1,2] These impairments profoundly affect the lives of not only the survivors but also their family members.

The diagnosis of PICS in our country is usually made after a critical event. The symptoms, however, are prolonged and the entity is mostly underdiagnosed, given that there is no specific period after a critical illness following which a diagnosis of PICS is given. The economic impact of PICS can also overburden the health system.[3]

In the recent past, our country has been ravaged by the COVID pandemic and millions were admitted to various intensive care units (ICUs) with acute respiratory distress syndrome. Many died and in those who survived a new battle began in the form of PICS. The recent COVID pandemic has made it all the more important that we understand this common yet underdiagnosed entity.

This chapter will focus on understanding the PICS and on the various modalities for its management.

EPIDEMIOLOGY

The diagnosis of critical illnesses such as sepsis and acute respiratory distress syndrome (ARDS) is made through consensus guidelines based on various clinical, radiological, and laboratory data. These are also under constant scrutiny and are subject to frequent change. The existing resources especially in developing countries such as India make it challenging to study critical illnesses which are associated with early mortality. Mortality in critical illness can at times be a consequence of the clinicians' decision to withdraw ventilation citing a low likelihood of survival.[4]

Studies have shown that 25–75% of ICU survivors have a cognitive defect. Psychiatric illnesses are seen in >60% of patients discharged from ICU. Approximately one-fourth of ICU survivors will also manifest some form of physical component of PICS in the form of critical illness polyneuropathy, or critical illness myopathy.[5]

RISK FACTORS AND CLINICAL MANIFESTATIONS

When a cognitive, psychiatric, and physical sign is newly detected or worsens after a critical illness, the patient is said to have PICS. They characteristically present with weakness, anxiety, depression, low mood, poor concentration, and decreased mobility. These three components are linked with each other and impairment in one can lead to the development of worsening of the other.

Risk factors **(Table 1)** and clinical manifestations of the three components will be discussed below.

Cognitive Domain

In a study by Pandharipande et al., duration of delirium during ICU stay was independently associated with poor cognition after a critical illness.[6] The presence of pre-existing impaired cognition at the time of critical illness can lead to further cognitive dysfunction. This can be further aggravated if the patient is elderly and has other comorbid conditions.[7] It has also been observed that lower levels of plasma β-amyloid 42/40 cause significant cognitive impairment, especially among the elderly population.[8] Patients with sepsis had three times higher risk of developing moderate/severe cognitive impairment.[9] ARDS is another major risk factor with studies showing at least 73% of patients developing cognitive dysfunction.[10] Various other risk factors for cognitive impairment are hypotension, hypoxemia, poor glycemic control, respiratory failure, sleep disorders, heart failure, blood transfusion, use of sedatives, and renal replacement therapy.[6] Despite the identification of numerous risk factors leading to the development

TABLE 1: Patients at high risk for developing postintensive care syndrome (PICS).

	Phase of critical illness		
Domain	***Pre***	***During***	***Post***
Cognition	Pre-existing defect	• Sedation • Sepsis • Hypoxia • Shock • ARDS • Ventilatory support • Prolonged delirium	
Mental health	Pre-existing anxiety, depression, and PTSD	Retention of bad memories and experiences during ICU stay	Anxiety, depression, and PTSD
Physical	• Pre-existing functional and cognitive defect • Frailty		

(ARDS: acute respiratory distress syndrome; ICU: intensive care unit; PTSD: post-traumatic stress disorder)
(*Adapted from*: Mikkelsen ME, Still M, Anderson BJ, Bienvenu OJ, Brodsky MB, Brummel N, et al. Society of critical care medicine's international consensus conference on prediction and identification of long-term impairments after critical illness. Crit Care Med. 2020;48(11):1670-9.)

of cognitive dysfunction, the exact mechanism of its development is not known and it is hypothesized that ischemia, and blood–brain barrier disruption might be causative.

The most commonly affected cognitive functions are memory and executive function.[11] This prevents the patient from collecting and analyzing data and eventually leads to poor decision-making abilities.

Cognitive impairment can vary from the inability to carry out complex executive tasks to not being able to carry out activities of daily living. A cognitive defect is usually missed as there is no routine screening or formal testing is carried out and lack of ICU physician awareness.

Psychiatric Domain

Intensive care unit-related post-traumatic stress disorder (PTSD) is a common entity seen in 1 out of every 10 survivors.[12] Apart from this, other psychiatric morbidities such as depression are also frequently seen and are associated with poor health-related quality of life.[13] Depression can present in the form of fatigue, loss of appetite, poor sleep, and feeling of hopelessness. The presence of irritability, restlessness, and persistent worry can be a manifestation of anxiety. Flashback, hyperarousal, recollection of events, sexual dysfunction, and avoiding provocative ICU experiences can be suggestive of PTSD.

Sepsis, ARDS, hypoglycemia, hypoxemia, trauma, and respiratory failure which affect cognition are also known risk factors for the development of psychiatric impairment in the form of depression, PTSD, etc.[10] These symptoms are increased if the patient has a pre-existing psychiatric disease and can be compounded by the presence of factors such as younger age (<50 years), female gender, poor education status, alcohol abuse, use of sedative and analgesic in ICU, and recollection of disconcerting ICU experiences.

Intensive care unit survivors were also found to be at an increased risk of suicide and self-harm.[14]

Physical Domain

Intensive care unit-acquired weakness (ICUAW) is an umbrella term constituting generalized muscle weakness, poor mobility, critical illness myopathy, critical illness polyneuropathy or both, and tetraparesis due to prolonged neuromuscular blockade. Malnutrition and hearing and vision impairment can also contribute to physical impairment.[15]

Weakness after critical illness is seen in frail individuals and those with pre-existing functional and cognitive impairment. It can also be seen in patients with prolonged mechanical ventilation, multiorgan failure, prolonged bed rest, and sepsis. Other risk factors leading to the formation of physical signs include ARDS, older age, use of corticosteroids and vasoactive agents, and glucose derangement. Prolonged immobility during a critical illness can also cause functionally significant joint contractures commonly affecting the elbow and ankle joints.[16]

OTHER DERANGEMENTS THAT ARE SEEN IN POSTINTENSIVE CARE SYNDROME

Malnutrition

Critical illness can cause weight loss and it has been shown that patients can often lose around 18% of their body weight sometimes leading to persistent functional disability.[17] This is especially seen in those receiving mechanical ventilation who receive <60% of their prescribed daily energy requirements. Malnutrition, both under and overnutrition, is highly prevalent in India and can be pre-existing morbidity that can adversely affect ICU patients.

Reduced Lung Function

Compromise in pulmonary function commonly seen in the form of reduced diffusion capacity is known to affect patients who have been mechanically ventilated for ARDS and this defect can even last for >5 years. In a systematic review of 22 studies, sleep disturbance was frequently seen postcritical illness affecting >50% of the patients.[18]

POSTINTENSIVE CARE SYNDROME-FAMILY

Relatives of critically ill patients are at risk of being affected physically and mentally leading to the development of an entity called postintensive care syndrome-family (PICS-F). This can be in the form of PTSD, anxiety, sleep deprivation, and depression. This is more frequently seen in female relatives, adult child of the patient, and belonging to lower socioeconomic strata. PICS-F can also persist for many months to years.

Diagnosis

All patients admitted to an ICU should be screened right from the day of admission for the presence of PICS. This is in consensus with the Society of Critical Care Medicine (SCCM) guidelines which recommend that serial assessment for PICS should be carried at the beginning of ICU admission, to 2–4 weeks postdischarge. Patients at high risk for developing PICS should be evaluated on a priority basis.

Cognitive Domain

Patients suspected of PICS should be formally evaluated with available screening tools for the presence of a cognitive defect. Early identification and rehabilitation are known to be beneficial in improving executive function in postcritical illness patients.[19]

Various screening tests are available for the validation of cognitive impairment. The most used are mini-mental state examination (MMSE) and Mini-Cog; however, neither can predict the cognitive impairment at 6 months.[20] The Montreal Cognitive Assessment (MoCA) is a sensitive tool and can be used to identify mild cognitive impairment and MMSE is more useful in advanced cases.[21] MoCA is an ideal tool for early detection of executive dysfunction, which is seen in most ICU survivors. Mild cognitive impairment is indicated by a MoCA score of <26 and a score <18 is suggestive of a severe defect.

PSYCHIATRIC DOMAIN

There are various scales such as Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory, and Beck Anxiety Inventory to assess anxiety and depression. In addition, Impact of Events Scale-Revised (IES-R) and six-item Impact of Event Scale-6 are ideal for screening of PTSD. Evaluation for mental health in a patient suspected of PICS should be carried out with the above tools when feasible. In patients who survived acute respiratory failure, Medical outcomes Study Short Form (SF)-36 is a good tool for the assessment of mental health.[22]

INTENSIVE CARE UNIT ACQUIRED WEAKNESS

When a patient develops clinically evident weakness and there is no underlying etiology apart from critical illness, the patient is said to have ICUAW. Early identification for ICUAW should start in the ICU preferably by a team consisting of a physical and occupational therapist. Close relatives should be interviewed regarding the preadmission functional status of the patient and also for any other familial illness that could contribute to weakness. The muscle strength should be assessed and it should be correlated with the time course of appearance of the weakness. Factors such as sepsis, mechanical ventilation, multiorgan failure, hyperglycemia, and exposure to drugs such as glucocorticoids and neuromuscular blocking agents should also be identified during screening for patients for ICUAW. Evaluation should be continued, and patient should be assessed for functional disabilities including the ability to swallow, eat, bathing, and dressing. Studies have shown that ICU-acquired paresis is an independent predictor of mortality and can be easily determined by bedside tests such as handgrip strength which itself is a predictor of increased duration of hospitalization.[23] Patients with acute respiratory distress especially those relieved from mechanical ventilation and those with chronic lung diseases should undergo pulmonary function tests including a 6-minute walk test.

WHAT ARE THE DIFFERENTIALS?

All patients suspected of PICS should be evaluated for a pre-existing cognitive, physical, or mental impairment that can remain unchanged or can progress following the critical illness. This can be in the form of developmental disorders, brain injury, substance abuse, failure to thrive, etc. Vitamin B_{12} deficiency, hypothyroidism, stroke, cancer, and obstructive sleep apnea can also simulate PICS. Other conditions which are usually obvious at the time of admission are rhabdomyolysis and Guillain–Barré syndrome can also mimic PICS.

PREVENTION

Sedatives and analgesics are prescribed in the ICU, especially in mechanically ventilated patients for better patient-ventilator synchrony, stress relief, and control of pain and anxiety. Liberal use of these medications may prove detrimental and can increase the risk of developing PICS and hence its judicious use is always advised.

ABCDEF bundle has been proposed to prevent PICS.[24] The various components are:

ABC—awakening and breathing coordination with sedation interruption
C—choice of sedative and analgesia
D—delirium monitoring and treatment
E—early mobilization
F—family empowerment/engagement.

ABC was derived from the Awakening and Breathing Controlled trial[25] which showed that spontaneous breathing trial when done daily after sedation interruption leads to significant reduction in hospital stay and mortality.

When considering sedation, clinicians should consider using drugs such as dexmedetomidine (DEX) which is an α-2 agonist rather than routinely using opioids, benzodiazepines, propofol, etc. These have been shown to reduce the length of ICU stay as well as are known to reduce delirium.

Delirium is known to affect >60% of critically ill patients on ventilator support and is known to increase the length of hospital stay and even cause death. Early detection of delirium using scales such as Confusion Assessment Method for the ICU (CAM-ICU), Delirium Detection Score (DDS), and Nursing Delirium Screening Scale (Nu-DESC) should be done in critically ill patients.

Intensive care unit patients should be mobilized early, and more physical and occupational therapy should be administered. This can help avoid adverse consequences such as ICUAW.[26]

Hypoglycemia is a frequent occurrence in the ICU as most clinicians attempt to maintain normoglycemia in patients. It can however lead to long-term neuropsychological harm in the critically ill and hence close monitoring is required in patients receiving insulin. To prevent the consequences of hypoglycemia, a target blood sugar level of 140–180 mg/dL should be maintained in all patients admitted to ICU.

To prevent PICS-F, clinicians should encourage family presence with more flexible timings in the ICU. In our country, families are usually available to participate in the process of recovery of the patient. They should be actively involved in the bedside care of the patient. Communication with relatives should be focused on valuing family statements, acknowledging their emotions, and being ready to answer their questions. Families should be made aware of the disease and the prognosis of the patient through the availability of brochures and online material. Trained staff can be made available to support, guide, and communicate with the families of critically ill patients. The lack of manpower and infrastructure can be a hindrance to the recovery of the patient in most hospitals of our country. Families when allowed to participate in the various stages of the patients' recovery can make up for this shortcoming and also help prevent PICS and identify it early during the postdischarge period. Animal-assisted therapy (AAT) is also practiced in the western ICUs wherein pets or trained animals are allowed to visit ICU patients. This is believed to reduce the incidence of delirium and PICS. Varying cultural and religious beliefs existing in our country and the lack of trained therapists and organizations however make AAT a difficult prospect.

TREATMENT AND FOLLOW-UP

Each component of PICS need to be addressed separately by a concerned expert. Early physical rehabilitation has been shown to reduce psychiatric and cognitive impairment. A multidisciplinary team consisting of cardiac, geriatric, pulmonary, and physical rehabilitation experts should be involved in the management of physical dysfunction. There are multiple pharmacologic and nonpharmacologic modalities for the management of cognitive defects, depression, anxiety, PTSD, and sexual dysfunction.

Most patients of PICS will be on regular follow-up for many years at frequent intervals as the natural history of the disease is not known. During each visit, they should be reviewed by a multidisciplinary team of specialists, psychiatrists, counselors, and physical and occupational therapists. As discussed earlier, patients going on discharge from ICU should be evaluated extensively for all three components of PICS. Discharge summary handed to patients should carry these instructions to inform the outpatient team to carry out the same without fail. Patients should also be encouraged to join support groups that can offer better social support and help reduce psychological stress.[27] Western countries have also started introducing PICS clinics to identify patients and families with PICS and ensure their rehabilitation.

OUTCOME

Functional status at the time of discharge from ICU is directly linked to postdischarge mortality, with patients having a poor functional status having an increased chance of mortality.[28] There is however minimal evidence on the benefit of preventive and therapeutic interventions on outcome in PICS.

In a systematic review of 53 studies, quality of life was lower in ICU survivors[29] and improvements can be seen over time but it generally does not return to normal. Health-related quality of life (HRQOL) is poor in those individuals with pre-existing disease and those with ARDS, sepsis, malignancy, and prolonged mechanical ventilation.[30] Relatives have also been affected adversely and a prospective multicenter observational study revealed poor mental health in relatives with 35.9% requiring anxiolytics and 8.4% having to take psychotropic medications after the death or discharge from ICU of the patient.

Cognitive impairment initially tends to show minimal improvement over the first 6–12 months but impairment usually persists for many years. Psychiatric impairment after

showing an improvement in the first few months will also persist for many years. The physical domain of PICS is the most likely to improve especially in the first 12 months as was shown by Fan E et al., wherein 36% of patients with acute lung injury had physical dysfunction at the time of discharge which persisted in only 12 and 9% after 12 and 24 months, respectively.[31]

As most of these patients remain unemployed for more than a year due to their illness, thereby leading to further financial stress on the patient as well as their families.[3]

Mortality after critical illness is relatively common, especially in the first 3-6 months. This can be attributed to multiple factors such as pre-existing illnesses, new or worsening organ dysfunction, and acute illnesses arising out of PICS.[32]

REHOSPITALIZATION

Rehospitalization is a frequent risk seen in patients with PICS with >15% of ICU survivors getting readmitted within the first 30 days.[33] Certain factors such as discharge to a long-term facility, metastatic cancer, and longer duration of hospitalization were associated with an increased likelihood of rehospitalization. Further studies have also brought to the forefront that >40% of rehospitalization could have been prevented if the patient had access to good follow-up care.[34]

CONCLUSION

The care of an ICU survivor does not end with his or her discharge. PICS can be devastating and can have longstanding implications on the patients as well as the family. Each critically ill patient should be evaluated for PICS right from the day of admission to 1-2 years post-discharge for cognitive, physical, and mental function. The families should be considered as major stakeholders in the recovery and discharge from ICU and for the prevention of PICS. ABCDEF bundle represents one of the few changes that can be incorporated into the ICU treatment protocol that can help prevent PICS.

REFERENCES

1. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit: Report from a stakeholders' conference. Crit Care Med. 2012;40(2):502-9.
2. Elliott D, Davidson JE, Harvey MA, Bemis-Dougherty A, Hopkins RO, Iwashyna TJ, et al. Exploring the scope of post-intensive care syndrome therapy and care: Engagement of non-critical care providers and survivors in a second stakeholders meeting. Crit Care Med. 2014; 42(12):2518-26.
3. Hopkins RO, Girard TD. Medical and economic implications of cognitive and psychiatric disability of survivorship. Semin Respir Crit Care Med. 2012;33(4):348-56.
4. Cook D, Rocker G, Marshall J, Sjokvist P, Dodek P, Griffith L, et al. Withdrawal of Mechanical Ventilation in Anticipation of Death in the Intensive Care Unit. N Engl J Med. 2003;349(12):1123-32.
5. Rawal G, Yadav S, Kumar R. Post-intensive care syndrome: An overview. J Transl Intern Med. 2017;5(2):90-2.
6. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369(14):1306-16.
7. Davydow DS, Hough CL, Langa KM, Iwashyna TJ. Presepsis depressive symptoms are associated with incident cognitive impairment in survivors of severe sepsis: A prospective cohort study of older Americans. J Am Geriatr Soc. 2012;60(12):2290-6.
8. Yaffe K, Weston A, Graff-Radford NR, Satterfield S, Simonsick EM, Younkin SG, et al. Association of plasma beta-amyloid level and cognitive reserve with subsequent cognitive decline. JAMA. 2011;305(3):261-6.
9. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA. 2010;304(16):1787-94.
10. Mikkelsen ME, Christie JD, Lanken PN, Biester RC, Thompson BT, Bellamy SL, et al. The adult respiratory distress syndrome cognitive outcomes study: Long-term neuropsychological function in survivors of acute lung injury. Am J Respir Crit Care Med. 2012;185(12):1307-15.
11. Sukantarat KT, Burgess PW, Williamson RCN, Brett SJ. Prolonged cognitive dysfunction in survivors of critical illness. Anaesthesia. 2005;60(9):847-53.
12. Patel MB, Jackson JC, Morandi A, Girard TD, Hughes CG, Thompson JL, et al. Incidence and risk factors for intensive care unit-related post-Traumatic stress disorder in veterans and civilians. Am J Respir Crit Care Med. 2016;193(12):1373-81.
13. Davydow DS, Gifford JM, Desai SV, Bienvenu OJ, Needham DM. Depression in general intensive care unit survivors: A systematic review. Intensive Care Med. 2009;35(5):796-809.
14. Fernando SM, Qureshi D, Sood MM, Pugliese M, Talarico R, Myran DT, et al. Suicide and self-harm in adult survivors of critical illness: population based cohort study. BMJ. 2021;373.
15. Ferrante LE, Pisani MA, Murphy TE, Gahbauer EA, Leo-Summers LS, Gill TM. Factors associated with functional recovery among older intensive care unit survivors. Am J Respir Crit Care Med. 2016;194(3):299-307.
16. Clavet H, Hébert PC, Fergusson D, Doucette S, Trudel G. Joint contracture following prolonged stay in the intensive care unit. CMAJ. 2008;178(6):691-7.
17. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med. 2003;348(8):683-93.
18. Altman MT, Knauert MP, Pisani MA. Sleep disturbance after hospitalization and critical illness: A systematic review. Ann Am Thorac Soc. 2017;14(9):1457-68.
19. Cicerone KD, Dahlberg C, Kalmar K, Langenbahn DM, Malec JF, Bergquist TF, et al. Evidence-based cognitive rehabilitation: Recommendations for clinical practice. Arch Phys Med Rehabil. 2000;81(12):1596-615.
20. Woon FL, Dunn CB, Hopkins RO. Predicting cognitive sequelae in survivors of critical illness with cognitive screening tests. Am J Respir Crit Care Med. 2012;186(4):333-40.
21. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695-9.

22. Pfoh ER, Chan KS, Dinglas VD, Cuthbertson BH, Elliott D, Porter R, et al. The SF-36 offers a strong measure of mental health symptoms in survivors of acute respiratory failure: A tri-national analysis. Ann Am Thorac Soc. 2016;13(8):1343-50.
23. Ali NA, O'Brien JM, Hoffmann SP, Phillips G, Garland A, Finley JCW, et al. Acquired weakness, handgrip strength, and mortality in critically III patients. Am J Respir Crit Care Med. 2008;178(3):261-8.
24. Pun BT, Balas MC, Barnes-Daly MA, Thompson JL, Aldrich JM, Barr J, et al. Caring for critically ill patients with the ABCDEF bundle: Results of the ICU Liberation Collaborative in over 15,000 adults. Crit Care Med. 2019;47(1):3-14.
25. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet. 2008;371(9607):126-34.
26. Morandi A, Brummel NE, Ely EW. Sedation, delirium and mechanical ventilation: The "ABCDE" approach. Curr Opin Crit Care. 2011;17(1):43-9.
27. Haines KJ, Beesley SJ, Hopkins RO, McPeake J, Quasim T, Ritchie K, et al. Peer support in critical care: A systematic review. Crit Care Med. 2018;46(9):1522-31.
28. Rydingsward JE, Horkan CM, Mogensen KM, Quraishi SA, Amrein K, Christopher KB. Functional status in ICU survivors and out of hospital outcomes: A cohort study. Crit Care Med. 2016;44(5):869-79.
29. Oeyen SG, Vandijck DM, Benoit DD, Annemans L, Decruyenaere JM. Quality of life after intensive care: a systematic review of the literature. Crit Care Med. 2010;38(12):2386-400.
30. Orwelius L, Nordlund A, Nordlund P, Simonsson E, Bäckman C, Samuelsson A, et al. Pre-existing disease: The most important factor for health related quality of life long-term after critical illness: A prospective, longitudinal, multicentre trial. Crit Care. 2010;14(2):R67.
31. Fan E, Dowdy DW, Colantuoni E, Mendez-Tellez PA, Sevransky JE, Shanholtz C, et al. Physical complications in acute lung injury survivors: A two-year longitudinal prospective study. Crit Care Med. 2014;42(4):849-59.
32. Wunsch H, Guerra C, Barnato AE, Angus DC, Li G, Linde-Zwirble WT. Three-year outcomes for medicare beneficiaries who survive intensive care. JAMA. 2010;303(9):849-56.
33. Hua M, Gong MN, Brady J, Wunsch H. Early and late unplanned rehospitalizations for survivors of critical illness. Crit Care Med. 2015;43(2):430-8.
34. Prescott HC, Langa KM, Iwashyna TJ. Readmission diagnoses after hospitalization for severe sepsis and other acute medical conditions. JAMA. 2015;313(10):1055-7.

SECTION 6

Gastroenterology and Nutrition

CHAPTER

40

Enteral Feeding in Patients on Noninvasive Ventilation and Prone Position

Ganshyam Jagathkar, Pradeep Reddy Pakanati

INTRODUCTION

Patients admitted to the intensive care unit (ICU) are at a high risk of malnutrition and associated poor outcomes. Most of the literature supports early initiation and advancement of enteral feeds to the prescribed target goals as early as possible. However, this may not be possible more so in patients admitted with severe respiratory failure requiring noninvasive ventilation (NIV) and prone ventilation. This chapter tries to highlight the various concerns in this cohort and suggest a pragmatic solution to the same.

ENTERAL NUTRITION DURING NONINVASIVE VENTILATION SUPPORT

Respiratory failure is a very common indication for admission to the ICU, requiring various levels of support. NIV as a means of respiratory support is quiet extensively used across the world. Traditionally, NIV has been widely used for the management of acute exacerbations in chronic obstructive pulmonary disease (COPD), pulmonary edema, and respiratory failure in the immunocompromised; however, its use for other indications is on the rise.[1] The recent coronavirus disease 2019 (COVID-19) pandemic-related acute respiratory distress syndrome (ARDS) has only contributed to the increased use of NIV in the management of patients with hypoxemic respiratory failure.[2] The outcomes of such patients depend not only on the appropriate respiratory support, but also on other optimal supportive therapies including nutrition. There are well-established guidelines recommending the initiation of early enteral feeds in ICU patients including patients on the ventilator; however, the same is lacking for patients who are on NIV support.[1,3] Literature, describing the enteral feeding practices during NIV support in critically ill patients, are very few and most of the data has been generated from patients with COPD.

Patients admitted to the ICU, requiring NIV support, could be malnourished at admission because of their background illness (COPD, heart failure, etc.)[4] or are at risk of malnutrition because of their current illness requiring prolonged admission. Malnutrition has been shown to contribute toward poor outcomes in patients admitted to the ICUs.[5] Both delayed feeding and inability to achieve the required nutritional targets are associated with poor outcomes. Despite the guidelines recommending early enteral nutrition and the need to achieve target calories, it is not uncommon to see a large number of patients not reaching their nutritional goals.[6] In the absence of established guidelines, this could be a major concern in patients who are on NIV support. Some of the concerns interfering with achieving optimal nutrition in patients on NIV are the unpredictability of NIV success or failure and the need for emergency intubation, the fear of inducing a leak around the mask because of the nasogastric (NG) tube resulting in decreasing the efficiency of NIV, the risk of vomiting and aspiration in the absence of airway protection, the interplay between breathing and swallowing in critically ill population, and lastly the chance of worsening respiratory failure when given breaks for oral feeds.

Reeves and colleagues,[7] in a prospective observational study, measured the energy and protein intake in ICU patients managed with NIV for respiratory failure. In one of the first trials looking at nutritional delivery in patients requiring NIV support, the authors found that a significant number of patients (78 and 75%) received <80% of the prescribed calorie and protein. The factors associated with poor intake were oral nutrition, prolonged NIV requirement, and a high body mass index (BMI). This study emphasizes the fact that patients receiving NIV in the ICU are at a high risk of malnutrition and associated poor outcomes.

A retrospective study by Kogo et al.[8] highlighted the risk of aspiration with enteral feeding in patients on NIV. They found that patients who received enteral nutrition had a higher risk of aspiration as compared to those who did not receive enteral nutrition (53 vs. 32%). The authors also reported a longer duration of NIV (16 vs. 8 days) requirement in patients who were on enteral feeds as compared to those

who were not. However, the study had some limitations—authors did not clearly report the size of the NG tube, the lack of a standardized nutrition protocol, the measurement of gastric residual volumes (GRVs) 8 hourly (routine measurements of GRVs are no longer recommended), and the peak inspiratory pressures which could be a key factor in compromising the lower esophageal sphincter, gastric distension, and vomiting—all of which can influence the risk of aspiration.

The French group of Nicolas Terzi et al.[9] studied the nutritional management and the associated outcomes in a group of patients requiring NIV support. This was a multicentric retrospective study involving 20 French ICU patients requiring NIV support for >48 hours. The authors reported that about 57.9% of patients did not receive any nutrition during the first 48 hours. Contrary to the popular belief, this fasting for the first 48 hours was not associated with a higher 28-day mortality; however, the patients who received enteral and parenteral nutrition in the initial 48 hours were associated with an increased need of mechanical ventilation and a higher 28-day mortality in the enteral nutrition group, though the causality could not be attributed in view of the observational nature of the study. This study, along with the study by Bendavid et al.,[10] raises a very practical concern about the clinicians' focus in making the NIV work in the initial stages of respiratory support and a possible inherent lack of drive to feed these patients with the fear of decreasing the efficiency of NIV due to the placement of a NG tube or by giving breaks during oral feeds. Just like the study done by Kogo et al., the French study did not have any specific feeding protocol nor did they report the amount of nutrition in both the groups.

A recent prospective observational Indian study by Sharma et al.[11] looked at the impact of a protocolized nutritional strategy on the delivery of enteral nutrition and associated complications in patients requiring NIV support. All patients were screened by subjective global assessment and nutritional prescription was standardized. All patients on enteral nutrition were monitored for nutrition delivery, tolerance of enteral feeds (GRV), complications, and clinical outcomes. The authors found that 76% of patients were malnourished and the average time to initiate feeds was 12.4 hours, with impending intubation being the most common reason for delay in initiating feeds. About 41.1% of patients were able to achieve 80% or more calories and 66.6% protein by day 3. The reported incidence of intolerance to enteral nutrition was insignificant. This study highlighted that following a standardized protocol for enteral nutrition in the patients requiring NIV support can result in a safe and acceptable delivery of nutritional targets.

Both the Indian and the French studies excluded postoperative patients, patients with neuromuscular diseases, and patients requiring NIV postextubation.

Proposed Strategy for Enteral Feeding during Noninvasive Ventilation

Noninvasive ventilation is an important way of supporting patients with respiratory failure in the ICUs. In the absence of established guidelines, individualizing nutritional support during NIV becomes a key aspect in the management of these patients. The following points could help in the safe and appropriate delivery of enteral nutrition during NIV.

- All patients requiring respiratory support including NIV should undergo nutritional screening and stratified accordingly.
- Team approach—the nutritional prescription and delivery in these patients should be closely supervised by the team of critical care physician, clinical nutritionist, and the bedside nurse as per a standardized protocol.
- All patients with NIV support to be nursed in 30–45° head elevated position.
- Patients with a high probability of intubation, while on NIV, avoid enteral nutrition and reassess at periodic intervals. If the patient does not improve and the need for NIV is prolonged, it is ideal to initiate mechanical ventilation along with tube feedings, as delaying intubation and prolonging NIV are associated with poor outcomes.
- Look for alternative ways of respiratory support [high-flow nasal oxygen (HFNO), invasive ventilation, etc.] wherever applicable.
- Patients on NIV support should be reassessed frequently; if the respiratory mechanics start to stabilize, small breaks allowing oral intake can be tried. A close monitoring on the total nutrition prescribed and delivered is needed, identifying the reasons for inadequate delivery and addressing them appropriately.
- If oral intake is inadequate, a small-bore NG tube to be placed and silicone dressings can be used to reduce air leaks and the risk of pressure damage.
- High inspiratory pressures during NIV can cause gastric distension, impair diaphragmatic function, and increase the risk of aspiration. Close monitoring of the pressures during NIV support is needed. It is also important to use continuous feeds with a feeding pump instead of bolus feeding to decrease the risk of aspiration.
- Though the guidelines recommend against the routine measurement of GRVs in the critically ill patients, there could be a potential role of measuring GRVs regularly in patients on NIV support which was shown by the Indian study[8] with a cutoff GRV < 500 mL being reasonable to continue feeding.
- Early use of prokinetics like metoclopramide and erythromycin could be useful in promoting gastric emptying and decreasing the risk of aspiration.
- Ultrasound can also be used to monitor gastric distension and the risk of aspiration. A gastric content > 300 mL or an

antral cross-sectional area > 400 mm^2 increases the risk of aspiration.[12] In such situations, enteral feeds are to be withheld with initiation of prokinetics and remeasuring the values. If the values remain consistently elevated, it would be prudent to initiate invasive ventilation.

- Parenteral nutrition should be considered early if enteral nutrition is not feasible or inadequate, especially in patients with preexisting malnutrition. It can also be used as a supplement to enteral nutrition in achieving the nutritional targets. Though there is no strong data suggesting the same in patients with NIV, this seems to be a reasonable approach considering it is an acceptable way of feeding patients with invasive ventilation.

Enteral Nutrition in Prone Position

Acute respiratory distress syndrome is a complex disease characterized by hypoxemia and acute inflammation of air spaces. ARDS usually progresses in three phases: (1) exudative phase, (2) proliferative phase, and (3) fibrotic phase. The pathologic hallmark of ARDS is diffuse alveolar damage which results from intense inflammation of alveolar spaces. Though more than 5 decades have passed after the initial description of ARDS by Ashbaugh et al.,[13] the severity and mortality of the disease have not changed much.[14] Despite adequate treatment, the mortality from ARDS is reported to be as high as 25–45%.[15] ARDS is defined as hypoxemic respiratory failure [P/F (PaO_2/FiO_2) ratio < 300], of acute onset (< or = 7 days), and bilateral infiltrates on chest imaging which cannot be explained by either cardiac status or volume overload.[16] In the last 2 years, especially during the COVID-19 pandemic, we have seen that >85% of ICU admissions due to COVID-19 are due to hypoxemic respiratory failure.[17]

Prone position ventilation is an important intervention in the management of moderate-to-severe ARDS patients. It is proven that prone ventilation is beneficial in terms of both morbidity and mortality when used along with other lifesaving interventions such as lung-protective ventilation strategy and other interventions used in the management of ARDS patients. Prone position ventilation involves turning the patient from supine position to ventral decubitus position so that the alveoli in the dorsal portions of the lung are better opened up and thereby oxygenation improves. From the time Luciano Gattinoni's paper in 2001[18] which has shown improvement in the oxygenation, a number of trials including the PROSEVA (Proning Severe ARDS Patients) trial in 2013[19] and several metanalyses[20] which have been published from time to time have showed that prone position ventilation improves mortality, oxygenation, and length of stay in the ICU. The beneficial effects of prone position ventilation are more visible with extended duration of prone beyond 12 hours.[21,22]

During the last 2 years of COVID-19 pandemic, majority of patients getting admitted to ICU are due to hypoxemic respiratory failure. During this period, the concept of awake proning has gained a lot of importance. A recently published article in Intensive Care Society (ICS) recommends prone position ventilation of conscious COVID-19 patients wherein 30 minutes to 2 hours of timed position changes have shown to be beneficial.[23] We have seen that many patients who tolerated prolonged hours of proning, either awake proning [in patients requiring oxygen by high-flow nasal cannula (HFNC)/NIV] or with the help of sedation and paralysis in invasively ventilated patients, had better outcomes.

Nutrition is a very important aspect in the management of critically ill patients. Early enteral nutrition therapy is a proactive strategy which helps in modulation of immune responses within the gut as well as prevents gut bacterial translocation. Nutrition also helps to preserve the lean body mass which aids in recovery during later stages.[24,25] Many established guidelines recommend commencement of early enteral nutrition, i.e., within 24 hours of admission,[26,6] and increase the calorie and protein intake in a stepwise manner so as to reach the desired targets in the next 72–96 hours. Despite these recommendations, most of the times we may not be able to attain the desired nutritional target. The treatment of ARDS patients with opioid sedatives and neuromuscular blocking agents may pose some unique challenges in the nutrition of patients even in supine position.

A patient who requires the prone position strategy for maintaining oxygenation is definitely more sick and maybe malnourished in view of his comorbidities and by virtue of his prolonged stay in the ICU. Though there are many guidelines and recommendations for early enteral nutrition, there is limited data available on enteral nutrition in the prone position.

Though prone position ventilation has gained wider acceptance after COVID-19 pandemic, it is not without risks. During awake prone, the patient will have the same risks as any other patient requiring oxygen or NIV support such as risk of vomiting, aspiration, leaks, and worsening of respiratory failure during breaks for feeds. All these risks may be higher in prone position and if the patient is invasively ventilated in prone position, there is always the risk of displacement of endotracheal (ET) tube, feeding tube, and vascular access during the turning process. Traditionally, it was a practice to stop the NG feeds in prone position for the perceived fear of feed intolerance, vomiting, aspiration, and increase in ventilator-associated pneumonia (VAP).[27] The fact that the patient is needing prone position ventilation itself means that the patient is much sicker and may have reduced gastrointestinal (GI) motility. On top of this, if the prone positioning is not done correctly, it can lead to increased intra-abdominal pressure which can cause regurgitation, vomiting, and aspiration. In a prospective survey done by L'Her E and colleagues reported that enteral nutrition was

discontinued in 25% of the patients who were proned.[21] Another study by Ponseti and his colleagues found that administration of enteral feeding in the prone position was insufficient in 82.9% of the patients resulting in a negative energy and protein balance.[28]

- The apprehensions of feeding in a prone position are manifold. It is assumed that there is an increase in the GRVs leading to gastric intolerance.
- Displacement of feeding tubes
- Increased vomiting due to intolerance and increased intra-abdominal pressure
- Aspiration
- Increase in the VAP.

In a systematic review, de Souza et al.[29] found that out of five studies which they included in their meta-analysis three of them did not show any difference in the GRVs between prone and supine positions, while one study reported a higher GRV in patients enterally fed in prone position.[30-34] In one study, Reignier found that the frequency of vomiting was higher in the prone position.[31] Majority of studies assessed GRV at an interval of 6 hours after changing the position. The GRV varied between 150 and 500 mL in various studies.[30,31] Though routine measuring of GRVs is not recommended, for practical purposes a GRV of >300 mL in 4 hours after proning is to be considered for interruption of feeds.[35] One French study evaluated the incidence of aspiration pneumonia between supine and prone positions and found no significant difference in the rates of aspiration pneumonia in prone position versus supine position.[31]

Routine monitoring of GRV is not recommended by any of the guidelines as the present evidence does not support higher GRV to be a predictor of aspiration.

There are no established protocols for enterally feeding patients in the prone position. Enteral feeding of patients in prone position should be individualized based on whether the patient is awake or if he is requiring additional oxygen support in the form of HFNC or NIV. Enteral feeding of awake patients in prone position can be achieved by oral diet or by means of enteral nutrition through a feeding tube. If the patient is on oral diet, it is important to feed the patient in small quantities and more frequently and it is essential to time the meals to coincide with supine positioning. If the patient is unable to meet the nutritional targets orally, enteral nutrition should be initiated and should be preferred over parenteral nutrition.

Proposed Strategy for Enteral Nutrition in Prone Position

The British Dietetic Association (BDA) critical care specialists group has given the best practice guidance on enteral feeding in prone position.[36]

The following points help us in safe delivery of enteral nutrition in prone position.

- Assume that all patients of ARDS requiring prone position ventilation are very sick and malnourished and are going to require longer stay in the ICU.
- For patients who can be fed through oral diet, it is important to feed the patient in small quantities and more frequently and it is essential to time the meal coincided with the supine positioning. If the patient is unable to meet the desired nutritional target by oral means, enteral nutrition should be initiated and is preferred over parenteral nutrition unless contraindicated.
- In patients who are awake and being proned and requiring HFNC/NIV, the same enteral nutrition practices are to be followed as in patients requiring invasive ventilation.
- First, determine the frequency and duration of prone position. Patients are typically proned for long periods, approximately 16–18 hours.
- Nasogastric or orogastric tube should be placed in supine position and the position of feeding tube should be checked by means of a chest X-ray and the position should be noted. 1 hour prior to proning, stop the feeds and if the patient is on insulin infusion stop the insulin infusion to prevent the chances of hypoglycemia. Aspirate the NG contents just prior to proning, disconnect the tube from the feeding bag, and secure the feeding tube to the patient during rotation to prevent displacement of the feeding tube.
- Once the patient is prone, place the bed in reverse Trendelenburg position of approximately 30° head up unless contraindicated. Wait for 1 hour, recheck the position of feeding tube, and resume feeds after confirming the position of feeding tube clinically, at the same rate which the patient tolerated in the supine position.
- Continuous enteral feeding via a feeding pump is advocated rather than bolus feeds. The rate of infusion of enteral feeds is to be increased gradually so that the desired nutrition targets are met over the next 3–4 days. The safe maximum feeding rate in prone position has been suggested to be between 65 and 85 mL/hr.
- Assess for enteral feed intolerance by measuring GRV every 4 hours after position change. If the GRV is <300 mL in 4 hours, return the contents and continue to feed enterally. Increase the rate of feeds gradually to attain the desired targets. If the GRV is >500 mL, hold the feed for a couple of hours and resume feeds at a rate which is half that of the present rate.
- Have a very low threshold for the initiation of prokinetics in prone position. If the GRV is >300 mL, start either metoclopramide or erythromycin. If the patient is not tolerating despite the initiation of prokinetics, consider placing a nasojejunal (NJ) tube when in supine position and initiate postpyloric feeds.
- If for any reason enteral nutrition is not feasible or after initiating enteral nutrition the desired nutritional targets

are not met within 4–5 days, consider supplemental parenteral nutrition.

- Before making the patient supine, stop enteral feeds 1 hour prior to change of position. Disconnect the tube from the feeding bag and fix it to the patient before turning. Once the patient is turned to the supine position, reconfirm the position of the feeding tube and if it is safe resume feeds at maximum rate tolerated and increase the rate so as to catch up for lost hours.
- Keeping a close watch on the volume is essential as all patients requiring prone ventilation are by definition having moderate-to-severe ARDS. Use the lowest volume possible to deliver the calorie and protein requirement by using high-density feeds.

CONCLUSION

Respiratory failure is a common cause for ICU admission with nutrition playing a key role in influencing the outcomes. NIV and prone positioning are important ways of supporting respiratory failure, however, they can compromise the nutritional management of these patients. The absence of established guidelines complicates the issue further. The nutritional strategy in such situations cannot be generalized and has to be individualized based on each patient's need and clinical status.

REFERENCES

1. Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med. 1995;333:817-22.
2. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al.; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20.
3. Antonelli M, Conti G, Rocco M, Bufi M, De Blasi RA, Vivino G, et al. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. N Engl J Med. 1998;339(7):429-35.
4. Meduri GU, Turner RE, Abou-Shala N, Wunderink R, Tolley E. Noninvasive positive pressure ventilation via face mask. First-line intervention in patients with acute hypercapnic and hypoxemic respiratory failure. Chest. 1996;109(1):179-93.
5. Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. N Engl J Med. 2014;370:1227-36.
6. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019;38(1):48-79.
7. Reeves A, White H, Sosnowski K, Tran K, Jones M, Palmer M, et al. Energy and protein intakes of hospitalised patients with acute respiratory failure receiving non-invasive ventilation. Clin Nutr. 2014;33(6):1068-73.
8. Kogo M, Nagata K, Morimoto T, Ito J, Sato Y, Teraoka S, et al. Enteral nutrition is a risk factor for airway complications in subjects undergoing noninvasive ventilation for acute respiratory failure. Respir Care. 2017;62:459-67.
9. Terzi N, Darmon M, Reignier J, Ruckly S, Garrouste-Orgeas M, Lautrette A, et al. Initial nutritional management during noninvasive ventilation and outcomes: A retrospective cohort study. Crit Care. 2017;21(1):293.
10. Bendavid I, Singer P, Theilla M, Themessl-Huber M, Sulz I, Mouhieddine M, et al. Nutrition day ICU: A 7 year worldwide prevalence study of nutrition practice in intensive care. Clin Nutr. 2017;36(4):1122-9.
11. Sharma G, Venkataraman R, Rajagopal S, Ramakrishnan N, Abraham BK, Savio RD. Nutrition therapy in patients requiring noninvasive ventilation in the intensive care unit: Feasibility, tolerance, and complications. Indian J Respir Care. 2021;10:289-93.
12. Bouvet L, Mazoit JX, Chassard D, Allaouchiche B, Boselli E, Benhamou D. Clinical assessment of the ultrasonographic measurement of antral area for estimating preoperative gastric content and volume. Anesthesiology. 2011;114(5):1086-92.
13. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet. 1967;2(7511):319-23.
14. Fan E, Brodie D, Slutsky AS. Acute respiratory distress syndrome: Advances in diagnosis and treatment. JAMA. 2018;319(7):698-710.
15. Maca J, Jor O, Holub M, Sklienka P, Burša F, Burda M, et al. Past and present ARDS mortality rates: a systematic review. Respir Care. 2017;62(1):113-22.
16. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al.; ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012;307(23):2526-33.
17. Ziehr DR, Alladina J, Petri CR, Maley JH, Moskowitz A, Medoff BD, et al. Respiratory pathophysiology of mechanically ventilated patients with COVID-19: a cohort study. Am J Respir Crit Care Med. 2020;201(12):1560-4.
18. Gattinoni L, Tognoni G, Pesenti A, Taccone P, Mascheroni D, Labarta V, et al.; Prone-Supine Study Group. Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med. 2001;345(8):568-73.
19. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al.; PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368(23):2159-68.
20. Munshi L, Del Sorbo L, Adhikari NKJ, Hodgson CL, Wunsch H, Meade MO, et al. Prone position for acute respiratory distress syndrome. A systematic review and meta-analysis. Ann Am Thorac Soc. 2017;14(Suppl_4):S280-88.
21. L'Her E, Renault A, Oger E, Robaux MA, Boles JM. A prospective survey of early 12-h prone positioning effects in patients with the acute respiratory distress syndrome. Intensive Care Med. 2002;28(5):570-5.
22. Kallet R. A comprehensive review of prone position in ARDS. Respir Care. 2015;60(11):1660-87.
23. Bamford P, Bentley A, Dean J, Whitmore D, Wilson-Baig N. ICS Guidance for Prone Positioning of the Conscious COIVD Patient 2020. Intensive Care Society. 2020.
24. Fraser IM. Effects of refeeding on respiration and skeletal muscle function. Clin Chest Med. 1986;7(1):131-9.
25. Turner KL, Moore FA, Martindale RG. Nutrition support for the acute lung injury/ARDS Patient: A review. Nutr Clin Pract. 2011;26(1):14-25.

26. McClave SA, Taylor BE, Martindale RG, Malissa MW, Johnson DR, Braunschweig C, et al.; Society of Critical Care Medicine; American Society for Parenteral and Enteral Nutrition. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2016;40(2):159-211.
27. Sabaretnam S. Continuing enteral nutrition in prone ventilation. Sri Lankan Journal of Anaesthesiology. 2021;29(1):3-6.
28. Ponseti EJ, Millán AV, Chinchilla DO. Analysis of complications of prone position in acute respiratory distress syndrome: quality standard, incidence and related factors. Enferm Intensiva. 2017;28(3):125-34.
29. de Souza Machado L, Rizzi P, Silva FM. Administration of enteral nutrition in the prone position, gastric residual volume and other clinical outcomes in critically ill patients: a systematic review. Rev Bras Ter Intensiva. 2020;32(1):133-42.
30. de la Fuente IS, de la Fuente JS, Estelles MDQ, Gigorro RG, Almanza LJT, Izquierdo JAS, et al. Enteral nutrition in patients receiving mechanical ventilation in a prone position. JPEN J Parenter Enteral Nutr. 2016;40(2):250-5.
31. Reignier J, Thenoz-Jost N, Fiancette M, Legendre E, Lebert C, Bontemps F, et al. Early enteral nutrition in mechanically ventilated patients in the prone position. Crit Care Med. 2004;32(1):94-9.
32. Chen SS, Tzeng YL, Gau BS, Kuo PC, Chen JY. Effects of prone and supine positioning on gastric residuals in preterm infants: a time series with crossover study. Int J Nurs Stud. 2013;50(11):1459-67.
33. van der Voort PH, Zandstra DF. Enteral feeding in the critically ill: comparison between the supine and prone positions: a prospective crossover study in mechanically ventilated patients. Crit Care. 2001;5(4):216-20.
34. Lucchini A, Bonetti I, Borrelli G, Calabrese N, Volpe S, Gariboldi R, et al. [Enteral nutrition during prone positioning in mechanically ventilated patients]. Assist Inferm Ric. 2017;36(2):76-83.
35. Aloupis M, Dolan JBJ, Fotiou E. Clinical nutrition support services-Hospital of the University of Pennsylvania. (2020). [online] Available from: https://www.med.upenn.edu/uphscovid19education/assets/user-content/documents/curricula/cnss-tips-for-enteral-nutrition-for-proned-patients.pdf [Last accessed March, 2022].
36. BDA Critical Care Specialist Group; Intensive Care Society. BDA Critical Care Specialist Group covid-19 best practice guidance: feeding patients on critical care units in the prone position (awake and sedated). Second edition. (2020). [online] Available from: https://www.bda.uk.com/uploads/assets/3f487dea-81e4-4277-bf1def44abc075bd/e319c889-23a3-4c7c-ab49e5efc9d82f91/201209-CCSG-BP-Guidance-for-Prone-Enteral-Feeding-Formatted-v2.pdf [Last accessed March, 2022].

41

CHAPTER

Optimizing Calorie and Protein Goals in Acute Hypoxemic Respiratory Failure

Anushka Mudalige, Lilanthi Subasinghe, Manoj Edirisooriya

INTRODUCTION

Administration of appropriate nutrition is an important aspect of caring for the critically ill. Maintaining muscle integrity, ventilator drive, and lung defense system by nutrition improve outcome in hypoxic respiratory failure. However, management of medical nutrition in critically ill patients on mechanical ventilation is a fundamental challenge in intensive care. It is complicated not only due to the heterogeneous nature of these patients, but also due to frequent interruptions to the delivery of nutrition, e.g., surgical procedures, intolerance of feeds, and weaning plans. On the other hand, presence of pre-existing comorbidities, sarcopenia, and ongoing inflammatory response associated with positive pressure ventilation, frequent use of medications such as sedatives, neuromuscular blockers, and steroids make these patients extremely vulnerable for malnutrition, subsequently leading to poor outcome. The occurrence of iatrogenic malnutrition in the critically ill patient population is considerably high. Unmet nutritional needs lead to undesirable effects that increase morbidity and mortality, reduce quality of life, prolong length of mechanical ventilation, and lengthen intensive care unit (ICU) stay, resulting in increased cost. Unfortunately, the scarcity of strong evidence-based therapies makes this exercise further difficult, highlighting the importance of individualizing nutritional therapy for this specific group of critically ill patients to achieve an acceptable clinical outcome. Provision of adequate nutrition consists of evaluation of nutritional status, setting standardized protocols, implementation, reassessment, and regular consistent adjustments according to the necessity.

ENERGY AND PROTEIN REQUIREMENT OF PATIENTS WITH HYPOXIC RESPIRATORY FAILURE

Hypoxic or type 1 respiratory failure, a deficiency in gas exchange at alveolar level resulting in a partial pressure of oxygen below 60 mm Hg, is a leading cause of critical illness frequently encountered in ICUs.[1] Energy expenditure during critical illness associated with respiratory failure is dynamic, variable, and lasts up to weeks from the onset.[2] Vermeeran et al. in their study demonstrated that the initial energy requirement in patients with acute exacerbation of chronic obstructive pulmonary disease reduces over the first 3 days of the course significantly.[3] Contradictory to this finding, another study in which patients with COVID-19 were followed up for a prolonged period, a steady rise in the resting energy expenditure to a maximum by the third week was noted.[4] Ample evidence points out that matching the energy and protein demand against the energy supply is a balancing art that requires dedication and commitment by a multidisciplinary ICU team.

Accurate measurement of energy expenditure is achieved through indirect calorimetry, which is the gold standard.[5,6] Due to impracticalities of the method, alternatives such as simplistic weight-based equations and predictive equations are used frequently.[5] Of these methods, the former equation is considered more accurate[7] and accordingly in general ICU practice a calorie requirement of 25–30 kcal/kg/day and protein requirement of 1–1.5 g/kg/day were considered adequate. A trophic or hypocaloric energy supplementation (70–80% of energy requirement) within the first week, compared to establishment of full caloric requirement has not shown a difference in outcome.[8,9] Contradictory to the previous recommendation, a recent publication recommended an energy goal of 15–20 kcal/kg/day (actual body weight) for patients with COVID-19.[10] Extrapolation of these findings to a heterogeneous group of patients in ICU may not be without error and therefore an individualized plan possibly incorporating measurement of energy expenditure would be the optimum mode of nutrition supplementation to patients.

ASSESSMENT OF NUTRITIONAL STATUS OF PATIENTS WITH RESPIRATORY FAILURE

Since patients with moderate or severe malnutrition are likely to develop more complications and need intense

management, it is important to identify this cohort early.[11] It is estimated that about one-third of patients who admit to ICU are malnourished with associated negative outcome.[12] The fundamental value of a comprehensive history-taking and objective examination cannot be overestimated in this situation and are the paving stones to the subjective global assessment tool.[5] The NUTRIC (Nutrition Risk in Critically ill) score, nutritional risk screening (NRS 2002), and malnutrition screening tool (MST) are few of the scoring systems that are used in the current context. They use various parameters such as chronic disease states and acute disease severity along with nutritional data to calculate the risk score. The reliability of these systems is yet to be validated and the current tool recommended by the European Society for Parenteral and Enteral Nutrition (ESPEN) guideline is the Global Leadership Initiative on Malnutrition (GLIM) criteria for diagnosis of malnutrition.[13] Use of albumin or prealbumin is inaccurate as inflammation and stress itself reduce their values irrespective of the level of nutrition. Loss of lean body mass is a hallmark of malnutrition.[5] Loss of weight can be nonspecific due to water retention and fluid shifts. Other accepted methods to measure the muscle mass include use of ultrasound, computed tomography (CT) scan, isotope studies, and use of bioelectric impedance. An objective, integrated, institution-specified method can be used to detect malnutrition early.

THE CORRECT TIMING TO INITIATE MEDICAL NUTRITION

Acute phase of an illness consists of an early period and late period lasting 1–2 and 3–7 days, respectively.[5] During the early period, there is metabolic instability and severe catabolism, whereas in the late period, there is muscle wasting and stabilization of the metabolic disturbances. This is followed by a late phase in which regeneration and rehabilitation occur if the disease progresses into convalescence. Based on this theory, most of the guidelines recommend nutrition therapy to be considered in all patients who are expected to stay in the ICU for >48 hours unless contraindicated. The energy requirement necessary for the initial 36–72 hours is fulfilled by the endogenous energy production through catabolism and full feeding in this state can lead to overfeeding and its complications. If there is an inability to initiate oral intake, enteral nutrition (EN) is recommended within 24–36 hours of ICU admission or within 12 hours of intubation and placement on mechanical ventilation.[10] If there are constrains to both oral and EN, parenteral nutrition (PN) should be established within the first 3–7 days of critical illness. It is also important to remember the calorie provided by propofol. This lipid emulsion contains 1.1 kcal/mL of energy, so during rates above 10 mL/hour, the energy contribution is considerable and can lead to overfeeding and hypertriglyceridemia.

SPECIFICATIONS OF MEDICAL NUTRITION THERAPY FOR PATIENTS IN HYPOXIC RESPIRATORY FAILURE: ROUTE OF DELIVERY, INITIATION, AND ESCALATION

It is encouraging to witness some quality evidence to guide medical nutrition therapy in critically ill patients on mechanical ventilation, emerging during the last decade. Commencement of early (within 48 hours of admission to ICU) EN in the mechanically ventilated patients is well recommended.[14] Moreover, initiation with permissive underfeeding, gradually escalated to the provision of target rate of energy and protein within 3–7 days is another recommendation with strong evidence.[9] The optimal protein and calorie goals in respiratory failure among both invasively and noninvasively ventilated patient cohorts and the carbohydrate-to-lipid ratio are not defined separately in some studies,[5] the ESPEN guideline 2020 on COVID-19 states the fat-to-carbohydrate ratios to be changed from 30:70 to 50:50 in patients with no respiratory deficiency to patients who are ventilated. Thus, in patients with hypoxic respiratory failure, the amount of glucose (in PN) or carbohydrates (in EN) administered should not exceed 5 mg/kg/min, while progressive delivery of protein equivalents per day should be 1.3 g/kg. The administration of intravenous lipid emulsions should generally be a part of PN and it (including non-nutritional lipid sources) should not exceed 1.5 g lipids/kg/day adapting to individual tolerance.[5] Thus, it is interesting to note that augmented energy delivery in mechanically ventilated patients has not shown any survival benefit as opposed to the standards of care.[15] Adding to this, initial tropic feeding has shown better gastrointestinal tolerance, indicating the potential underperfusion of bowel in mechanically ventilated patients in circulatory shock.[8] Additional enteral/parenteral glutamine is not recommended, except in burn and trauma patients. Apart from micronutrient supplementation in PN, the other recommended additional therapy is omega-3 fatty acids (FAs).[5] EN enriched with omega-3 FA within nutritional doses can be administered, however high doses of omega-3-enriched enteral formulas are not recommended by bolus or on routine basis. ESPEN guidelines further recommend parenteral lipid emulsions enriched with EPA (eicosapentaenoic acid) + DHA (docosahexaenoic acid) (fish oil dose 0.1–0.2 g/kg/day) in patients receiving PN. Measurement of gastric residual volume (GRV) in mechanically ventilated patients as a surrogate parameter of gastrointestinal dysfunction during the progression of enteral feeding in the early phase of critical illness has been the routine among the majority of ICU nutrition protocols. However, it is of questionable use, as there are unnecessary interruptions to the delivery of nutrition unless there is a genuine concern regarding the absorption of feeds.[7] Furthermore, patients with acute respiratory failure may

require a restricted fluid strategy and this needs to be considered when providing enteral and/or PN.

FEEDING DURING NONINVASIVE VENTILATION/PRONE POSITION/ EXTRACORPOREAL MEMBRANE OXYGENATION

Emerging evidence in intensive care has made the use of noninvasive ventilation (NIV) and some of the novel therapies such as prone ventilation and extracorporeal life support (ECLS) frequent in modern ICUs. In fact, these therapies have revolutionized the survival of patients with respiratory failure, at the expense of creating more issues in delivering nutritional therapy in these patients. NIV is evidence-proven to improve the outcome of patients with cardiogenic pulmonary edema, hypercapnic chronic obstructive pulmonary disease (COPD) exacerbation, and patients weaning from mechanical ventilation at risk of reintubation. Importantly, NIV has been massively used during the COVID pandemic making critical care as well as noncritical care staff more familiar with the therapy. Unfortunately, the focus on nutrition is grossly neglected during the delivery of NIV due to the concern of aspiration pneumonia, ultimately requiring invasive ventilation. Again, despite lack of quality evidence, careful medical nutrition in terms of enteral route is shown to be feasible and safe with NIV.

Prone position (PP) is defined as turning of the patient from supine position (SP) to ventral decubitus position, which allows better recruitment of dorsal lung regions improving oxygenation. Invasive mechanical ventilation in PP for patients with severe hypoxemic respiratory failure has become the standards of care all over the world, based on good evidence as well as related to the management of critically ill patients with COVID pneumonia. Underfeeding or no feeding is a common drawback in patients on prone ventilation. Among the limited number of observational studies, GRV has been identified as the main concern making the intensive care staff nervous to feed them optimally. However, the existing evidence suggests that EN with nasogastric/orogastric feeding is feasible and well tolerated.[16] The required amounts of calories and proteins in PP are comparable to that in SP.

Extracorporeal membrane oxygenation therapy has been used exponentially during the recent past particularly during the COVID-19 pandemic as a bridge to recovery or lung transplantation in patients with severe respiratory failure. However, there is an extreme scarcity of quality evidence to recommend nutritional therapy in this category of complex patients. ECLS system is accompanied by an accentuated loss of macronutrients and micronutrients because of the metabolic stress response. Nonetheless, early EN is feasible and is being practiced frequently in patients on ECMO, as recommended by recent observational studies.[17] Until better evidence is available, current standards of care in nutritional therapy must be practiced on patients on ECLS.

ROLE OF PARENTERAL NUTRITION IN HYPOXEMIC RESPIRATORY FAILURE

There is minimal sum of evidence on PN in patients with acute hypoxemic respiratory failure. Literature suggests following the equivalent guidelines advocated for PN in critically ill for this cohort of patients as well.[5,18,19] The route of administration is a critical determinant of the outcomes of nutritional support in these patients and PN is more effective in achieving dietetic targets.[18] PN is recommended in patients who do not tolerate the prescribed dose of EN during the first week in the ICU.[5,19] When the level of energy needs and protein requirement provided by EN is below 60% by day 3 of ICU admission, supplementary PN should be initiated to reach the full energy demand, to negate the deleterious effects of negative energy balance.[7] Energy need should be determined with indirect calorimetry wherever feasible. Timing of initiation should be between day 4 and 7[5] and between day 7 and 10.[7] PN can be considered earlier in uncontrolled life-threatening hypoxemia, hypercapnia, or acidosis since it is advised to delay EN in these conditions.[5] It is advocated to initiate PN as a hypocaloric intake (80% of target).[19] The amounts of glucose, intravenous lipid, including non-nutritional lipid sources and proteins in the form of amino acids are the same as that for EN.[5] Addition of parenteral glutamine is not recommended in respiratory failure, while addition of omega-3 FA is recommended as mentioned above. It is suggested to add daily nutritional doses of micronutrients (copper, selenium, zinc, and vitamins E and C), especially in acute respiratory distress syndrome (ARDS) associated with oxidative damage.

ASSESSING ADEQUACY OF NUTRITION IN HYPOXEMIC RESPIRATORY FAILURE

Monitoring for adequacy is an essential step in guaranteeing successful delivery of nutritional therapy, reducing the vent between the prescription and actual dose delivered. The main aims of monitoring nutrition in the ICU are to assure that optimal nutritional support is provided as prescribed, to prevent or detect any possible complications including refeeding, and to monitor response to feeding.[5] Adequacy is assessed mainly by monitoring laboratory parameters to ensure normoglycemia and normal electrolyte values. Blood glucose level should be measured initially (on admission or after initiating artificial nutrition), then 4 hourly, for the first 48 hours, and at an increased frequency in more unstable patients. Defective glycemic control in critically ill, resulting in severe hyperglycemia [>10 mmol/L (>180 mg/dL)], marked glycemic variability (coefficient of variation >20%), and mild hypoglycemia [<3.9 mmol/L (70.9 mg/dL)], has strong association with increased mortality, thus needs to

be avoided.[20] One should target a central venous or arterial blood glucose concentration of 4–10 mmol/L (72–180 mg/dL) measured with blood gas analyzer or central laboratory analyzer, which has been shown to be associated with improved outcome. Insulin is indicated when glucose levels exceed 10 mmol/L (180 mg/dL). It should be administered as a continuous intravenous infusion during ongoing nutritional support (EN or PN) and the algorithm used to titrate the dose should be a dynamic scale rather than a sliding scale.[5] Electrolytes, especially phosphate, potassium, and magnesium, should be measured once daily for the first week. It is also suggested to monitor triglyceride level, liver function tests, energy expenditure, and body composition during artificial feeding.[21]

ASSESSING FOR COMPLICATIONS AND ENSURING SAFETY DURING FEEDING IN HYPOXEMIC RESPIRATORY FAILURE

Recognized complications of nutritional therapy in patients with respiratory failure are mainly the effects due to caloric overfeeding, increased protein intake, and refeeding syndrome. Caloric overfeeding is associated with increased risk of nosocomial infections, hyperglycemia, enhanced CO_2 production, diaphragmatic dysfunction, and increased lipogenesis leading to hepatic steatosis and higher insulin requirements. Increased CO_2 production and diaphragmatic dysfunction are important factors in patients with respiratory failure as they may exacerbate CO_2 retention and restricted ventilation. The fact that PN is associated with systemic infections more than EN[22] is currently not appreciated following the findings of recent major studies.[14,23] High protein intake can lead to azotemia, hypertonic dehydration, and metabolic acidosis.[19] Refeeding syndrome is characterized by significant fluid and electrolyte shifts that occur when malnourished/at-risk patients are commenced on artificial refeeding. The condition is potentially fatal, thus needs to be detected early to prevent complications. Thus, patients who are scheduled for EN/PN should undergo nutritional assessment at the outset, especially with electrolyte levels (phosphate, potassium, and magnesium) which should be repeated daily and corrected accordingly.[5,19] The occurrence of hypophosphatemia early during refeeding is considered as a herald of the syndrome. In patients with refeeding hypophosphatemia [<0.65 mmol/L (mg/dL) or a drop of >0.16 mmol/L (0.5 mg/dL)], electrolytes should be measured two to three times a day and supplemented if needed. Moreover, their energy supply should be restricted for 48 hours and gradually increased afterward.

CONCLUSION

Predicted favorable outcome in critically ill patients with respiratory failure depends, among other supportive and definitive therapies, on targeted, titrated nutritional supplementation. Identifying the importance and implementation of early, appropriate nutrition to ensure adequate provision of energy, protein, and other macro- and micronutrients is the collective responsibility of the ICU team. Despite the presence of numerous equations, and recommendations, a distinct, dynamic plan for each individual, depending on their biological status, comorbidities, and severity of the acute illness, should be formulated, executed, and reformulated according to regular assessments in order to optimize overall outcome of patients.

REFERENCES

1. Sbaih N, Hawthorne K, Lutes J, Cavallazzi R. Nutrition therapy in non-intubated patients with acute respiratory failure. Curr Nutr Rep. 2021; 31(4):1-10.
2. Moonen, HPFX, Beckers, KJH, van Zanten, ARH. Energy expenditure and indirect calorimetry in critical illness and convalescence: current evidence and practical considerations. J Intensive Care. 2021;9(8).
3. Vermeeren MA, Schols AM, Wouters EF. Effects of an acute exacerbation on nutritional and metabolic profile of patients with COPD. Eur Respir J. 1997;10(10):2264-9.
4. Whittle J, Molinger J, MacLeod D, Haines K, Wischmeyer PE; LEEP-COVID Study Group. Persistent hypermetabolism and longitudinal energy expenditure in critically ill patients with COVID-19. Crit Care. 2020;24(1):581.
5. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MC, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019;38(1):48-79.
6. Wischmeyer PE, Molinger J, Haines K. Point-counterpoint: Indirect calorimetry is essential for optimal nutrition therapy in the intensive care unit. Nutr Clin Pract. 2021;36(2):275-81.
7. Taylor BE, McClave SA, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2016;40(2):159-211.
8. Rice TW, Wheeler AP, Thompson BT, Steingrub J, Hite RD, Moss M, et al. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. JAMA. 2012;307(8):795-803.
9. Arabi YM, Aldawood AS, Haddad SH, Al-Dorzi HM, Tamim HM, Jones G, et al. Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults. N Engl J Med. 2015;372(25):2398-408.
10. Martindale R, Patel JJ, Taylor B, Arabi YM, Warren M, McClave SA. Nutrition therapy in critically ill patients with coronavirus disease 2019. J Parenter Enter Nutr. 2020;44(7):1174-84.
11. Siobal M, Baltz JE, Richardson J. (2013). A guide to the nutritional assessment and treatment of the critically ill patient, 2nd edition. [online] Available from: https://www.aarc.org/wp-content/uploads/2014/11/nutrition_guide.pdf. [Last accessed February 2022].
12. Norman K, Pichard C, Lochs H, Pirlich M. Prognostic impact of disease-related malnutrition. Clin Nutr. 2008;27(1):5-15.

13. Jensen GL, Cederholm T, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition: a consensus report from the global clinical nutrition community. J Parenter Enteral Nutr. 2019;43(1):32-40.
14. Harvey SE, Parrott F, Harrison DA, Bear DE, Segaran E, Beale R, et al. CALORIES Trial Investigators. Trial of the route of early nutritional support in critically ill adults. N Engl J Med. 2014;371(18):1673-84.
15. Chapman M, Peake SL, Bellomo R, Davies A. Energy-dense versus routine enteral nutrition in the critically ill. N Engl J Med. 2018;379:1823-34.
16. Savio RD, Parasuraman R, Lovesly D. Feasibility, tolerance and effectiveness of enteral feeding in critically ill patients in prone position. J Intensive Care Soc. 2021;22(1):41-6.
17. Stoppea C, Nesterovab E, Elke G. Nutritional support in patients with extracorporeal life support and ventricular assist devices. Curr Opin Crit Care. 2018;24(4):269-76.
18. Terzi N, Darmon M, Reignier J, Ruckly S, Garrouste-Orgeas M, Lautrette A, et al. Initial nutritional management during non-invasive ventilation and outcomes: a retrospective cohort study (OUTCOMEREA). Crit Care. 2017;21(1):293.
19. Zonies D, Codner P, Park P, Martin ND, Lissauer M, Evans S, et al. AAST Critical Care Committee clinical consensus: ECMO, nutrition. Trauma Surg. Acute Care Open. 2019;4:e000304.
20. Braunschweig C, Sheean PM, Peterson SJ, Gomez Perez S, Freels S, Gurka D, et al. Intensive nutrition in acute lung injury: a clinical trial (intact). J Parenter Enteral Nutr. 2015;39(1):13-20.
21. Berger MM, Reintam-Blaser A, Calder PC, Casaer M, Hiesmayr MJ, Mayer K, et al. Monitoring nutrition in the ICU. Clin Nutr. 2019; 38(2):584-93.
22. Casaer MP, Wilmer A, Hermans G, Wouters PJ, Mesotten D, Van den Berghe G. Role of disease and macronutrient dose in the randomized controlled EPaNIC trial. A post hoc analysis. Am J Respir Crit Care Med. 2013;187(3):247-55.
23. Reignier J, Boisrame-Helms J, Brisard L, Lascarrou JB, Ait Hssain A, Anguel N, et al. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). Lancet. 2018;391(10116):133-43.

CHAPTER 42

Individualized Nutritional Strategies in Intensive Care Unit

Kanwalpreet Sodhi, Ruchira Khasne, Ujwala Mhatre

INTRODUCTION

Nutrition for in-hospital patients is a highly cost-effective intervention to reduce hospital-associated complications and improving outcomes.[1] Comprehensive nutrition programs including malnutrition screening, dietician consultation, and appropriate nutritional support right from the time of admission should be implemented.[2] FASTHUG is a well-accepted mnemonic which includes key aspects of general care of critically ill patients admitted in the intensive care unit (ICU). It begins with "F" for feeding; highlights that nutrition should be started right from the time of ICU admission and reassessed.

Nutrition prescription should be individualized based on comorbidities, disease process, clinical condition, ongoing therapy, surgical intervention, and critical illness itself being associated with a catabolic state. Most of the critically ill patients are in hypercatabolic state causing delayed recovery, increase in length of stay (LOS), increased complications, and mortality. Catabolic events are associated with increased glycogenolysis, decreased protein synthesis, increased protein breakdown, increased insulin resistance, and increased lipolysis leading to protein breakdown hyperglycemia, sarcopenia, weight loss, and undernutrition. The hypercatabolic illness has different phases: Early acute phase within first 48 hours followed by late acute phase over next 3–7 days and chronic phase after 8 days. Enteral nutrition (EN) preferably oral or through nasogastric route is the most preferred method, which should be initiated within 24–48 hours of admission to ICU. Start with hypocaloric nutrition for 48 hours (20 kcal/kg, to be achieved over 3 days) followed by isocaloric nutrition (25 kcal/kg). Protein intake should be 1.3–1.5 g/kg/day which can be increased up to 2 g/kg/day.[3] Initiate parenteral nutrition (PN) if enteral feeding is insufficient on 3rd to 7th day after admission to ICU. Refeeding syndrome is the real threat in catabolic state with pre-existing malnutrition. These patients should be monitored for underfeeding with evaluation of electrolytes (phosphate, potassium, and magnesium) and replacement as required. Liver function test and triglyceride levels should be monitored every 3–4 days.

Mehta et al. published Indian practical guidelines for nutrition in critically ill patients.[4] This chapter provides a broad framework of individualized nutrition prescription based on the clinical disease.

NUTRITION IN SEPSIS

Sepsis is an acute catabolic response. As per the recommendations, EN should be initiated within 72 hours once hemodynamics have stabilized, and resuscitation is complete.[5-7] NUTRIREA-2 trial 2018,[8] comparing targeted normocaloric supplementation in form of either early EN (61%) or PN (64%) in invasively ventilated adults needing vasopressors for shock, found that early EN was associated with a greater risk of gastrointestinal complications and no mortality benefit. As per the available evidence, full feeding should be avoided during acute phase of shock. ESICM Working Group on Gastrointestinal Function[9] also suggests to delay EN in patients with uncontrolled shock, hypoxemia, and acidosis.

European Society for Parenteral and Enteral Nutrition (ESPEN) have strong consensus of replacing progressive PN if EN is contraindicated, to reduce progressively increasing energy debt. However, this is not supported by American Society for Parenteral and Enteral Nutrition (ASPEN) guideline. EPaNiC (Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients) study[10] showed longer hospital and ICU stays, longer duration of organ support, and a higher incidence of ICU-acquired infection with PN.

Due to wide variations in calculation of energy expenditure in septic shock patients, guidelines suggest administering low-dose enteral feeding in the first week of ICU stay. In the initial phase of sepsis, start with trophic feeding of 10–20 kcal/hr, up to 500 kcal/day. After 24–48 hours, advance to 60–70% of target energy goal over the first week along with protein intake of 1.2–2 g/kg/day. Fish oil-containing lipids have shown to reduce LOS and infectious complications

versus traditional soy-only lipids.[11] REDOXS (REducing Deaths due to OXidative Stress) study[12] has shown intravenous glutamine (GLN) to cause harm as did METAPLUS trial[13] with a high-dose enteral mixture of different nutrients including GLN.

Serum micronutrients with antioxidants are decreased in septic patients but there is no strong recommendation for their supplementation or for immune-modulating formulas. Marik showed significantly reduced mortality in patients with septic shock with thiamine, vitamin C, and low-dose steroids.[14] But VITAMINS; the randomised clinical trial compared vitamin C, hydrocortisone and thiamine with hydrocortisone alone in patients with septic shock. They observed that this treatment has not facilitated rapid resolution of septic shock compared to hydrocortisone alone.[15] Vitamin D levels should be monitored and replenished; however, larger trials are currently underway.

Once acute phase of sepsis is over and patients stabilize during recovery, increased calorie (25–30 kcal/kg/day), and protein (1.2–2.0 g/kg/day) supplementation is recommended to reduce further losses, allow for early mobilization, and encourage functional recovery.

NUTRITION IN ACUTE KIDNEY INJURY

Kidney Disease Improving Global Outcomes (KDIGO) recommends a calorie intake of 25–30 kcal/kg/day for critically ill patients with acute kidney injury (AKI)[16], whereas the Society of Critical Care Medicine (SCCM) suggests 25–35 kcal/kg/day,[6] equivalent to 100–130% of resting energy expenditure (REE). Energy contribution from solutions such as lactates and citrate should be counted particularly those on continuous renal replacement therapy (CRRT). Protein intake should not be restricted, rather positive nitrogen balance is associated with significantly better ICU and hospital survival in AKI patients. CRRT is associated with a large amount of amino acid losses, up to 10–15 g/day in the effluent. Scheinkestel[17] reported that an increase in nitrogen balance by 1 g/day improved survival by 21% in the CRRT group. Based on type of renal replacement therapy (RRT), protein intake should be as follows:

- *Not on RRT*: 1.3 g/kg/day up to 1.7 g/kg/day.
- *On intermittent RRT*: 1 g/kg/day up to 1.5 g/kg/day.
- *On CRRT*: Up to 1.7 g/kg/day.

Cochrane review concluded that the use of essential amino acids (EAAs) shortened the overall duration of kidney dysfunction and improved survival in dialysis-dependent AKI.[18] Micronutrient deficiency is common in critically ill with severe AKI patients irrespective of CRRT status; however, its impact on outcome is still unclear.

NUTRITION IN LIVER DISEASE

Malnutrition is common in patients with end-stage liver failure and hepatic encephalopathy (HE) due to inadequate dietary intake, altered synthesis/absorption of nutrients, increased protein losses, hypermetabolism, and inflammation, which increases morbidity and mortality. EN is associated with decreased infection rates and fewer metabolic complications and should be preferred.[19] Continuous enteral feeding permits constant saturation of carrier transport proteins and facilitates intestinal adaptation. A standard polymeric isotonic enteral formula is well tolerated. Elemental formulae are avoided due to hypertonicity, expense, and lack of evidence supporting benefit. A sodium restriction to 2 g/day is recommended in patients with ascites.[20] Protein restriction should be avoided in refractory encephalopathy.[21] A whole-protein formula providing 35–40 kcal/kg body weight (BW)/day energy intake and 1.2–1.5 g/kg BW/day protein is recommended.[22] Branched chain amino acids (BCAAs) use in HE is based on their reduced concentrations in liver failure, competing for binding sites in the central nervous system with aromatic amino acids, and their stimulatory effect on ammonia detoxification but no beneficial effects were documented.[23]

NUTRITION IN CARDIOVASCULAR DISEASES

Heart failure (HF) nutrition strategies have shown positive outcomes in HF patients.[24] Strong evidence supports reducing sodium to a "normal" level, i.e., 2–3 g/day along with fluid restriction of 1–1.5 L/day.[25] Literature shows compared to low sodium, normal sodium diets resulted in decreased readmissions and mortality. The role of macronutrients, nitrogen, and energy balance in HF nutrition is a matter of research and there are no recommendations on these. Mediterranean and DASH (Dietary Approaches to Stop Hypertension) diets are recommended for cardiovascular diseases including acute coronary syndrome.[26,27] Dietary patterns lower in meat, higher in fish oils and unsaturated fat, are associated with significant reductions in complications in cardiac patients.

NUTRITION IN RESPIRATORY DISEASES

Chronic obstructive pulmonary disease (COPD) patients are usually hypermetabolic with elevated REE even at rest. The nutritional requirements should be assessed based on clinical stability and disease severity (mild, moderate, or severe). American Lung Association recommends limiting simple carbohydrates, trans-fats, and saturated fats along with sodium restriction.[28] Energy requirements for individuals with COPD for weight maintenance are @ 30 kcal/kg BW/day, higher @ 45 kcal/kg BW/day to encourage weight gain along with a daily protein intake of 1.0–1.2 g/kg BW/day.[29-31] The diet must include high-fiber foods targeting 20–30 g fiber/day.[28] Several vitamins that exert anti-inflammatory and antioxidant effects, such as vitamins A, C, and E, are recommended as they are likely to be protective in the progression of COPD.

Acute respiratory distress syndrome (ARDS) is a hypercatabolic state with significant nutrition deficits causing deterioration of respiratory muscle strength.[32] EN should be started early, within 24–48 hours of ICU admission with either full or trophic feedings during first few ICU days and the role for PN is extremely limited.[33] Literature suggests no benefit of glutamine, antioxidants, and ω-3 fatty acids in critically ill patients.[33] Patients with severe COVID pneumonia admitted in ICUs also have significant immobility, catabolic stress, and muscle wastage, and thereby at high risk of malnutrition. Optimal nutritional management of these patients are based on available evidence from ARDS.[34] Micronutrients and antioxidants including vitamins A, C, D, E, B6, and B12, zinc, and selenium have been shown to reduce oxidative stress and regulate the immunological response in COVID by contributing to cell-mediated immunity and affecting antibody production and function.

NUTRITION IN PANCREATITIS

A meta-analysis of eight trials demonstrated significantly reduced mortality, multiple organ failure, systemic infections, and the need for surgery in acute pancreatitis with EN as compared with PN.[35] In four of seven trials that included patients with mild-to-moderate pancreatitis, early feeding was associated with a reduction in hospital LOS.[36] In the absence of ileus, oral feeding can be initiated within 24 hours. In patients with severe or necrotizing pancreatitis, oral feeding may not be tolerated due to postprandial pain, nausea, or vomiting related to gastroduodenal inflammation and/or extrinsic compression from fluid collections leading to gastric outlet obstruction and nasogastric or nasojejunal route may be used.

Due to a reduction in pancreatic digestive enzymes, high protein, low fat, and semi-elemental feeding formulae are preferred. Begin at 25 mL/hour and advance to at least 30% of the calculated daily requirement (25 kcal/kg ideal body weight), even in the presence of ileus. A recent meta-analysis including 17 studies identified that 16.3% of patients with acute pancreatitis will subsequently have intolerance to oral feeding.[37] Drainage of fluid collections may allow resumption of oral intake. Oral food intake in patients undergoing minimally invasive necrosectomy is safe and feasible and should be initiated in the first 24 hours after the procedure.

NUTRITION IN SHORT BOWEL SYNDROME

Acute phase is characterized by high intestinal losses and metabolic derangement lasts for 3–4 weeks. The adaptation phase, which lasts for 1–2 years, is characterized by structural and functional changes to increase nutrient absorption and slow the gastrointestinal transit. Patients with a small bowel stoma may have an increased output resulting in fluid loss and dyselectrolytemia and bacterial overgrowth in dilated areas of bowel aggravating the malabsorption.

The goal of EN is to reduce fecal calorie loss, increase energy absorption, and improve net weight absorption. Supplementation with medium chain triglyceride oil, essential fatty acids, and vitamin B12 should be considered.[38] Intestinal rehabilitation programs are planned to transition from parenteral to enteral feeding which includes frequent small feeds, protein-rich diet (20%), high fat (30–40%), and complex carbohydrates to avoid osmotic diarrhea. Fiber supplementation enhances adaptation and water absorption but can be constipating. Oxalate restriction and avoidance of foods high in vitamin C may be needed for patients with ileal resection >100 cm. Hypertonic fluids contribute to diarrhea and hypotonic fluids will lead to dehydration. Use of teduglutide, a long-acting glucagon-like peptide-2, released in response of luminal nutrients helps in maintenance of small bowel adaptive responses to resection and improves nutrient absorption.[39] Patients with both irritable bowel syndrome may benefit from a low fermentable oligo-, di-, and monosaccharides and polyols (FODMAP) diet.

NUTRITION IN OBESITY

As per the class of obesity **(Table 1)**, previous history of weight loss surgery, medical conditions affecting absorption of nutrients, and concurrent metabolic conditions as diabetes mellitus nutrition prescription is individualized.

Indirect calorimetry, nutritional risk screening, or malnutrition universal screening tool have been recommended for nutrition assessment.[23] Normal weight or overweight patients can be fed at 20–25 kcal/kg/day. For patients with body mass index (BMI) is >30 kg/m^2, the goal of nutrition regimen is 11–14 kcal/kg/day. For BMI >50 kg/m^2 calories would be 22–25 kcal/kg/day with 2.5 g/kg/day protein. Low calories and high protein diet has shown to decrease insulin requirements, short ICU stay, and decreased ventilator duration.[23] Sodium requirement is 100–150 mEq. Potassium requirement is 50-80 mEq.[40]

TABLE 1: Classification of obesity.

Underweight—BMI <18.5 kg/m^2	Obesity class I—BMI of 30.0–34.9 kg/m^2
Normal weight—BMI ≥18.5–24.9 kg/m^2	Obesity class II—BMI of 35.0–39.9 kg/m^2
Overweight—BMI ≥25.0–29.9 kg/m^2	Obesity class III—BMI ≥40 kg/m^2
Obesity—BMI ≥30 kg/m^2	
Severe obesity—BMI ≥40 kg/m^2	
Super obesity—BMI ≥50 kg/m^2	

(BMI: body mass index)

NUTRITION IN BURNS

Severe burns [>40% total body surface area (TBSA)] are hypermetabolic response characterized by hyperdynamic circulation with profound metabolic, physiologic, catabolic, and immunological derangements increase susceptibility to infection or result in multiorgan dysfunction and death. Early continuous enteral feeding with high protein and high carbohydrate feeds opposing catabolism stimulating anabolism markedly decrease morbidity in the acute phase post severe burn injury. Nutrition should be tailored to promote wound healing, increase resistance to infection, and prevent persistent loss of muscle protein. The primary goal of nutritional support is to satisfy acute, burn-specific requirements, and not to overfeed. The major energy source should be carbohydrates providing glucose for metabolic pathways, serving as fuel for wound healing, and sparing the amino acids needed for catabolism. Recommendations for severe burn injury are 25 kcal/kg/day plus 40 kcal per percent TBSA burn per day.[41] Fat should be no >30% of nonprotein calories, or about 1 g/kg/day of intravenous lipids in total parenteral nutrition (TPN).[42] Diets rich in ω-3 free fatty acids (FFAs) have shown reduced incidence of hyperglycemia, an improved inflammatory response and outcomes.[43] Protein catabolism in burn patients can exceed 150 g/day, requiring protein intake of 1.5–2 g/kg/day.[44] GLN supplementation at 25 g/kg/day decreases infections, LOS, and reduces mortality.[45,46] BCAAs improved nitrogen balance, but there was no effect on survival.[47] Vitamins A, C, and D, iron, zinc, and selenium improved wound healing and immune dysfunction in severely burned patients.[48] PN should be reserved primarily for those who have enteral feeding intolerance or prolonged ileus.

CONCLUSION

Nutritional support in critically ill patients requires skills, a specific technical knowledge, feeding protocol, asepsis, and should be individualized. Each critical care unit should devise and strictly adhere to nutritional protocols as per the institutional policies. The intensivist should have frequent interactions with the dietician and nutritional prescription should be modified regularly, keeping account of actual calories and proteins being received by the patient. EN is preferred and should be the primary aim. Larger randomized controlled trials (RCTs) are awaited for developing nutrition guidelines in ICU patients which can address individual nutrition needs of critically ill patients and implemented universally.

REFERENCES

1. Schuetz P, Sulo S, Walzer S, Vollmer L, Stanga Z, Gomes F, et al. Economic evaluation of individualized nutritional support in medical inpatients: Secondary analysis of the EFFORT trial. Clin Nutr. 2020;39(11):3361-8.
2. Hersberger L, Dietz A, Bürgler H, Bargetzi A, Bargetzi L, Kägi-Braun N. Individualized nutritional support for hospitalized patients with chronic heart failure. J Am Coll Cardiol. 2021;77(18):2307-19.
3. Mishra RC, Sodhi K, Prakash KC, TyagiN, Chanchalani G, Annigeri RA, et al. ISCCM Guidelines on Acute Kidney Injury and Renal Replacement Therapy. Indian J CritCare Med 2021; https://www.ijccm.org/doi/IJCCM/pdf/10.5005/jp-journals-10071-24109.
4. Mehta Y, Sunavala JD, Zirpe K, Tyagi N, Garg S, Sinha S. Practice Guidelines for Nutrition in Critically Ill Patients: A Relook for Indian Scenario. Indian J Crit Care Med. 2018;22(4):263-73.
5. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47(11):1181-247.
6. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical care Medicine (SCCM) and American Society. J Parenter Enter Nutr. 2016;40(2):159-211.
7. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019;38:48-79.
8. Reignier J, Boisramé-Helms J, Brisard L, Lascarrou JB, Hssain AA, Anguel N, et al. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). Lancet. 391;2018(10116):133-43.
9. Reintam Blaser A, Starkopf J, Alhazzani W, Berger MM, Casaer MP, Deane AM, et al. OSHEWG on GFE enteral nutrition in critically ill patients: E clinical practice guidelines. Intensive Care Med. 2017;43(3):380-98.
10. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et.al. Early versus Late Parenteral Nutrition in Critically Ill Adults. New Eng J Med. 2011;365:506-17.
11. Pradelli L, Mayer K, Muscaritoli M, Heller AR. n-3 fatty acid-enriched parenteral nutrition regimens in elective surgical and ICU patients: a meta-analysis. Crit Care. 2012;16(5):R184.
12. Heyland D, Muscedere J, Wischmeyer PE, Cook D, Jones G, Albert M, et al. A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med. 2013;368(16):1489-97.
13. van Zanten AR, Sztark F, Kaisers UX, Zielmann S, Felbinger TW, Sablotzki AR, et al. High-protein enteral nutrition enriched with immune-modulating nutrients vs standard high-protein enteral nutrition and nosocomial infections in the ICU: a randomized clinical trial. JAMA. 2014;312(5):514-24.
14. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, vitamin C and thiamine for the treatment of severe sepsis and septic shock: a retrospective beforeafter study. Chest. 2016;151(6):1229-38.
15. Fujii T, Luethi N, Young PJ, Frei DR, Eastwood GM, French CJ, et al. Effect of vitamin c, hydrocortisone, and thiamine vs hydrocortisone alone on time alive and free of vasopressor support among patients with septic shock: The VITAMINS Randomized Clinical Trial. JAMA. 2020;323(5):423-31.
16. Kidney disease: Improving Global Outcomes (KDIGO) acute kidney injury workgroup. KIDGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1-138.

17. Scheinkestel CD, Kar L, Marshall K, Bailey M, Davies A, Nyulasi I, et al. Prospective randomized trial to assess caloric and protein needs of critically Ill, anuric, ventilated patients requiring continuous renal replacement therapy. Nutrition. 2003;19(11-2):909-16.
18. Li Y, Tang X, Zhang J, Wu T. Nutritional support for acute kidney injury. Cochrane Database Syst Rev. 2010;1CD005426.
19. Scolapio JS, Fleming CR, Kelly DG, Wick DM, Zinsmeister AR. Survival of home parenteral nutrition-treated patients: 20 years of experience at the Mayo Clinic. Mayo Clin Proc. 1999;74(3):217-22.
20. Rai R, Nagral S, Nagral A. Surgery in a patient with liver disease. J Clin Exp Hepatol. 2012;2(3):238-46.
21. Krenitsky J. Nutrition for patients with hepatic failure. Pract Gastroenterol. 2003;6:23-42.
22. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. J Hepatol. 2019;70(1):172-93.
23. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) American College of Critical Care Medicine, Society of Critical Care Medicine. J Parenter Enteral Nutr. 2009;37(5):277-316.
24. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. Circulation. 2014;129(3):e28-292.
25. Abshire M, Xu J, Baptiste D, Almansa JR, Xu J, Cummings A, et al. Nutritional interventions in heart failure: A systematic review of the literature. J Card Fail. 2015;21(12):989-99.
26. Tektonidis TG, Åkesson A, Gigante B, Wolk A, Larsson SC. A Mediterranean diet and risk of myocardial infarction, heart failure and stroke: A population-based cohort study. Atherosclerosis. 2015;243(1):93-8.
27. Levitan EB, Lewis CE, Tinker LF, Eaton CB, Ahmed A, Manson JE, et al. Mediterranean and DASH diet scores and mortality in women with heart failure: The Women's Health Initiative. Circ Heart Fail. 2013;6(6):1116-23.
28. American Lung Association. Nutrition and COPD. [online] Available from: https://www.lung.org/lung-health-diseases/lung-disease-lookup/copd/living-with-copd/nutrition. [Last accessed February 2022].
29. Slide F, Gronberg AM, Svantesson U, Hulthén L, Larsson S. Energy expenditure in chronic obstructive pulmonary disease-evaluation of simple measures. Eur J Clin Nutr. 2011;65(12):1309-13.
30. Ganzoni A, Heilig P, Schonenberger K, Hügli O, Fitting JW, Brändli O. High-caloric nutrition in chronic obstructive lung disease. Schweiz Rundsch Med Prax. 1994;83(1):13-6.
31. Deutz NE, Bauer JM, Barazzoni R, Biolo G, Boirie Y, Bosy-Westphal A, et al. Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. Clin Nutr. 2014;33(6):929-36.
32. Krzak A, Pleva M, Napolitano LM. Nutrition therapy for ALI and ARDS. Crit Care Clin. 2011;27(3):647-59.
33. Stapleton RD, Suratt BT. Obesity and nutrition in acute respiratory distress syndrome. Clin Chest Med. 2014;35(4):655-71.
34. Chapple L, Tatucu-Babet OA, Lambell KJ, Fetterplace K, Ridley EJ. Nutrition guidelines for critically ill adults admitted with COVID-19: Is there consensus? Clin Nutr ESPEN. 2021;44:69-77.
35. McClave SA, Chang WK, Dhaliwal R, Heyland DK. Nutrition support in acute pancreatitis: a systematic review of the literature. J Parenter Enteral Nutr. 2006;30(2):143.
36. Alexander JW, Management of acute pancreatitis. Am Coll Gastroenterol. 2013;108(9):1400.
37. Adiahmah A, Psaltis E, Crook M, Lobo DN. A systematic review of epidemiology, pathophysiology and current management of hyperlipidaemic pancreatitis. Clin Nutr 2018;37:1810e22.
38. Mishkin S. Dairy sensitivity, lactose malabsorption, and elimination diets in inflammatory bowel disease. Am J Clin Nutr. 1997;65(2):564-7.
39. Jeppesen PB, Hartmann B, Thulesen J, Graff J, Lohmann J, Hansen BS, et al. Glucagon-like peptide 2 improves nutrient absorption and nutritional status in short-bowel patients with no colon. Gastroenterology. 2001;120(4):806-15.
40. Nelson BV, Van Way CW 3rd. Nutrition in the critically-ill obese patient. Mo Med. 2012;109(5):393-6.
41. Curreri PW, Richmond D, Marvin J, Baxter CR. Dietary requirements of patients with major burns. J Am Diet Assoc. 1974;65(4):415-7.
42. Demling RH, Seigne P. Metabolic management of patients with severe burns. World J Surg. 2000;24(6):673-80.
43. Alexander JW, Saito H, Trocki O, Ogle CK. The importance of lipid type in the diet after burn injury. Ann Surg. 1986;204(1):1-8.
44. Saffle JR, Graves, C. Nutritional support of the burned patient. In: Herndon DN, (Ed). Total Burn Care, 3rd edition. London: Saunders Elsevier; 2007. p. 398-419.
45. Garrel D. The effect of supplemental enteral glutamine on plasma levels, gut function, and outcome in severe burns. JPEN J Parenter Enteral Nutr. 2004;28(2):123.
46. Zhou YP, Jiang ZM, Sun YH, Wang XR, Ma EL, Wilmore D. The effect of supplemental enteral glutamine on plasma levels, gut function, and outcome in severe burns: a randomized, double-blind, controlled clinical trial. JPEN J Parenter Enteral Nutr. 2003;27(4):241-5.
47. Cerra FB, Mazuski JE, Chute E, Nuwer N, Teasley K, Lysne J, et al. Branched chain metabolic support. A prospective, randomized, double-blind trial in surgical stress. Ann Surg. 1984;199(3):286-91.
48. Gamliel Z, DeBiasse MA, Demling RH. Essential microminerals and their response to burn injury. J Burn Care Rehabil. 1996;17(3):264-72.

CHAPTER 43

Recent Trials in Stress Ulcer Prophylaxis

Srinivas Samavedam

INTRODUCTION

Stress ulcer prophylaxis (SUP) is recognized as one of the components of the standard-of-care bundles meant to improve outcomes among patients admitted to an intensive care unit (ICU). Ever since Vincent et al.[1] published their checklist in 2005, incorporating SUP as part of the FASTHUG process, SUP became a standard practice in ICUs across the world. Critically ill patients are inherently at risk of erosions of the gastric mucosa during the period of critical illness (stress).[2] Clinically, significant gastrointestinal (GI) bleeding can occur in a significant percentage of these patients with the literature quoting a prevalence of 2–5%.[3,4] Significant bleeding episodes contribute to increased morbidity and mortality among this cohort of patients.[5] A number of risk factors have been identified which confer this risk on a critically ill patient.[6] These include mechanical ventilation, hemodynamic instability, coagulopathy, hepatic failure, kidney injury, and disease severity. It is therefore logical to presume that a prophylactic strategy to minimize these episodes would improve the outcomes of critically ill patients. Enteral nutrition may seem to be the easiest way to execute this strategy.[2] However, recent data does not seem to indicate a benefit with this approach.[6]

Pharmacoprophylaxis with either H_2 receptor antagonists (H_2RAs) or proton pump inhibitors (PPIs) therefore seems to be the next best strategy.[3] Sucralfate has also been evaluated as a preventive strategy but with no convincing benefits. Over the years, PPIs have gained in popularity and have secured an edge over H_2RAs.[7] In the last decade, PPIs have extensively been used as agents to achieve SUP. Enhanced vigilance on nosocomial infections and patient safety have brought the issue of increased nosocomial infections like pneumonia and clostridium difficile (C. diff) diarrhea into focus. One of the factors that has been identified as correlating with the higher incidence of these two infections, is the use of SUP, more so with PPIs.[4,8] Inevitably, this has prompted several new randomized controlled trials (RCTs) which have attempted to re-evaluate the risk benefit equation with the use of SUP among critically ill patients. This review attempts to examine the recent high-quality trials addressing the issue of SUP in a critically ill cohort. The review will also discuss the results of the most recently published meta-analysis of the topic.

FIVE RECENT TRIALS

The first study which explored the feasibility of comparing the role of PPIs against placebo was the POP-UP trial.[9] This single center prospective double-blind RCT evaluated the benefits and harm of prescribing pantoprazole as SUP. The cohort included in this study was mechanically ventilated critically ill patients who were suitable for enteral nutrition. This study evaluated the strategy of giving either pantoprazole or placebo, to the cohort, against the primary outcome of clinically significant gastrointestinal (GI) bleeding, pneumonia, and C. diff infection. The study was able to recruit 216 patients and was able to evaluate all but two of the recruited cohort. Close to half the patients recruited into either arm were receiving inotropes/vasopressors at enrollment. Trauma and neurological and respiratory diseases were the top three subgroups in this cohort. More than 85% of the cohort were deemed to be eligible for enteral nutrition. About one-fifth of the cohort were coagulopathic. This study was unable to show a superiority of pantoprazole (40 mg IV once daily) over placebo in preventing clinically significant GI bleeding. Surrogate markers like hemoglobin concentration and need for red cell transfusion were also comparable between the groups. On the other hand, pantoprazole use was not associated with higher incidence of infectious complications mentioned earlier. The "take home message" from this RCT seems to be that pantoprazole does not confer any benefit in reducing the incidence of GI bleeding among critically ill patients in whom enteral feeding can be initiated in the first 48 hours. The percentage of patients with sepsis was rather low in this sample. This particular subset may have higher oxygen demand-supply imbalances at the mucosal level. This cohort needs to be studied separately. Patients in

whom enteral nutrition cannot be started within 48 hours of ICU admission also need to be studied separately. The Surviving Sepsis Campaign guidelines[10] have issued a strong recommendation in favor of using SUP for high-risk ICU patient with sepsis. But, these recommendations are based on low quality of evidence.

Another study with a reasonably large sample size evaluating the role of pantoprazole in reducing the mortality was the SUP-ICU study.[3] The authors evaluated the role of PPIs in reducing mortality among ICU patients at risk of GI bleeding. This study was a multicenter placebo-controlled blinded RCT carried across 33 ICUs in Europe. This study aimed at detecting a 5% difference in 90-day mortality. They included patients with any of the risk factors for GI bleeding which have been discussed earlier. The study compared a 40-mg daily single dose of pantoprazole with a placebo. The primary outcome measured was 90-day mortality. Incidence of clinically important adverse effects such as GI bleeding, pneumonia, C. diff infection, and myocardial ischemia were observed as secondary outcomes. In the initial analysis, the authors could not find any difference in the primary outcome between the two groups. No difference was observed in the secondary outcomes either, prompting the authors to conclude that pantoprazole does not have an impact on reducing mortality among patients at risk of GI bleeding. However, there were concerns about the statistical significance of the secondary outcomes being confounded by multiple comparisons. The standout-point from this RCT, however, was that the incidence of significant GI bleeding was lower in the intervention arm. The mortality among critically ill patients is determined by several factors—one of them being GI bleed. Mitigating this risk may in itself be a positive contribution of PPIs. A subsequent post-hoc analysis of this database, studying sicker patients, negated this optimism.[11] Marker et al. in a post-hoc analysis including patients with simplified acute physiology score II (SAPS II) score of >53 suggested an increased mortality with the use of pantoprazole. The relative risk of dying after having been prescribed pantoprazole stood at 1.13. The percentage of days alive without life support was higher in those in the group who did not receive pantoprazole. This finding should trigger a specific evaluation of sicker patients in future studies on SUP.

The discussion so far has focused on PPIs. It is likely that this particular group of drugs might be linked to adverse events and negate the benefits. SUP can also be provided by other agents such as H_2RAs. The PEPTIC study[12] compared these two pharmacological groups head-to-head, with in-hospital mortality as the deciding factor. The cohort involved patients who needed mechanical ventilation. This was a multicenter open label cluster randomized trial done across 50 countries, over 3 years. This study began with infections and GI bleed as its primary endpoints of interest, but changed to in-hospital mortality before the data collection was complete. Infections, clinically significant GI bleed and length of stay in ICU and hospital, became the secondary endpoints. This study, to date, is the best powered study with the largest sample size in the history of critical care trials. Nearly half the patients in this cohort were postoperative patients having undergone either elective or emergency surgery. The mean APACHE III score of the cohort was 65, indicating significance disease severity. There was no difference in 90-day mortality between the two groups [18.3% for PPI vs. 17.5% for H_2RAs (risk ratio: 1.05; 95% CI: 1.00–1.01; $p = 0.05$)]. The overall rates of infection and length of stay were comparable between the groups. However, the pantoprazole group had lesser incidence of clinically significant GI bleed. Statistical analysis seems to suggest that for every 1,000 patients who are mechanically ventilated, upper GI bleed occurs in five fewer patients when PPI is prescribed. This would translate into 3/1,000 lesser transfusion rate and 2/1,000 lesser endoscopy requirement. On the flip side, among patients who underwent cardiac surgery, the mortality was higher in the PPI group [2.5% vs. 1.9% (risk ratio: 1.27; 95% CI: 1.04–1.51)] with no benefit in terms of clinically significant GI bleed. The most significant drawback of this large study was the crossover rate from H_2RAs to PPIs (20%). The inferences which can safely be drawn from this study are that (a) PPIs have an advantage in reducing the incidence of clinically significant GI bleeds; (b) overall mortality does not change with the use of PPIs; and (c) sicker cohort of patients, especially those undergoing cardiac surgery with high APACHE III scores might have higher mortality with the use of PPIs.

A new RCT—*R*e-*Ev*aluating the *I*nhibition of *S*tress *E*rosions (REVISE)—is currently underway with the primary objective of assessing the efficacy of PPIs on clinically important GI bleed, ventilator-associated pneumonia (VAP), C. diff infection, acute kidney injury (AKI), and mortality. This study aims to recruit >4,000 patients and is a collaborative effort by the Canadian Critical Care Trials group, the Australian and New Zealand Intensive Care Society Critical Care Trials group, and other consortia and collaborators under the auspices of the International Forum for Acute Care Trialists.

One of the principles of prevention of stress ulceration has been to ensure enteral nutrition. Enteral nutrition (EN) may be as effective as pharmacoprophylaxis in the prevention of stress bleeding.[13,14] Adding PPIs to EN may or may not confer any additional advantage in terms of preventing significant GI bleeding. Definitive guidelines and recommendations regarding the role of EN for SUP are lacking.[2] This aspect was evaluated in an RCT by El-Kersh et al.[15] The authors hypothesized that early EN could be an effective SUP. The patients were enrolled if they required mechanical ventilation for >48 hours and if EN could be initiated within 24 hours of ICU admission. Pantoprazole

was the drug used in the study (40 mg IV). All patients received a standard commercially available formula for EN. The authors considered significant GI bleed as the primary endpoint. Infections with C. diff was the secondary outcome. The study could not find any difference in either of the outcomes studied in both the groups. Major percentage of patients in this cohort were admitted to the ICU for respiratory problems, sepsis, and neurological issues. The use of gastric residual volumes (GRV) measured every 4 hours is a debatable point in this study. The process was, however, same in both the groups. Surgical patients were not part of this study group. The inference which could be drawn from this study is that, among medical patients who could be initiated on EN early in course of ICU stay, PPIs do not confer additional benefit in preventing significant GI bleed.

Trauma is another key ICU population who are at risk of GI bleeding. Data regarding the benefit of using pharmacoprophylaxis in this subset is lacking. Palm et al.[16] carried out a retrospective analysis of patients admitted to a surgical trauma ICU at the Cleveland Clinics. They evaluated patients who were ventilated for at least 48 hours, beginning within 48 hours of ICU admission and received full caloric EN. Coagulopathic patients were excluded. Incidence of clinically significant GI bleed among those not receiving pharmacological SUP was the primary endpoint. Three quarters of the patients had traumatic brain injury. The authors could not find a higher incidence of stress-related GI bleed among those who did not receive pharmacoprophylaxis in addition to EN.

In the end, it is worthwhile looking at two meta-analyses and the Cochrane review which were published in the same year (2018). Alhazzani et al.[17] carried out a network meta-analysis of randomized trials evaluating the efficacy and safety of SUP among critically ill patients. This study evaluated 7,293 patients across 57 eligible studies comparing SUP strategies. Their conclusion was that while PPIs are superior to both H_2RAs and sucralfate in preventing significant GI bleed, the magnitude of benefit is not large. Moreover, PPIs tend to result in a higher incidence of pneumonia. The net benefit with the use of PPIs for SUP is therefore questionable. Huang et al.[18] carried out a meta-analysis of all relevant RCTs published between 1994 and 2017 to determine if there are differences between pharmacoprophylaxis and placebo among patients who were fed enterally. Clinically, significant GI bleeding was the primary outcome studied in this meta-analysis. They were able to identify 7 RCTs enrolling 889 patients for their final analysis. In their analysis, pharmacoprophylaxis did not prevent significant GI bleed if the patients were enterally fed. Infection rates were also not higher in the SUP group. A Cochrane review[19] evaluated the effect and risk benefit profile of interventions for preventing upper GI bleeding among ICU patients. This study looked at 129 records pertaining to 121 studies (12 of which were ongoing then), with 106 studies included in quantitative synthesis. This yielded a total of 15,057 patients involving 14 different treatment modalities. The group concluded that H_2RAs, antacids, and sucralfate might be better than placebo in preventing clinically important upper GI bleeding. "Evidence of low certainty" in the authors' own words suggested that PPIs were more effective that H_2RAs in preventing upper GI bleeding among ICU patients.

CONCLUSION

Data available so far seems to suggest that enteral feeding still remains the safest form of SUP. PPIs may be better than other agents in preventing significant GI bleeding, but may increase the risk of infections. However, questions still remain on the best mode of SUP for very high risk, coagulopathic, hemodynamically unstable patients, in whom EN cannot be established early in the course of their stay in the ICU.

REFERENCES

1. Jean-Louis V. Give your patient a fast hug (at least) once a day. Criti care med. 2005;33(6):1225-9.
2. Marik PE, Vasu T, Hirani A, Pachinburavan M. Stress ulcer prophylaxis in the new millennium: a systematic review and meta-analysis. Crit Care Med. 2010;38:2222-8.
3. Krag M, Perner A, Wetterslev J, Wise MP, Borthwick M, Bendel S, et al. Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. Intensive Care Med. 2015;41:833-45.
4. MacLaren R, Reynolds PM, Allen RR. Histamine-2 receptor antagonists vs proton pump inhibitors on gastrointestinal tract hemorrhage and infectious complications in the intensive care unit. JAMA Intern Med. 2014;174:564-74.
5. Cook DJ, Fuller HD, Guyatt GH, Marshall JC, Leasa D, Hall R, et al. Risk factors for gastrointestinal bleeding in critically ill patients. Canadian Critical Care Trials Group. N Engl J Med. 1994;330:377-81.
6. Krag M, Perner A, Wetterslev J, Wise MP, Hylander Møller M. Stress ulcer prophylaxis versus placebo or no prophylaxis in critically ill patients: a systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. Intensive Care Med. 2014;40:11-22.
7. Alshamsi F, Belley-Cote E, Cook D, Almenawer SA, Alqahtani Z, Perri D, et al. Efficacy and safety of proton pump inhibitors for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis of randomized trials. Crit Care. 2016;20:120.
8. Charlot M, Ahlehoff O, Norgaard ML, Jørgensen CH, Sørensen R, Abildstrøm SZ, et al. Proton-pump inhibitors are associated with increased cardiovascular risk independent of clopidogrel use: a nationwide cohort study. Ann Intern Med. 2010;153:378-86.
9. Selvanderan SP, Summers MJ, Finnis ME, Plummer MP, Ali Abdelhamid Y, Anderson MB, et al. Pantoprazole or Placebo for Stress Ulcer Prophylaxis (POP-UP). Crit Care Med. 2016;44:1842-50.

10. Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. Intensive Care Med. 2018;44(6): 925-8.
11. Marker S, Perner A, Wetterslev J, Krag M, Lange T, Wise MP, et al; SUP-ICU investigators. Pantoprazole prophylaxis in ICU patients with high severity of disease: a post hoc analysis of the placebo-controlled SUP-ICU trial. Intensive Care Med. 2019;45(5):609-18.
12. The PEPTIC Investigators for the Australian and New Zealand Intensive Care Society Clinical Trials Group, Alberta Health Services Critical Care Strategic Clinical Network, and the Irish Critical Care Trials Group, Young PJ, Bagshaw SM, Forbes AB, et al. Effect of Stress Ulcer Prophylaxis with Proton Pump Inhibitors vs Histamine-2 Receptor Blockers on In-Hospital Mortality Among ICU Patients Receiving Invasive Mechanical Ventilation: The PEPTIC Randomized Clinical Trial. JAMA. 2020;323(7):616-26.
13. Pingleton SK, Hadzima SK. Enteral alimentation and gastrointestinal bleeding in mechanically ventilated patients. Crit Care Med. 1983;11(1):13-6.
14. Raff T, Germann G, Hartmann B. The value of early enteral nutrition in the prophylaxis of stress ulceration in the severely burned patient. Burns. 1997;23(4):313-8.
15. El-Kersh K, Jalil B, McClave SA, Cavallazzi R, Guardiola J, Guilkey K, et al. Enteral nutrition as stress ulcer prophylaxis in critically ill patients: A randomized controlled exploratory study. J Crit Care. 2018;43:108-13.
16. Palm NM, McKinzie B, Ferguson PL, Chapman E, Dorlon M, Eriksson EA, et al. Pharmacologic Stress Gastropathy Prophylaxis May Not Be Necessary in At-Risk Surgical Trauma ICU Patients Tolerating Enteral Nutrition. J Intensive Care Med. 2018;33(7):424-9.
17. Alhazzani W, Alshamsi F, Belley-Cote E, Heels-Ansdell D, Brignardello-Petersen R, Alquraini M, et al. Efficacy and safety of stress ulcer prophylaxis in critically ill patients: a network meta-analysis of randomized trials. Intensive Care Med. 2018;44(1):1-11. Epub 2017 Dec 4. Erratum in: Intensive Care Med. 2017 Dec 11.
18. Huang HB, Jiang W, Wang CY, Qin HY, Du B. Stress ulcer prophylaxis in intensive care unit patients receiving enteral nutrition: a systematic review and meta-analysis. Crit Care. 2018;22(1):20.
19. Toews I, George AT, Peter JV, Kirubakaran R, Fontes LES, Ezekiel JPB, et al. Interventions for preventing upper gastrointestinal bleeding in people admitted to intensive care units. Cochrane Database Syst Rev. 2018;6: CD008687.

SECTION 7

Cardiac Critical Care

CHAPTER

44

Intraoperative and Postoperative Transfusion Threshold in Cardiac Surgery

Naman Shastri, Chirag Mehta, Kalpana Jain, Anil Jain

INTRODUCTION

It is believed that cardiac surgery is considered in the "more than normal risk" category routinely which needs higher care and attention. Chances of volume exchange rate are high so blood transfusion requirement is also very high. The decision for transfuse red blood cells (RBCs) was based upon the blood hemoglobin (Hb) concentration above 10 g/dL (100 g/L) and above 30 hierocrats.[1] But that led to increase in the expenditure and most importantly the morbidity that has opened the eyes of clinicians and after advisory release by National Institutes of Health Consensus Conference on perioperative RBC transfusions to avoid any transfusion on the basis of single parameter.[2]

WHAT IS AN OPTIMAL TRANSFUSION TRIGGER?

Transfusion trigger is defined as when blood transfusion is given on the basis of fix level of any parameter. Usually level of Hb.

We are looking for the ideal trigger which should have positive impact on the patient population. At the same time, we have to be cautious enough so that we do not delay or under transfuse on the base of Hb number or over transfuse to maintain plasma volume. Our aim is to maintain optimum Hb with optimum oxygen delivery even in the high risk patient having multiorgan diseases and in surgical cases. There are certain group of patients who are living on the edge with high morbidity with plan or emergency surgery such as oncosurgical patient and patients with hepatobiliary dysfunction such as cirrhosis.[3] There are chances of having poor outcome due to major surgery and having multiple transfusion in patients having comorbidities and ultimately blood transfusion may take blame but many comorbidities are responsible for the poor outcome. In these situations, it is very important to have perfect decision whether to give packed red blood cell (PRBC) or not or how many units which should be optimum for the patients? For example, if we start with the age that is also a very important contributor for the transfusion-related morbidity. Association of specific organ involvement such as nephropathy and cardiac condition such as associated heart failure also affects the transfusion-related complication, so it is very difficult to define the right transfusion trigger for the right patient.[4]

THRESHOLD OF BLOOD TRANSFUSION AFTER CARDIAC SURGERY

As discussed, the cardiac surgery itself is carrying high chances of blood transfusion so it is very important to have right number at which transfusion can be offered. Now important question is which number? Is only Hb number ok? Or we are missing something else also. Since there are many controversial literatures available in favor and against liberal category (transfusion at higher Hb) in certain observational trials.

There are few indices on which the triggers for the transfusion are carried out and not necessary that only single parameter works well. In spite, one should look for more such parameters. They are Hb-based transfusion triggers, the electrocardiogram as a transfusion trigger, SvO_2 and $ScvO_2$ as transfusion triggers, arterial lactate and near-infrared spectroscopy as a transfusion trigger, though not available in routine practice at every center still can be subjected as important parameters to guide us for transfusing PRBC.

WHAT IS RATIONALE OF HEMOGLOBIN-BASED TRANSFUSION TRIGGERS?

Most of the practice otherwise is purely based on Hb as a marker for the transfusion. The "10/30" rule was considered the gold standard for transfusion where 10 is Hb and 30 is hematocrits. If we go in to physiological aspect of function of Hb is to deliver oxygen to the peripheral tissue which is considered as DO_2 which depends up on three main parameters: Along with Hb, cardiac output (CO), and oxygen saturation. CO can be measured by special monitors and oxygen saturation can be measured by pulse oximeter or blood gas analysis.

The formula to obtain DO_2 is (Hb × 1.34 × SaO_2 + 0.0031 × PaO_2) × CO, where SaO_2 is arterial oxygen saturation and PaO_2 is arterial partial pressure of oxygen.

Normally oxygen is delivered to the peripheral tissue in excess of requirements nearly four times.[5] Since CO is a direct contributor for the delivery of oxygen, variation of cardiac output leads to major fluctuation on the oxygen delivery. Oxygen demand can range from 3.0 to >50 mL/kg/min or even much more than this in heavy exercise and heavy sports.[6] Value given cannot be a strict number as they can vary with many external influencing factor. It is so important to have an idea about the critical DO_2 below which the oxygen delivery may hampers, that leads to tissue hypoxia, so it is necessary to have parameters on hand like cardiac output and monitoring DO_2. It is proved that below 9–11 mL/kg/min is critical DO_2 limit for anemia, hypoxia and low cardiac output.[7]

Physiological parameters can vary with individual and individual organ in the same individual which depends on the work by organ. So, standard physiological consideration cannot be applied in every situation such as anemia tolerance of different organs such as brain, heart, and kidney can vary with association of many clinical situations such as vascular stenosis and sepsis.[8]

In real case scenario, anemia never exists alone and always accompanied by associated hypovolemia or hypoxemia. In general, there is tendency to transfuse PRBC once Hb falls below 7 g/dL. But contrary to that in one investigation, there was comparison between liberal versus restrictive transfusion regime in cardiac compromised patients, there was no difference at 60-day mortality.[9]

SHOULD WE USE TRANSFUSION RECOMMENDATIONS STRICTLY ON CURRENT HEMOGLOBIN-BASED?

As per the common practice otherwise is to transfuse blood at or below Hb of 7 g/dL in patients without any comorbidities, but when patients have cardiac dysfunction, then it is usually transfused at little higher Hb level may be at Hb of 9 g/dL or less to the common practice. So transfusion trigger depends on the many clinical condition and not only at the level of Hb number. In one retrospective analysis, it is stated that PRBC transfusion has an advantage provided the patient is not having multiorgan involvement such as cirrhosis, nephropathy, or malignancy.[10] However, in cardiac surgery though patient does not have any comorbidity, but considering that patients are subjected to the lot of fluid shift and volume exchange, it may be difficult to decide the transfusion triggers only on the basis of the Hb numbers.

Due to the understanding of the risk involved in the transfusion which carries morbidity considering the transfusion is itself like organ transplant, at least it is almost clear number of transfusion, it may be beneficial even in a patient without any other comorbidity, except undergoing cardiac surgery. Over and above relying on which parameters works well and identifying the different parameter are also very important as blinded dependency on one parameter may mislead the decision-making. Relying on only single parameter as decision goes wrong many times so, we need to search for the other parameter more than or at least as accurate as Hb. This can help us in supporting clinical decision-making. As Hb has direct concern with the oxygenation, we should see more parameters which have direct relation with the oxygenation delivery mechanism.

ARE THERE OTHER CLINICALLY USEFUL TRANSFUSION TRIGGERS?

Why Hb should not only Base for Transfusion…..

DO^2 as a Transfusion Trigger

In certain conditions where oxygen demand increases such as sepsis, stress, or fever, along with the oxygen delivery, even oxygen uptake from arterial; blood by peripheral tissue cell also goes down so much the returning oxygen (SVO_2) does not drop in beginning as oxygen extraction is less. It is inability of tissue to uptake oxygen. That means that one should not rely mainly on the oxygen delivery by increasing the level of Hb.[11] The main influencing parameters of delivery of oxygen are Hb, SaO_2, PaO_2, and CO and all are interdependent. That means that dealing with one of them does not mean that will change the result as increasing one will reduce the other and ultimately the net result is delivery of oxygen is unchanged. Like adding PRBC will change the level of Hb and ultimately blood becomes thick if Hb goes above 10 g/dL and that leads to hamper the microcirculation in peripheral tissue.

Monitoring the Venous Blood Oxygen Saturation as Transfusion Triggers

Most commonly two parameters are applied in clinical practice to monitor venous oxygen saturation, they are SVO_2 (mixed venous saturation) and $ScVO_2$ (superior vena cava saturation). This has been studied in the guidelines for sepsis once and also became rational for delivering transfusion to increase oxygen carrying capacity. In certain condition when there is increased demand of oxygen by peripheral tissue, we expect the reduction of mixed venous oxygen saturation (SVO_2), but at the same time, there may be compensatory mechanism play role which may maintain the SvO_2 like increase in CO or reduced oxygen extraction. But if this mechanism does not work when patient having anemia, then venous oxygen saturation reduces.[12] When we notice the venous oxygen saturation reducing with anemia, that is the time of trigger threshold for infusing blood

transfusion. But as we discussed earlier that it is not necessary that venous saturation will drop such as in the condition of sepsis where SvO_2 remains high.[13] When patient is having anemia and sepsis with maintained SVO_2, then transfusion is even more dangerous as it increases viscosity of blood which ultimately hampers the peripheral circulation.

There are other parameters also such as electrocardiogram (ECG) changes, arterial lactate, infrared spectrophotometry (NIRS) but not used in routine practice.

Basically in cardiac surgery, there are two types of factors which make the difference:

1. Uncomplicated cardiac surgeries
2. Complicated cardiac surgeries

Blood transfusion in uncomplicated cardiac patients: Uncomplicated cardiac surgery means cardiac surgery without any other organ involvement. In such patients, it is found that RBCs transfused in the cardiac surgery during cardiopulmonary bypass (CPB) had longer ventilator support times, length of stay (LOS), and decreased long-term survival when compared to nonanemic patients or untreated anemia patients. These patients were having >25% hematocrit during CPB time.[14]

So, overall transfusion of RBCs in uncomplicated cardiac surgery patients with low- to moderate-risk profiles showed increased morbidity with cardiac and noncardiac complication in postoperative phase when compared to those who did not receive any blood transfusion.[15]

Blood transfusion in complicated cardiac surgical patients: All those patients who come with compensated or uncompensated heart failure, with any metabolic derangement or involvement of more than one organ, are termed as complicated patients, and they always carry more chance of morbidity. In one study to evaluate outcome of patients with recent myocardiac infarction undergoing emergency surgery from 2005 to 2013, concluded high morbidity around 19.3% (p <0.001) in whom transfusion was given as compared to 18.1% in whom transfusion was not given.[16] It is also found in patients subjected for plain coronary artery bypass graft (CABG) with or without anemia that if transfusion given to the patient without preoperative anemia has high rate of death as compared to the transfusion given to the patients with anemia.[17] So transfusion trigger is a very important single marker which decides morbidity.

RESTRICTIVE OR LIBERAL RED-CELL TRANSFUSION FOR CARDIAC SURGERY

Usually restrictive is termed as 7 g/dL and liberal is considered above 10 g/dL. There are still many conflicting evidence. Many times PRBC may be helpful in critically ill patients but still there remain issue of cost, blood availability, and possible complication with blood transfusion.

So, it is very important to come to the conclusion to give or not to give as it is double-edged sword and clinician must choose one between restrictive or liberal strategy of transfusion.

In one of the randomized controlled trial showing 30-day mortality as primary outcome, secondary outcome was to check the impact of anemia-related hypoxia and transfusion-related morbidity. There were 4,545 patients randomized in total 13 trials who were included in this study. In conclusion, restrictive strategy did not have a statistically significant effect on the risk of MI [relative risk (RR) 1.01, 95% confidence interval (CI) 0.81–1.26; I2 = 0], stroke (RR 0.93, 95% CI 0.68–1.27, I2 = 0), renal failure (RR 0.96, 95% CI 0.76–1.20, I2 = 0), or infection (RR 1.12, 95% CI 0.98–1.29, I2 = 0).[18]

Two trials which are throwing interesting light in the decision are the Transfusion Requirement in Critical Care (TRICC)[19] and Transfusion Requirements in Cardiac Surgery (TRICS) II and TRICS III.[20] In TRICC trial, it has been clearly mentioned in favor using restrictive thresholds for transfusions of PRBCs which according to them are *noninferior* to liberal thresholds. Though they have not mentioned that restrictive is better than liberal approach.

In TRICS II, restrictive strategy was considered to transfuse red cells with <7.5 g/day, during cardiac surgery <8.5 g/dL, and <9.5 g/dL if in the ICU. In this trial, Mazer and colleagues selected randomized trial of 5,243 adult patients undergoing cardiac surgery. They studied mainly all-cause morbidity and mortality including renal failure, stroke, and MI, while secondary outcomes were clinical outcomes which included RBC transfusions-related complication and anemia-related hypoxemic effect.

In the study, there were mix variety of cardiac surgeries including CABGs only, CABG with valve surgery, and only valve surgery in 26, 19, and in 29%, respectively, and rest others. Mean CPB time was approximately 120 minutes. Most of the patients were given tranexamic acid (around 90%). The requirement of blood transfusion was more in liberal group around 72.6% against 52.3% in the restrictive group. The restrictive group has shown composite primary outcome of 11.4% rather liberal group has shown 12.5%. MI and stroke were nearly same with 5.9% in both groups. There was comparatively more difference in the new renal failure, whereas 2.5% in restrictive group versus 3.0% in liberal group.

In Mazer and colleagues' follow-up study TRICS III, they reported additional clinical outcomes 6 months after surgery in their 5,243 adult patients. The defined primary composite outcome occurred in 17.4% in the restrictive group compared with 17.1% in the liberal group with a p value of 0.006 for noninferiority, and mortality was 6.2% in restrictive compared with 6.4% in the liberal group [odds ratio (OR) 0.95], again without differences in secondary

outcomes.[21] So, overall take home message of both these trials was restrictive strategy is not inferior.

Our practice in real world is to go with numerical value such as Hb levels without understanding patient character and comorbidities. Is there any physiological difference clearly defined between Hb of 7.5 g/dL versus 9 g/dL in cardiac surgical patients? When we talk about cardiac surgery, usually their mobility is restricted, when they are discharged in such cases, energy kinetics are totally different as compared to those who are mechanically ventilated. In fact in cardiac surgery, patients mitigated by inactivity and reduced oxygen demand. Despite our extensive routine use of platelet transfusions in our patients, there is no high-quality evidence to determine the appropriateness of platelet transfusions with bleeding.[22] There is less evidence to guide blood components and their benefits to reduce the transfusion.

So, there are many unanswered questions in this discussion but overall conclusion remarks say that restricted strategy is not inferior to liberal with many benefits, patient overall clinical reading is very important than single number. We need to use multiple parameters to use as triggering threshold. Blood banks have limited transfusion units and each one carries its cost involved, so all these should also be considered. We are hoping to have some alternatives to replace the PRBC transfusion...

REFERENCES

1. Desai N, Schofield N, Richards T. Perioperative patient blood management to improve outcomes. Anesth Analg. 2018;127(5):1211-20.
2. Shander A, Bracey AW Jr, Goodnough LT, Gross I, Hassan NE, Ozawa S, et al. Patient blood management as standard of care. Anesth Analg. 2016;123(4):1051-3.
3. Dejam A, Malley BE, Feng M, Cismondi F, Park S, Samani S, et al. The effect of age and clinical circumstances on the outcome of red blood cell transfusion in critically ill patients. Crit Care. 2014;18(4):487.
4. Kulier A, Levin J, Moser R, Rumpold-Seitlinger, Tudor IC, Snyder-Ramos SA, et al. Impact of preoperative anemia on outcome in patients undergoing coronary artery bypass graft surgery. Circulation. 2007;116(5):471-9.
5. Habler OP, Messmer KF. The physiology of oxygen transport. Transfus Sci. 1997;18(3):425-35.
6. Sergi G, Coin A, Sarti S, Perissinotto E, Peloso M, Mulone S, et al. Resting VO_2, maximal VO_2 and metabolic equivalents in free-living healthy elderly women. Clin Nutr. 2010;29(1):84-8.
7. Cilley RE, Scharenberg AM, Bongiorno PF, Guire KE, Bartlett RH. Low oxygen delivery produced by anemia, hypoxia, and low cardiac output. J Surg Res. 1991;51(5):425-33.
8. Lauscher P, Kertscho H, Schmidt O, Zimmermann R, Rosenberger P, Zacharowski K, et al. Determination of organ-specific anemia tolerance. Crit Care Med. 2013;41(4):1037-45.
9. Carson JL. Morbidity risk assessment in the surgically anemic patient. Am J Surg. 1995;170(6A Suppl):32S-6S.
10. Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev. 2016;10(5):CD002042.
11. Napolitano LM, Corwin HL. Efficacy of red blood cell transfusion in the critically ill. Crit Care Clin. 2004;20(2):255-68.
12. Kocsi S, Demeter G, Érces D, Kaszaki J, Molnár Z. Central venous-to-arterial CO_2-gap may increase in severe isovolemic anemia. PLoS One. 2014;9(8):e105148.
13. Vallet B, Adamczyk S, Barreau O, Lebuffe G. Physiologic transfusion triggers. Best Pract Res Clin Anaesthesiol. 2007;21(2):173-81.
14. Loor G, Li L, Sabik JF 3rd, Rajeswaran J, Blackstone EH, Koch CG. Nadir hematocrit during cardiopulmonary bypass: end-organ dysfunction and mortality. J Thorac Cardiovasc Surg. 2012;144(3):654-62.e4.
15. Paone G, Herbert MA, Theurer PF, Bell GF, Williams JK, Shannon FL, et al. Red blood cells and mortality after coronary artery bypass graft surgery: an analysis of 672 operative deaths. Ann Thorac Surg. 2015;99(5):1583-9; discussion 1589-90.
16. Acharya D, Gulack BC, Loyaga-Rendon RY, Davies JE, He X, Brennan JM, et al. Clinical characteristics and outcomes of patients with myocardial infarction and cardiogenic shock undergoing coronary artery bypass surgery: Data from the Society of Thoracic Surgeons National Database. Ann Thorac Surg. 2016;101(2):558-66.
17. Engoren M, Schwann TA, Habib RH, Neill SN, Vance JL, Likosky DS. The independent effects of anemia and transfusion on mortality after coronary artery bypass. Ann Thorac Surg. 2014;97(2):514-20.
18. Shehata N. Restrictive compared with liberal red cell transfusion strategies in cardiac surgery: a meta-analysis. Eur Heart J. 2019;40(13):1081-8.
19. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999;340(6):409-17.
20. Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K, et al. Restrictive or liberal red-cell transfusion for cardiac surgery. N Engl J Med. 2017;377:2133-44.
21. Shehata N, Whitlock R, Fergusson DA, Thorpe KE, MacAdams C, Grocott HP, et al. Transfusion Requirements in Cardiac Surgery III (TRICS III): study design of a randomized controlled trial. J Cardiothorac Vasc Anesth. 2018;32(1):121-9.
22. Levy JH, Rossaint R, Zacharowski K, Spahn DR. What is the evidence for platelet transfusion in perioperative settings? Vox Sang. 2017;112(8):704-12.

CHAPTER 45

Cardiogenic Shock: Role of Mechanical Support Devices

Ajmer Singh, Yatin Mehta

INTRODUCTION

Cardiogenic shock, a condition of circulatory failure, results from reduction in cardiac output (CO) due to left, right, or biventricular failure. It is associated with hypotension and evidence of end-organ damage. Hemodynamic criteria for the diagnosis of cardiogenic shock include systolic blood pressure <90 mm Hg or mean arterial pressure (MAP) 30 mm Hg below baseline, cardiac index ≤2.2 L/min/m^2, and pulmonary capillary wedge pressure >15 mm Hg.[1] Signs of impaired organ perfusion include altered mental state, reduced urine output, cold and clammy skin or extremities, tachypnea, and increased lactate >2 mmol/L levels despite normovolemia. Cardiogenic shock, characterized by multiorgan dysfunction, is often complicated by a systemic inflammatory response syndrome with severe cellular and metabolic abnormalities. Despite prompt diagnosis and goal-directed therapy to improve oxygen supply and tissue perfusion, the mortality with this condition remains around 40–50%.[2]

In up to 70% of cases, it results from acute myocardial infarction (AMI), and 5–10% of cases of AMI develop cardiogenic shock.[2] Other causes of cardiogenic shock include mechanical complications of AMI such as ventricular septal rupture, left ventricular (LV) free wall rupture, acute mitral regurgitation; myocarditis, right ventricular (RV) failure, and heart failure (HF) resulting from cardiomyopathies. The detailed etiology of cardiogenic shock is shown in **Box 1**. Predisposing factors for cardiogenic shock in patients with AMI include old age, hypertension, diabetes mellitus, multivessel coronary artery disease, anterior wall myocardial infarction (MI), prior MI or angina, ST elevation MI, history of HF, and left bundle branch block.

Based on the clinical features (such as volume status and peripheral circulation) and hemodynamic parameters (such as cardiac index, systemic vascular resistance index, pulmonary capillary wedge pressure), four different phenotypes of cardiogenic shock have been described in **Table 1**.

BOX 1: Etiology of cardiogenic shock.

- Acute myocardial infarction (AMI) with ventricular dysfunction
- Mechanical complications of AMI such as ventricular septal rupture, ventricular free wall rupture, and acute severe mitral regurgitation resulting from papillary muscle rupture
- Left/right ventricular dysfunction caused by acute myocarditis, pericarditis, stress-induced cardiomyopathy, hypertrophic cardiomyopathy, and postpartum cardiomyopathy
- Acute decompensated heart failure
- Postcardiotomy, cardiac tamponade, and postcardiac arrest
- Refractory tachyarrhythmias
- Aortic dissection and acute coronary dissection
- Acute valvular regurgitation caused by endocarditis, chordal rupture, and trauma
- Acute stress in the setting of aortic or mitral stenosis
- Massive pulmonary embolism
- *Others*: Hemorrhage, infection, bowel ischemia, hypothyroidism, and hyperthyroidism

TABLE 1: Cardiogenic shock: Phenotypes.

		Volume status	
		Wet	***Dry***
Peripheral circulation	Cold	Classic cardiogenic shock (↓CI, ↑SVRI, ↑PCWP)	Euvolemic cardiogenic shock (↓CI, ↑SVRI, ↔PCWP)
	Warm	Vasodilatory or mixed cardiogenic shock (↓CI, ↓/ ↔SVRI, ↑PCWP)	Vasodilatory (noncardiogenic) shock (↑CI, ↓SVRI, ↓PCWP)

(CI: cardiac index; SVRI: systemic vascular resistance index; PCWP: pulmonary capillary wedge pressure)

MANAGEMENT

The cardiogenic shock should be managed by "shock team" comprising of cardiologists, cardiothoracic surgeons, critical care physicians, specialized nurses, and auxiliary healthcare professionals to choose the most suitable therapy for a particular patient (class I C).[3] Therapeutic management

of cardiogenic shock complicating AMI consists of early revascularization, mechanical ventilation, transfusion regimens, adjunctive medications, and mechanical circulatory support (MCS) devices. Revascularization by either percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery has shown a mortality benefit at 6 months, 1 year, and 6 years in patients with cardiogenic shock (class I B).[4] The European Society of Cardiology (ESC) guidelines suggest multivessel PCI of all critically stenosed vessels in addition to the culprit lesion (class IIa B).[4,5] Intensive care treatment of cardiogenic shock consists of volume resuscitation to achieve normovolemia and use of vasoactive medications for the prevention and treatment of multiorgan dysfunction syndrome. When blood pressure is low, norepinephrine is preferred (IIa B) over dopamine (IIa C). Patients with vasodilatory shock refractory to norepinephrine may benefit from vasopressin infusion. The use of epinephrine in patients with cardiogenic shock is associated with higher lactate levels, increased oxygen consumption, arrhythmias, and higher mortality. Dobutamine can be used to augment myocardial contractility. Other agents such as levosimendan or phosphodiesterase-inhibitors cause vasodilation and improvement of myocardial contractility without increasing oxygen requirements. Additional supportive measures include noninvasive or invasive mechanical ventilation for respiratory insufficiency, renal replacement therapy for acute renal failure, nutritional support, prevention of thromboembolism, and stress-ulcer prophylaxis.

Mechanical Circulatory Support Devices

Mechanical circulatory support devices were introduced into clinical practice to overcome the limitations of inotropes and vasopressors. MCS devices include intra-aortic balloon pump (IABP), ventricular assist devices (VADs), and extracorporeal life-support systems. MCS devices can be widely divided into temporary (short-term) or durable (long-term) devices. Temporary MCS devices are either inserted percutaneously or implanted surgically. They can be used in one of the following ways:

- *As a bridge-to-recovery (BR)*: The MCS device is removed following an improvement in cardiac contractility.
- *Bridge-to-bridge (BB)*: The temporary device is inserted with a plan to changeover to durable MCS device after clinical stabilization.
- *Bridge to transplant (BTT)*: The use of MCS device till the availability of donor heart
- *Bridge-to-decision (BD)*: The use of MCS as a life-saving measure where the final treatment strategy remains uncertain

Examples of temporary MCS devices include IABP, peripheral or implantable VAD, and extracorporeal membrane oxygenation (ECMO). Durable MCS devices (durable VADs and destination VADs) are implanted surgically, and they can be used as a BR, as a BTT, or as destination therapy. Temporary over durable MCS devices are preferred when an urgent stabilization is required to allow restoration of the heart and other organ functions. The use of temporary MCS devices has increased over the years. A recent, large cross-sectional study of patients (n = 28,304) with cardiogenic shock has shown an increase in the use of intravascular microaxial LVADs, with a corresponding reduction in the use of IABPs.[6] There is, however, limited evidence of improved outcomes with the use of MCS devices. A substantial hospital-level variance in the use of MCS devices was also observed in this study.

Intra-aortic Balloon Pump

Intra-aortic balloon pump is the most widely used short-term MCS device. The IABP is percutaneously placed into the descending aorta just distal to the left subclavian artery. The IABP provides counterpulsation therapy and is synchronized with either electrocardiogram or pressure trigger timing to inflate during diastole and deflate during systole. The use of IABP improves diastolic pressure and reduces end-systolic pressure. This results in improved coronary perfusion and reduction of afterload. There is only a modest improvement in CO (0.8–1.0 L/min), MAP, serum lactate, and inotropic requirement with the use of IABP in cardiogenic shock. Till 2012, European and American guidelines supported the use of IABP in cardiogenic shock as a class I indication.[7] Since then, the recommendations have been downgraded to IIb B (2012 ESC guidelines) and IIa B (2013 American guidelines).[5,8] IABP-SHOCK II (Intra-aortic Balloon Support for Myocardial Infarction with Cardiogenic Shock) trial ($n = 600$) showed no significant differences in the IABP versus medical therapy group regarding 30-day mortality [39.7% IABP group vs. 41.3% medical therapy group, relative risk (RR) 0.96, 95% confidence interval (CI) 0.79–1.17, $p = 0.69$], nor the time to hemodynamic stabilization, the intensive care unit stay, serum lactate levels, the catecholamine requirement, renal function, and adverse events.[9] The outcomes of the IABP-SHOCK II trial prompted ESC guidelines with a more downgrading of recommendation to class III A for the routine use of IABP in cardiogenic shock. Mechanical complication of AMI is a class IIa C indication for the use of IABP. Axillary or subclavian IABPs have generated considerable interest recently as they have the potential advantages to permit upright sitting and ambulation during the waiting period for definitive therapy.

Ventricular Assist Devices

Current European and American guidelines recommend consideration of the use of a percutaneous VAD for circulatory support in intractable cardiogenic shock without any preference for device selection (IIa C recommendation).[5,8] The ideal candidates for short-term LVAD use include

INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) class 1 and 2.[10,11] For long-term LVAD use, the ideal candidates are INTERMACS clinical profiles 3 and 4 individuals. Before an LVAD is implanted, it is essential to rule out the following intracardiac abnormalities: Intracardiac clots, intracardiac shunts, aortic and tricuspid valve regurgitation, mitral stenosis, aortic stenosis, and aortic diseases. Currently used percutaneous MCS devices include the TandemHeart (TandemLife, Pittsburgh, PA, USA) and the micro-axial Impella 2.5 and CP systems (Abiomed, Danvers, MA, USA). The devices under investigation include the paracorporeal pulsatile iVAC 2L (PulseCath BV, the Netherlands) and the HeartMate Percutaneous Heart Pump (St. Jude Medical, Pleasanton, CA).

TandemHeart, with the use of a continuous flow centrifugal pump, can provide flows up to 4 L/min. The device is inserted through the femoral vein and is advanced into the left atrium (LA) after trans-septal puncture. The blood is withdrawn from the LA and is directed into the abdominal aorta or iliac arteries via a 15–17 F outflow cannula. The main advantages of TandemHeart include its robust CO support and nondependence on rhythm. The disadvantages include difficulty in insertion, the need for a trans-septal puncture, and vascular complications. Thiele et al., in their study on TandemHeart versus IABP for cardiogenic shock, found higher cardiac power and cardiac index in the former group.[12] The 30-day mortality was, however, similar (43% vs. 45%, $p = 0.86$) in both the groups.

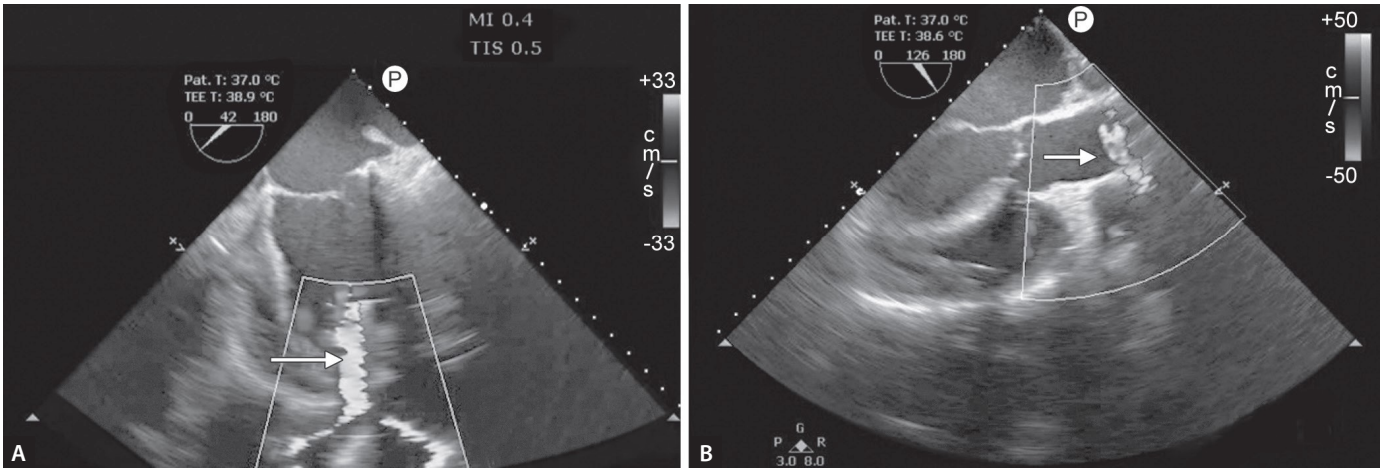
The *Impella* was the first percutaneously inserted continuous, nonpulsatile, microaxial flow device to unload the ventricle by pumping blood from the LV into the ascending aorta. The Impella device is positioned in a retrograde fashion across the aortic valve. It actively pumps blood from LV to the aorta to decrease LV size, pressure, and wall tension.[13] Impella 2.5, CP, and 5.0 can provide flows up to 2.5 L/min, 3.7 L/min, and 5 L/min, respectively. Recently, the Impella 5.5 with SmartAssist has been approved by Food and Drug Administration (FDA) for its safe and efficacious use in cardiogenic shock.[14] The motor housing of the Impella SmartAssist device is thinner and 45% shorter than Impella 5.0, which allows easier insertion in patients with smaller iliac arteries. The Impella RP device is used for RV support and is discussed later. The advantages of the Impella device include ease of insertion, robust CO support, and independence of rhythm. The Impella therapy provides hemodynamic stability even during tachyarrhythmia or electromechanical dissociation. The drawbacks include hemolysis, vascular complications, and the need for surgical insertion for Impella 5.0 system. In a recent systematic review and meta-analysis of randomized trials including 148 patients, the use of TandemHeart or Impella showed a similar 30-day mortality (RR 1.01, 95% CI 0.70–1.44, $p = 0.98$) compared with controls.[15]

The *PulseCath iVAC 2L* provides hemodynamic support during high-risk PCI, cardiogenic shock following AMI, and HF complications. It is a pulsatile device that is inserted across the aortic valve into the LV and driven by an IABP console to generate a pulsatile flow of 1.5 L/min over and above existing CO. The device is expected to receive approval from FDA in 2022. The HeartMate I used pneumatic actuated pusher plate pump, while HeartMate II is a rotary-pump-based LVAD that uses an axial flow blood pump. The HeartMate 3 is structured around a centrifugal blood pump that uses a magnetically levitated rotating assembly. It is compatible with 14 F-sheath and can expand to 24 F at the level of the aortic valve to deploy the nitinol cannula and the flexible impeller. The HeartMate can generate an output of up to 5 L/min at a speed of 20,500 revolutions per minute (RPM). The safety and efficacy of HeartMate will be addressed in future multicenter clinical trials.

The *CentriMag* (St. Jude Medical, Waltham, MA) VAD can be used for either a single ventricle or for biventricular support. The device can deliver flows up to 10 L/min. When CentriMag is serving as an LVAD, the inflow cannula is placed either in the LA or the LV apex, and the outflow cannula is sutured into the ascending aorta. When it is serving as an RVAD, the inflow and outflow cannulae are placed in the right atrium and the main pulmonary artery, respectively. The procedure requires median sternotomy. The Abiomed (Abiomed, Inc, Danvers, MA) VAD can be used for univentricular or biventricular support. By use of a pulsatile pump, it can generate up to 6 L/min blood flow. The implantation of Abiomed also requires median sternotomy. For both CentriMag and Abiomed systems, no randomized trials are assessing their effectiveness.

Durable Mechanical Circulatory Support

Long-term MCS as a BTT was first approved by the FDA in 1998. Subsequently, the REMATCH trial (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) reported improved 2-year survival compared to medical therapy, with the use of durable MCS devices in advanced HF.[16] All durable MCS devices are continuous-flow devices. The inflow and outflow cannulae are placed in the LV cavity and the ascending aorta, respectively **(Figs. 1A and B)**. Durable MCS devices can provide hemodynamic support with flow rates ranging from 5 to 10 L/min. The HeartMate II (St. Jude Medical) is approved for BTT and destination therapy, whereas the HeartWare HVAD (HeartWare, Framingham, MA) is approved as a BTT device. The HeartMate II uses an axial-flow pump, whereas HeartWare HVAD uses a centrifugal-flow, hydrodynamically levitated pump. Of all currently used durable MCS devices, the HeartMate II and HeartWare HVAD make up >95%. The HeartMate 3 LVAD (St. Jude Medical), the axial-flow Jarvik 2000 (Jarvik Heart Inc, New York, NY), and the Reliant



Figs. 1A and B: Transesophageal echocardiography showing laminar flow of blood in the inflow-cannula at left ventricular apex (A) and outflow cannula in the ascending aorta (B) during implantation of left ventricular assist device.

HeartAssist 5 (ReliantHeart, Inc, Houston, TX) are under investigation. About 15% of the cardiogenic shock patients with INTERMACS profile 1 receive MCS. The durable MCS can be implanted in a BR, BB, BTT, or destination therapy in judiciously selected patients with cardiogenic shock. Durable MCS devices can be considered in patients with cardiogenic shock who are unlikely to improve without them and do not have irreversible end-organ damage, systemic infection, or a relative contraindication to their use.

Right Ventricular Assist Devices

Right ventricular assist devices (RVAD) in current use include CentriMag, Impella RP, and the PROTEK Duo (Cardiac Assist Inc., Pittsburgh, PA) catheter with an extracorporeal centrifugal pump. Impella RP provides RV support through a 22 F motor attached to an 11 F catheter that is placed through the femoral vein. It is advanced through the venous system across the tricuspid and pulmonary valves. The inflow portion of the pump is situated in the inferior vena cava and the outflow portion is positioned into the pulmonary artery. RP Impella is contraindicated in the presence of right-sided mechanical valves, inferior vena cava filter, severe tricuspid or pulmonary stenosis, and right heart thrombus. Most studies with the use of RVAD in patients with cardiogenic shock have published a survival rate of 42–57% at discharge. The RECOVER RIGHT study evaluated the efficacy of the Impella RP device in patients with RV failure following LVAD implantation, AMI, or cardiotomy.[17] The 30-day survival to discharge rates were 83.3% (post-LVAD) and 58.3% (postcardiotomy), respectively, with an overall survival rate of 73.3%.

Extracorporeal Membrane Oxygenation

An ECMO circuit consists of a pump, membrane oxygenator, controller, cannulae for venous drainage and arterial outflow, a heat exchanger, and tubing. Most ECMO pumps are centrifugal-flow devices that can generate up to 8 L/min of blood flow. The venous cannula is 21–25 F in diameter and up to 60 cm in length. The outflow or the arterial cannula is generally 15–19 F in diameter and up to 20–25 cm in length. Peripheral cannulation can be performed even at the patient's bedside. Despite adequate peripheral unloading, distension of LV can occur due to increased venous return to the left heart mainly from the bronchial circulation. Methods to "vent" the LV in patients with venoarterial (VA) ECMO include the use of IABP, Impella 2.5, percutaneous atrial septostomy, and surgical placement of LV vent. The VA ECMO is frequently used in cardiogenic shock to support both cardiovascular and respiratory systems. Over the years, there has been a rise in the use of ECMO for cardiogenic shock. The extracorporeal life support organization registry has reported successful use of ECMO in patients with cardiac diseases, with a survival to discharge rate of 41%.[18] The survival rate, however, depends primarily on the etiology of cardiogenic shock. Patients with acute fulminant myocarditis fare better than those who develop postcardiotomy cardiogenic shock. ECMO is relatively contraindicated in patients who have advanced age (>75 years), life-expectancy less than 1-year, severe peripheral vascular disease, severe hepatic dysfunction, neurological injury, or contraindication to anticoagulation. Distal limb ischemia, Harlequin syndrome (differential cyanosis) bleeding, hemolysis, thromboembolism, stroke, and infection are potential complications of VA ECMO. With the use of distal perfusion catheters, which direct a part of the blood flow from the ECMO circuit to the cannulated leg, there is a reduction in the incidence of critical limb ischemia. The use of VA ECMO can be considered as a temporary MCS when there is hemodynamic instability not responding to alternative therapies or during cardiopulmonary resuscitation, the so-called eCPR. It has also been used as a bridge to transplantation of others organs.

CONCLUSION

The current management of cardiogenic shock includes early diagnosis and goal-directed therapeutic interventions to optimize tissue perfusion. The last decade has seen considerable advances in the field of temporary MCS devices for the management of patients with cardiogenic shock. A number of temporary and durable MCS devices are currently available. The selection of the device is guided by the level and duration of hemodynamic support needed, institutional experience, and device-specific risks. Timely intervention and the use of most appropriate MCS device may improve outcomes in such patients.

REFERENCES

1. Reynolds HR, Hochman JS. Cardiogenic shock. Current concepts and improving outcomes. Circulation. 2008;117(5):686-97.
2. Goldberg RJ, Spencer FA, Gore JM, Lessard D, Yarzebski J. Thirty-year trends (1975 to 2005) in the magnitude of, management of, and hospital death rates associated with cardiogenic shock in patients with acute myocardial infarction: a population-based perspective. Circulation. 2009;119(9):1211-19.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200.
4. Authors/Task Force members; Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, et al. ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014;35(37):2541-619.
5. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC) 1; Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33(20):2569-619.
6. Dhruva SS, Joseph JS, Mortazavi BJ, Hurley NC, Krumholz H, Curtis JP, et al. Use of mechanical circulatory support devices among patients with acute myocardial infarction complicated by cardiogenic shock. JAMA Network Open. 2021;4(2):e2037748.
7. Thiele H, Zeymer U, Neumann F-J. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med. 2012;367:1287-96.
8. O'Gara PT, Kushner FG, Ascheim DD, Casey Jr DE, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127(4):e362-425.
9. Menon V, White H, LeJemtel T, Webb JG, Sleeper LA, Hochman JS. The clinical profile of patients with suspected cardiogenic shock due to predominant left ventricular failure: a report from the SHOCK Trial Registry: Should we emergently revascularize Occluded Coronaries in cardiogenic shock? J Am Coll Cardiol. 2000;36(suppl A):1071-6.
10. Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, et al. Seventh INTERMACS annual report: 15,000 patients and counting. J Heart Lung Transplant. 2015;34(12):1495-504.
11. Alba AC, Rao V, Ivanov J, Ross HJ, Delgado DH. Usefulness of the INTERMACS scale to predict outcomes after mechanical assist device implantation. J Heart Lung Transplant. 2009;28(8):827-33.
12. Thiele H, Sick P, Boudriot E, Diederich KW, Hambrecht R, Niebauer J, et al. Randomized comparison of intra-aortic balloon support with a percutaneous left ventricular assist device in patients with revascularized acute myocardial infarction complicated by cardiogenic shock. Eur Heart J. 2005;26(13):1276-83.
13. Combes A, Price S, Slutsky AS, Brodie D. Temporary circulatory support for cardiogenic shock. Lancet. 2020;396(10245):199-212.
14. Thiele H, Ohman EM, de Waha-Thiele S, Zeymer U, Desch S. Management of cardiogenic shock complicating myocardial infarction: an update 2019. Eur Heart J. 2019;40(32):2671-83.
15. Thiele H, Jobs A, Ouweneel DM, Henriques JPS, Seyfarth M, Desch S, et al. Percutaneous short-term active mechanical support devices in cardiogenic shock: a systematic review and collaborative meta-analysis of randomized trials. Eur Heart J. 2017;38(47):3523-31.
16. Rose EA, Moscowitz AJ, Packer M, Sollano JA, Williams DL, Tierney AR, et al. The REMATCH Trial: Rationale, design, and end points. Ann Thorac Surg. 1999;67(3):723-30.
17. Anderson MB, Goldstein J, Milano C, Morris LD, Kormos RL, Bhama J, et al. Benefits of a novel percutaneous ventricular assist device for right heart failure: the prospective RECOVER RIGHT study of the Impella RP device. J Heart Lung Transplant. 2015;34(12):1549-60.
18. Extracorporeal Life Support Organization. ECLS Registry report. [online] Available from: https://www.elso.org/Registry/Statistics/InternationalSummary.aspx. [Last accessed February 2022].

CHAPTER 46

B-type Natriuretic Peptide Interpretation in Intensive Care Unit

BK Rao, Niraj Tyagi, Asish Kumar Sahoo

INTRODUCTION

Natriuretic peptides are a group of protein molecules secreted by myocardial cell in response to myocardial stress or volume overload. There are three types of natriuretic peptides: Atrial natriuretic peptide (ANP) released primarily from atria, brain natriuretic peptide or B-type natriuretic peptide (BNP) which was first identified from porcine brain but later found to be released from ventricles mainly, and C-type natriuretic peptide (CNP) produced by vascular endothelial cells and the kidney. In the setting of increased myocardial stress, they cause natriuresis, diuresis, decrease in the elevated blood pressure, and inhibit renin and aldosterone production.[1,2] Traditionally they have been used in critical care set ups to rule out heart failure in an acute dyspneic patient, but there are lots of other physiological and pathological conditions where they can be raised.[3,4] Due to easy availability of automated commercial assay for rapid point of care as well as more accurate laboratory assays of BNP and its congener N-terminal pro-B-type natriuretic peptide (NT-proBNP), it is now a widely used natriuretic peptide to diagnose heart failure. In normal persons, the levels of BNP is <20% of that of ANP, but can equal or exceed that of ANP in patients with heart failure. So this wider range makes BNP more useful than ANP in evaluation of patients with heart failure.[5]

With myocardial stress, the ventricles secrete pre-proBNP, which is cleaved into 108 amino acid proBNP, which in turn is cleaved into a 32 amino acid biologically active BNP and an inert 76 amino acid NT-proBNP.[6] Half-life of BNP is around 20 minutes, while that of NT-proBNP is around 120 minutes.[2] Due to longer half-life NT-proBNP is preferred for clinical practice. BNP is usually metabolized by neutral endopeptidase, while NT-proBNP has renal metabolism.[6] Although most validated to rule out heart failure in acute care settings, the values of both BNP and NT-proBNP are also raised in various other noncardiac conditions. Few other variables which affect BNP and NT-proBNP levels include the assay used, age (higher values with increased age), sex (higher values in females), body mass index (lower levels in obese), and genetic factors. In addition, there is intra-individual and analytic assay variation. So all these things need to be taken into account while interpreting the result.

VALUE INTERPRETATIONS

In normal persons, the plasma concentrations of BNP and NT-proBNP are similar (approximately 10 pmol/L). But in patients with heart failure, plasma NT-proBNP rises more than BNP and there is no simple conversion factor to compare BNP and NT-proBNP levels.

Value which can exclude heart failure in a dyspneic patient is:[7]

BNP: <100 pg/mL, NT-proBNP: <300 pg/mL

Values of BNP >400 pg/mL and NT-proBNP >450 pg/mL (age <50 years), >900 pg/mL (age 50–75 years), and >1,800 pg/mL (age >75 years) have high predictive value for heart failure.

So there is an indeterminate zone for values of BNP and NT-proBNP which requires careful evaluation and further testing. One should keep in mind that there are conditions other than heart failure that may cause mild elevation in natriuretic peptide levels, and appropriate attention should be paid to these conditions as well.

CONSIDERATIONS

Conditions which can Cause False High Levels in Absence of Heart Failure

- *Renal failure*: Both BNP and NT-proBNP are elevated in the patients of chronic kidney disease even in the absence of heart failure. The values of natriuretic peptides also fluctuate with hemodialysis.[4] NT-proBNP is mainly excreted by kidneys, while, BNP though metabolized by neutral endopeptidase, is passively excreted by kidneys.[6] Thus, there is even greater elevation in NT-proBNP concentrations in patients with renal failure. These patients require higher cut-off values to diagnose heart

failure and the exact values remain uncertain. In one study, the cut-off values to diagnose heart failure in patients with estimated glomerular filtration rate (eGFR) <60 mL/min were >900 pg/mL with age <50 years and >1,200 pg/mL in older patients.[8]

- *Females*: Females have higher values of BNP and NT-proBNP as compared to males in all age groups. It may be due to the effects of estrogen which increases the levels of BNP or due to less testosterone in females which has an inhibitory action on the release of BNP.[9]
- *Age*: Elderly age group has higher circulating BNP and NT-proBNP levels. So age-appropriate consideration should be taken into account.[9]
- *Medications*: BNP is degraded by neprilysin, so in patients who are treated with angiotensin receptor-neprilysin inhibitor sacubitril-valsartan, the circulating levels of BNP is increased.[10] NT-proBNP is not degraded by neprilysin, hence its levels are not increased by neprilysin inhibition. So NT-proBNP levels but not BNP levels can be used to guide therapy in such patients.
- *High cardiac output states*: Conditions such as sepsis, cirrhosis, and hyperthyroidism, which are associated with high cardiac output, may cause elevated levels of natriuretic peptides. The exact mechanism is unclear, and BNP in the diagnosis of heart failure as a cause of symptoms is less accurate in these conditions.[11,12]

Conditions which can Cause False Low Levels Despite Heart Failure

- *Obesity*: These patients have low circulating BNP and NT-proBNP levels despite strong clinical evidence of heart failure.[2] Despite the lower values with obesity, higher BNP value is associated with worse outcome. A low cut-off value may be needed to diagnose heart failure but the exact value is uncertain.
- *Pulmonary edema*: In initial hours, the levels of BNP or NT-proBNP may be low as natriuretic peptides are synthesized in a ventricle that is under acute pressure or volume overload, and very little of it is stored in the muscle at baseline for release during decompensation.
- *Mitral regurgitation (MR)/mitral stenosis (MS)*: In MS and MR patients, symptoms of heart failure are not due to left ventricular dysfunction. So the levels of BNP are only mildly elevated even when patient is overtly symptomatic of heart failure.

ASSAY VARIABILITY

Commercially available assays also measure precursors of BNP and NT-proBNP as well as various other degradation products. So the actual contribution of each peptide to the end result is unknown. Also there is variation within individuals due to genetic makeup and also variation in results with serial testing. These variations are maximum in rapid test as compared to central laboratory testing. Total variability determines the percentage change (the relative change value or RCV) needed to demonstrate a significant difference in results over time. In a review of studies of BNP and NT-proBNP variability, a mean 25% decrease in BNP was required for a significant within-day change and a mean 72% decline in BNP was required for a significant week-to-week change.[13] Variability for NT-proBNP testing was less, so RCVs were lower: An 11% decrease was required for a significant within-day change and a 47% for a significant week-to-week change.[14]

CLINICAL APPLICATION IN INTENSIVE CARE UNIT

Cardiac Conditions

Heart Failure

The best and most validated utility of BNP and NT-proBNP in acute care setting is diagnosing heart failure in a dyspneic patient where diagnosis is uncertain. This is supported by multiple studies and guidelines. Plasma BNP and NT-proBNP have high sensitivity, low specificity, and high negative predictive values. Plasma BNP values <100 pg/mL and NT-proBNP <300 pg/mL can rule out heart failure as a cause of dyspnea. The early use of BNP in acute care setting can establish timely diagnosis, prevent inappropriate delay in initiation of treatment, and reduce hospital length of stay and treatment costs. Low values of BNP and NT-proBNP help to triage patients away from imaging with echocardiography or computed tomography. The 2017 Guidelines from American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) give class I recommendation for use of natriuretic peptide in dyspneic patients to rule out heart failure.[3] Natriuretic peptides have a possible role in guiding adequacy of therapy in heart failure patients, although there are conflicting results so far. Majority of trials in acute heart failure have not found any differences in outcome with natriuretic peptide-guided therapy.[15,16] In chronic heart failure, two large meta-analyses have validated the use of natriuretic peptide-guided therapy.[17,18] Few other trials reported no overall difference in mortality in standard versus BNP-targeted therapy in chronic heart failure. Current ACC/AHA guidelines give class II recommendation to use BNP and NT-proBNP as a guide to treatment.[3] Natriuretic peptides also have prognostic value and can predict outcome in both acute and chronic heart failure patients.[3] ADHERE registry (Acute Decompensated HEart Failure National REgistry) was assessed for patients with acute heart failure which suggested that there was linear relationship between BNP quartiles and in-hospital mortality, quartiles 1 to 4: 1.9, 2.8, 3.8, and 6%, respectively. So patients who have persistently high values despite adequate therapy have poor prognosis.[19]

Predictor of Future Cardiovascular Events

Asymptomatic patients without heart failure who have raised plasma natriuretic peptides have higher risk of development of heart failure or other cardiovascular events in future.[20]

Screening for Left Ventricular Dysfunction

Plasma BNP and NT-proBNP can be used as screening test for asymptomatic left ventricular (LV) dysfunction, with the goal being early identification before heart failure sets in so that appropriate steps can be taken.

Acute Coronary Syndrome

Plasma BNP and NT-proBNP levels are elevated in patients with both stable and unstable anginas. It is useful in differentiating the cardiac origin of the chest pain from noncardiac causes. Combination of BNP and cardiac troponin (cTn) T significantly increases the sensitivity in detecting cardiac chest pain and was also satisfactory to rule out cardiac causes.[2] Plasma natriuretic peptides also have prognosticative values in patients with acute coronary syndrome (ACS). Higher values were associated with an increased risk of new or recurrent myocardial infarction and new or worsening heart failure. Few studies have also reported the prognostic values in patients with stable anginas, where risk or future cardiovascular events correlate with plasma BNP and NT-proBNP.[20]

Response to Cardiac Resynchronization Therapy

Studies have reported that patients with higher pre-implantation plasma BNP and NT-proBNP have better response to cardiac resynchronization therapy (CRT). Also serial measurement of BNP and NT-proBNP can be used to monitor response to CRT as levels will decrease with response.[21]

Pulmonary Hypertension

Although the levels of BNP and NT-proBNP are elevated in patients with primary and secondary pulmonary hypertension, this may be misleading since lung disease is responsible for the dyspnea unless the patient has secondary pulmonary hypertension due to left heart disease.[2]

Noncardiac Conditions

Sepsis and Septic Shock

B-type natriuretic peptide and NT-proBNP have been evaluated as a predictor of mortality in sepsis, with measurements taken within 5 days of admission. In a recent meta-analysis, BNP has been reported as mortality predictor in sepsis patients with specificity and sensitivity of 60 and 79%, respectively. However, various studies included in this analysis had significant heterogeneity (I^2 = 64%) and no optimal cut-off value for prognostication or mortality outcome was ascertained.[22] Rather than single time measurement, trending of natriuretic peptides in patients with sepsis has a greater clinical utility in prognostication, especially the comparison done between baseline to 72 hours has been associated significantly with 28-day mortality. As far as septic shock is concerned, a positive correlation has been demonstrated between BNP levels and sequential organ failure assessment (SOFA) for predicting the outcome.[2]

In conditions such as community-acquired pneumonia (CAP), various studies have demonstrated the role of BNP as an independent predictor of treatment failure and mortality. When compared to pneumonia severity index (PSI), alone BNP used in conjunction with PSI was better risk predictor for patients presenting with CAP in emergency.

Fluid Responsiveness in Intensive Care Unit

Natriuretic peptides also have been investigated as marker for fluid responsiveness and volume status.[23] Though being static variable, it cannot correctly estimate RV or LV preload; few studies have incorporated BNP in their protocol for fluid management and found trends of BNP to be closely related to fluid balance during resuscitation of sepsis patients.[23]

Postoperative Complications after Noncardiac Surgery

Studies have reported that both preoperative and post-operative elevation of plasma natriuretic peptides are associated with adverse cardiovascular outcomes.[24]

Prediction of Weaning from Mechanical Ventilation

B-type natriuretic peptide is a sensitive marker of myocardial stretch, and its relative change in patients during a spontaneous breadth trial (SBT) can provide prediction of successful weaning from mechanical ventilation. BNP having shorter half-life is preferred over NT-proBNP as a marker for weaning. One recently published meta-analysis reported that the relative change of BNP during a SBT (ΔBNP%) can predict successful liberation from mechanical ventilation. But they cannot be advised as stand-alone test and further studies are warranted.[25]

Role in Extracorporeal Membrane Oxygenation

Few studies have used serial measurement of BNP and NT-proBNP as a marker for weaning from extracorporeal membrane oxygenation (ECMO) and also to predict outcome of patients on ECMO. One recent study on ECMO in COVID-19 patients reported that addition of NT-proBNP to other variables such as RESP (Respiratory ECMO Survival Prediction) score can improve outcome prediction.[26] These are small studies and need further research.

Chronic Lung Diseases and Respiratory Failure

Levels of natriuretic peptides are elevated in patients with chronic lung diseases [chronic obstructive pulmonary disease (COPD)] mostly due to right ventricular dysfunction and is more during acute exacerbation. Raised BNP levels have been found to independently predict the need for intensive care unit (ICU). However, BNP levels failed to predict short- and long-term mortality in these patients.[27]

Intracranial Pathologies

Acute ischemic stroke: Acute ischemic stroke results in catecholamine and cortisol surge as a stress response. Natriuretic peptides are also elevated as a result of hypothalamus pituitary adrenal axis activation reflecting response due to direct myocardial damage or counterbalancing vasodilation of cerebral vessel which has occurred in response to cerebral ischemia. Increased levels of BNP and cortisol were found to be mortality predictor after stroke highlighting that post-stroke neurohormonal disturbances are unfavorable as far as prognosis is concerned.[2]

Subarachnoid hemorrhage (SAH): In patients with SAH due to aneurysms rupture, BNP levels >600 pg/mL were associated with increased mortality.[2] SAH occurring following trauma, increased BNP levels were associated with LV dysfunction, pulmonary edema, and necrosis of myocardium without echocardiography evidence of heart failure.

Epilepsy: BNP has been found to increase after epileptic activity originating from certain regions of the brain such as left frontotemporal regions and ventral region of third ventricle. NT-proBNP levels have been significantly increased in pediatric patients, especially 4 hours postseizure especially after tonic clonic seizures and febrile convulsions as compared to normal or partial motor seizures.[2]

FREQUENCY OF TESTING

There is no exact validated report on how many times levels of BNP and NT-proBNP should be tested during the disease process. In our clinical practice, we measure at least once at the time of admission in a patient with acute dyspnea and repeated as needed. Few suggested testing at admission, after 24 hours, and at discharge to identify patients at risk for readmission with a cardiac adverse event after hospitalization for heart failure.

CONCLUSION

The most validated use of BNP and NT-proBNP in ICU is to rapidly rule out heart failure as cause of dyspnea where diagnosis is uncertain to establish timely diagnosis and prevent inappropriate delay in initiation of treatment. There are many noncardiac and physiological conditions also where it may rise and offer prognosticative value but these are not well validated. The variations in the assay analysis should be borne in mind as discussed above.

REFERENCES

1. Kinnunen P, Vuolteenaho O, Ruskoaho H. Mechanisms of atrial and brain natriuretic peptide release from rat ventricular myocardium: effect of stretching. Endocrinology. 1993;132(5):1961-70.
2. Tsai SH, Lin YY, Chu SJ, Hsu CW, Cheng SM. Interpretation and use of natriuretic peptides in non-congestive heart failure settings. Yonsei Med J. 2010;51(2):151-63.
3. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2017;70:776-803.
4. Daniels LB, Maisel AS. Natriuretic peptides. J Am Coll Cardiol. 2007;50(25):2357-68.
5. de Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. Lancet. 2003;362(9380):316.
6. Martinez-Rumayor A, Richards AM, Burnett JC, Januzzi Jr JL. Biology of the natriuretic peptides. Am J Cardiol. 2008;101(3A):3-8.
7. Pagana KD, Pagana TJ, Pagana TN. Mosby's Diagnostic and Laboratory Test Reference, 14th edition. St. Louis: Elsevier; 2019.
8. Anwaruddin S, Lloyd-Jones DM, Baggish A, Chen A, Krauser D, Tung R, et al. Renal function, congestive heart failure, and amino-terminal pro-brain natriuretic peptide measurement: results from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study. J Am Coll Cardiol. 2006;47(1):91-7.
9. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide concentration: impact of age and gender. J Am Coll Cardiol. 2002;40(5):976-82.
10. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure. N Engl J Med. 2019;380(6):539-48.
11. Rudiger A, Gasser S, Fischler M, Hornemann T, von Eckardstein A, Maggiorini M. Comparable increase of B-type natriuretic peptide and amino-terminal pro-B-type natriuretic peptide levels in patients with severe sepsis, septic shock, and acute heart failure. Crit Care Med. 2006;34(8):2140-4.
12. Schultz M, Faber J, Kistorp C, Jarløv A, Pedersen F, Wiinberg N, et al. N-terminal-pro-B-type natriuretic peptide (NT-pro-BNP) in different thyroid function states. Clin Endocrinol (Oxf). 2004;60(1):54-9.
13. Wu AH. Serial testing of B-type natriuretic peptide and NTpro-BNP for monitoring therapy of heart failure: the role of biologic variation in the interpretation of results. Am Heart J. 2006;152(5):828-34.
14. Clerico A, Carlo Zucchelli G, Pilo A, Passino C, Emdin M. Clinical relevance of biological variation: the lesson of brain

natriuretic peptide (BNP) and NT-proBNP assay. Clin Chem Lab Med. 2006;44(4):366-78.
15. Carubelli V, Lombardi C, Lazzarini V, Bonadei I, Castrini AI, Gorga E, et al. N-terminal pro-B-type natriuretic peptide-guided therapy in patients hospitalized for acute heart failure. J Cardiovasc Med (Hagerstown). 2016;17(11):828-39.
16. Felker GM, Whellan DJ. Inpatient management of heart failure: Are we shooting at the right target? Ann Intern Med. 2017;166(3):223-4.
17. Felker GM, Hasselblad V, Hernandez AF, O'Connor CM. Biomarker-guided therapy in chronic heart failure: a meta-analysis of randomized controlled trials. Am Heart J. 2009;158(3):422-30.
18. Porapakkham P, Porapakkham P, Zimmet H, Billah B, Krum H. B-type natriuretic peptide- guided heart failure therapy: A meta-analysis. Arch Intern Med. 2010;170(6):507-14.
19. Fonarow GC, Peacock WF, Phillips CO, Givertz MM, Lopatin M; ADHERE Scientific Advisory Committee. ADHERE Scientific Advisory Committee and Investigators. Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. J Am Coll Cardiol. 2007;49(19):1943-50.
20. Kistorp C, Raymond I, Pedersen F, Gustafsson F, Faber J, Hildebrandt P. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. JAMA. 2005;293(13):1609-16.
21. Lellouche N, De Diego C, Cesario DA, Vaseghi M, Horowitz BN, Mahajan A, et al. Usefulness of preimplantation B-type natriuretic peptide level for predicting response to cardiac resynchronization therapy. Am J Cardiol. 2007;99(2):242-6.
22. Wang F, Wu Y, Tang L, Zhu W, Chen F, Xu T, et al. Brain natriuretic peptide for prediction of mortality in patients with sepsis: a systematic review and meta-analysis. Crit Care. 2012;16(3):R74.
23. Zhang Z, Zhang Z, Xue Y, Xu X, Ni H. Prognostic value of B-type natriuretic peptide (BNP) and its potential role in guiding fluid therapy in critically ill septic patients. Scand J Trauma Resusc Emerg Med. 2012;20:86.
24. Lurati Buse GA, Koller MT, Burkhart C, Seeberger MD, Filipovic M. The predictive value of preoperative natriuretic peptide concentrations in adults undergoing surgery: a systematic review and meta-analysis. Anesth Analg. 2011; 112(5):1019-33.
25. Deschamps J, Andersen SK, Webber J, Featherstone R, Sebastianski M, Vandermeer B, et al. Brain natriuretic peptide to predict successful liberation from mechanical ventilation in critically ill patients: a systematic review and meta-analysis. Crit Care. 2020;24(1):213.
26. Zayat R, Kalverkamp S, Grottke O, Durak K, Dreher M, Autschbach R, et al. Role of extracorporeal membrane oxygenation in critically Ill COVID-19 patients and predictors of mortality. Artif Organs. 2021;45(6):E158-70.
27. Stolz D, Breidthardt T, Christ-Crain M, Bingisser R, Miedinger D, Leuppi J, et al. Use of B-type natriuretic peptide in the risk stratification of acute exacerbations of COPD. Chest. 2008;133(5):1088-94.

47

CHAPTER

Acute Cor Pulmonale Management

Girish V Hiregoudar, Manoj Singh, Varun Byrappa

INTRODUCTION

Cor pulmonale is derived from a Latin word meaning "pulmonary heart". Cor pulmonale is defined as modification in the structural and functional aspects of the right side of the heart predominantly the right ventricle (RV) caused by issues with in the pulmonary system resulting in pulmonary hypertension. Right heart failure subsequently to a left heart failure is not categorized as cor pulmonale.[1]

Cigarette smoking is the most important etiological factor for the same. Chronic vasoconstriction (secondary to long-term hypoxia) produces proliferation of smooth muscle in small pulmonary arteries. Hypoxemia decreases endothelial cell production of nitric oxide (which is normally a vasodilator) and results in impaired smooth muscle relaxation. In toto it leads to increase in pulmonary vascular resistance (PVR) leading to elevation in the pulmonary arterial pressure.

Right ventricle dysfunction is detected by a right heart central catheter (gold standard for diagnosis) having a pulmonary capillary wedge pressure (PCWP) below 15 mm Hg.[2] The PCWP estimates the left atrial pressure which helps in differentiating right from left heart failure.

MANAGEMENT

The aim in managing an acute cor pulmonale patient is to identify and treat the underlying etiology. Oxygen therapy is the mainstay in the treatment which relieves hypoxemic pulmonary vasoconstriction, which then improves the cardiac output (CO). Other important aspects when faced with right ventricular failure include optimizing rate and rhythm, improving the preload and the organ perfusion, and enhancing myocardial contractility.[3] Sometimes surgical intervention like mechanical circulatory support can be occasionally used.

CORRECTION OF RATE AND RHYTHM

It is optimal to keep the rate fast and in a sinus rhythm. A relatively high heart rate (100–110 beats/min) prevents excessive RV distension and subsequently distorting the left ventricle and also reduces the tricuspid regurgitation. When stroke volume (SV) is limited like in failure, a high heart rate will promote CO but it is important to remember the ill effects of high rate on the left ventricular blood supply and its function.[4] Maintaining a sinus rhythm provides benefits to the hemodynamic by ameliorating the ventricular preload and promoting atrial emptying and thereby decreasing the atrial pressures. Patients with abnormal rhythm should be restored to sinus rhythm by chemical or electrical cardioversion.

MAINTAINING PERFUSION

Systemic hypotension has an adverse effect on the failing right-sided ventricle. Vasoconstrictors are frequently required to maintain global tissue perfusion[5] by improving the systemic arterial pressure and indirectly has a benefit on the RV function **(Table 1)**.

A circulatory assist device like an intra-aortic balloon pump counter pulsation generally provides left-sided support acts by improving the systemic and coronary blood flow also aids in improving RV function by increasing the right coronary perfusion.

PRELOAD OPTIMIZATION

Overdistension of RV has a detrimental effect hence optimizing the preload is essential in patients with RV dysfunction. It is important as we practice assessment of fluid responsiveness in patients with RV dysfunction by administrating small aliquots of fluid boluses (50–100 mL). Diuresis is often required to reduce the load on ventricles and thereby decreasing the right-sided filling pressures as dilated RV obstructs left ventricular filling.[6] Net changes in SV or CO using appropriate bedside monitoring technique are one of the best options available in assessing preload responsiveness and form the basis of fluid management in ICUs. Mechanical ventilation induces exaggerated changes in the SV and CO especially in a failing RV which is quite often misinterpreted as a sign of "fluid responsiveness".

TABLE 1: Drugs used for maintaining tissue perfusion in acute cor pulmonale.

Agent	*Dosage*	*Receptor*	*Action*	*Pros and cons*
Noradrenaline	0.02–0.2 µg/kg/min	α1, β1	Vasoconstrictor, ↑ SVR (systemic vascular resistance), myocardial oxygen delivery and PVR (pulmonary vascular resistance)	*Pros*: • Familiarity and easy to titrate *Cons*: • ↑ PVR in higher doses
Vasopressin	1–4 units/min	Vasopressin receptors V1 and V2	Vasoconstriction, ↑SVR and myocardial oxygen delivery	*Pros*: • Pulmonary vasodilates at low dose (endothelial nitric oxide) • Catecholamine sparing • ↑ PVR lesser than noradrenaline *Cons*: • Bradycardia and splanchnic ischemia
Dobutamine	2.5–10 µg/kg/min	β1, β2	Inotropy, ↓SVR and PVR	*Pros*: • Easy to titrate and • Inodilator *Cons*: • ↑O_2 demand • Tachyarrhythmias • Systemic hypotension
Milrinone	0.375–0.75 µg/kg/min	PDE3 inhibitor	Inotropy, ↓SVR and PVR	*Pros*: • Long half-life (2.5 h) • Inodilator • Pulmonary vasodilation *Cons*: • Systemic hypotension and expensive
Levosimendan	Loading dose: 6–12 µg/kg/min over 10 min followed by infusion of 0.1 µg/kg/min	Calcium sensitizer	Inotropy	*Pros*: • No effect on myocardial oxygen demand *Cons*: • Slow onset • Tachycardia • Hypotension • Headache
Sildenafil	Oral: 20–100 mg TID	PDE5 inhibitor	Inotropy	*Pros*: • ↓ PVR *Cons*: • Long terminal t1/2 (4–18 h) • ↓ SVR • Helpful only in chronic disease
Epoprostenol	1–2 ng/kg/min Nebulized: 0.2–0.3 mL/min of a 10–20 µg/mL solution	Prostacyclin	Increases cardiac output by ↓ pulmonary and right atrial pressure and ↑ heart rate	*Pros*: • ↓ PVR and quick action *Cons*: • ↑ V/Q mismatch • With IV administration systemic hypotension, flushing and headache are seen

(IV: intravenously; PDE3: phosphodiesterase type 3 inhibitor; PDE5: phosphodiesterase type 5 inhibitor)

REDUCE AFTERLOAD

Reducing the afterload is an important component in the management, although most patients with RV failure have chronic lung disease which cannot be easily reversed. In ICU causes which increase PVR should be minimized by preventing acidosis, hypercapnia, or hypoxia. While ventilating these patients conditions which increase PVR[7] should be prevented like high airway pressures and it is often recommended to use positive end-expiratory pressure (PEEP) judiciously as lower PEEP can cause atelectasis and higher PEEP can increase SVR. This becomes a challenge in patients with acute respiratory distress syndrome (ARDS) where high level of PEEP and permissive hypercapnia are commonly accepted and practiced.

TABLE 2: Summary for management of acute cor pulmonale.

Maintain rate and rhythm	*Optimize cardiac reserves*	*Improve contractility and perfusion*	*Reduce afterload*	*Mechanical circulatory support*
• Higher rate • Aim for sinus rhythm • Chemical/electrical cardioversion if required	• *Underfilled:* Small fluid boluses • *Overfilled:* Diuresis/ dialysis	• Inodilator • Vasopressors	• Prevent hypoxia, hypercapnia, and acidosis • Inhaled/IV pulmonary vasodilators	• IABP • ECMO • VAD

(IABP: intra-aortic balloon pump; IV: intravenously; ECMO: extracorporeal membrane oxygenation; VAD: ventricular assist device)

OPTIMIZE CONTRACTILITY

Inodilators like dobutamine or milrinone are useful in RV dysfunction as they promote inotropy with a simultaneous reduction in the systemic vascular resistance (afterload). The draw back of it being they produce reduction in SVR and thereby producing profound systemic hypotension.[8] Due to this reason sometimes, systemic vasoconstrictors are used to counteract the said adverse effect in conjunction with inodilators. Use of digitalis has been controversial as its benefits in the setting of left heart failure have neither been well appreciated nor recommended except in a small subset of patients with chronic cor pulmonale where it has some beneficial effect on the failing RV.

MECHANICAL SUPPORT

Mechanical support devices in the setting of isolated RV failure refractory to medical therapy should be considered early in the disease process to prevent irreversible end-organ damage.[9] Peripheral inserted venoarterial extracorporeal membrane oxygenation provides respiratory and biventricular support.

Surgically implanted ventricular assist devices (VADs) provide isolated RV support via cannulae in the right atrium or ventricle and an outflow cannula in the pulmonary artery. Example: Impella RP, TandemHeart system and Right Ventricular Assist Device (RVAD).

DIFFERENTIAL DIAGNOSIS

- Atrial myxoma
- Chronic thromboembolic pulmonary hypertension
- Biventricular heart failure
- Constrictive pericarditis
- Interstitial lung disease (ILD)
- Obstructive sleep apnea (OSA).

CONCLUSION (TABLE 2)

In a nutshell prognosis depends on the underlying pathology and more often cor pulmonale due to a primary pulmonary disease usually indicates a poor prognosis.[10]

TAKE HOME MESSAGE

- The aim in the management is to identify and treat the underlying etiology.
- Oxygen therapy is the mainstay in the treatment which relieves hypoxemic pulmonary vasoconstriction.
- In case of RV failure encountered in ICU focus should be on rate, rhythm, and perfusion along with optimizing preload and reducing afterload.
- Drugs included in the management include combination of inotropes, vasopressors, and pulmonary vasodilators.

REFERENCES

1. Vieira JL, Távora FRF, Sobral MGV, Vasconcelos GG, Almeida GPL, Fernandes JR, et al. Chagas Cardiomyopathy in Latin America Review. Curr Cardiol Rep. 2019;21(2):8.
2. Vieillard-Baron A, Naeije R, Haddad F, Bogaard HJ, Bull TM, Fletcher N, et al. Diagnostic workup, etiologies and management of acute right ventricle failure: A state-of-the-art paper. Intensive Care Med. 2018;44:774-90.
3. Niwa K. Aortic dilatation in complex congenital heart disease. Cardiovasc Diagn Ther. 2018;8(6):725-38.
4. Lee S. Comprehensive Nursing Management for Valvular Disease. Crit Care Nurs Clin North Am. 2019;31(1):31-8.
5. Murphy E, Shelley B. The right ventricle—structural and functional importance for anaesthesia and intensive care. BJA Educ. 2018;18:239-45.
6. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62:D34-41.
7. Thenappan T, Ormiston ML, Ryan JJ, Archer SL. Pulmonary arterial hypertension: pathogenesis and clinical management. BMJ. 2018;360:j5492.
8. Yoon YS, Jin M, Sin DD. Accelerated lung aging and chronic obstructive pulmonary disease. Expert Rev Respir Med. 2019;13(4):369-80.
9. van Cleemput J, Sonaglioni A, Wuyts WA, Bengus M, Stauffer JL, Harari S. Idiopathic Pulmonary Fibrosis for Cardiologists: Differential Diagnosis, Cardiovascular Comorbidities, and Patient Management. Adv Ther. 2019;36(2):298-317.
10. Kim M, Tillis W, Patel P, Davis RM, Asche CV. Association between asthma/chronic obstructive pulmonary disease overlap syndrome and healthcare utilization among the US adult population. Curr Med Res Opin. 2019;35(7):1191-6.

CHAPTER

48

Intra-aortic Balloon Pump in Cardiogenic Shock: Are We Done and Dusted?

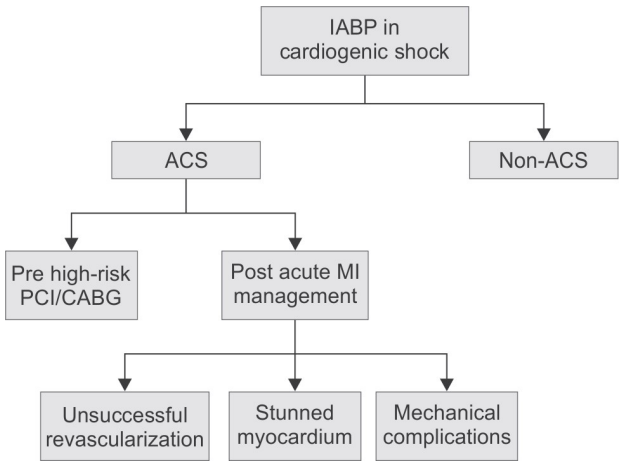
Justin A Gopaldas, Pradeep Rangappa

INTRODUCTION

Intra-aortic balloon pump (IABP) is the first peripheral mechanical circulatory support (MCS) approved for clinical use. Since its use in 1985, utility increased with expanding indications over time **(Flowchart 1)**. One in five patients who was placed on IABP support, has cardiogenic shock (CS) as the main indication.[1] But more recently a reduction in its use either due to reduced clinical need, in part due to evolving evidence contradicting its usefulness (Level I C to level III) or due to the availability of newer and at times superior MCS.[2,3] Though facilities to initiate IABP and alternative MCS (which are capable of producing larger hemodynamic changes compared to IABP) are increasingly available world over now-a-days, it is the IABP which failed to show consistent benefit despite being the sole MCS over prolonged period of time.

Done and dusted is a phrase we associate with successful completion of a task. In case of IABP, could we truthfully say "successfully" or "completed" in setting of CS despite its use over 3 decades? Swan Ganz catheter use was met with multiple obituary articles after its prolonged and extensive use in cardiac and noncardiac critically ill patients.[4] It feels like a similar fate is going to be bestowed upon IABP use noting a lack of clear benefit. Evolving evidence went further by calling its use in clinical practice to be a consequence of *action or intervention bias* rather than evidence-based therapy following publication of Cochrane review.[5,6] A brief deliberation about the physiological rationale for device use and the clinical scenario of CS before we could come to a conclusion about its future in management of CS.

Flowchart 1: Indications.



(ACS: acute coronary syndrome; IABP: intra-aortic balloon pump; PCI: primary coronary intervention; CABG: coronary artery bypass grafting; MI: myocardial infarction).

PHYSIOLOGICAL RATIONALE

Cardiovascular consequences following IABP are due to a concept of counterpulsation (balloon deflating during systole and inflating during diastole of cardiac cycle in simplistic terms). Compared to other MCS, IABP's influence on blood column is between left ventricle (LV) and aorta. IABP increments diastolic coronary flow and arguments systolic systemic flow by its actions on LV as described in **Table 1**.

But such positive changes are likely to be marginal in patients with right ventricle (RV) abnormalities (poor RV contractility, high pulmonary pressures, etc.).[7]

CARDIOGENIC SHOCK

Cardiogenic shock is defined as pump failure along with drop in perfusion pressure and in need of vasoactive medication use to restore perfusion pressure.[8] Acute coronary syndrome (ACS) forms the main indication for the acute causes and decompensated heart failure for acute on chronic causes (<5% of IABP use) for IABP use.

When CS is reviewed in setting of IABP use, it is predominantly in relation to ACS related CS. In these cases, shock is secondary and proportional to the myocardial injury. Over the last 2 decades, understanding of the ACS has increased. Ischemia-infarction from macro-circulatory interruption (epicardial obstruction) leads to coronary autoregulatory changes in the offending territory and others but also leads to significant microvascular changes. While the visible macro-circulation account for <10% of vasculature, majority of microcirculation is not readily

TABLE 1: Hemodynamic effects of IABP.

IABP balloon	*Timing*	*Physiological effect*	*Projected hemodynamic effects*
Inflation	• At the beginning of diastole or • Closure of aortic valve or • Coinciding with *end of T wave* on ECG or • 40 milliseconds before dicrotic notch on arterial waveform	• Blood in aorta moves in both directions (towards coronaries and peripheries). • *Towards coronaries:* Increase in early diastolic aortic pressure (diastolic argumentation) and in turn increase in coronary blood flow. • *Towards peripheries:* "Windkessel effect": Exacerbating a pulsatile heart pumping into a continuous flow of blood in aorta and peripheral circulation.	• *Increases diastolic pressure and diastolic perfusion gradient:* Increased coronary perfusion (40–70%) • Increase in arteriovenous gradient and peripheral perfusion • *Activation of aorta baroreceptors:* Peripheral vascular resistance decreased
Deflation	• At the very end of diastole or • At opening of aortic valves or • Coinciding with *peak of R wave* on ECG or • 40 milliseconds before the end of diastolic runoff of arterial trace	• Causes suction effect to move blood towards peripheries. • Reduces end-diastolic aortic pressure (up to 30%) • Decrease in peak LV pressure rise (up to 20%) • Systolic pressure drop (up to 10%)	• *Reduction in afterload:* (Systolic unloading) • Reduces myocardial oxygen consumption • Increase in ejection fraction • Increase in cardiac output (0.5 to 1.0 LPM or up to 30%)

visible on traditional evaluation.[9] With more research into this area, autoregulatory and microvascular changes seem to drive the morbidity and mortality as long as the macrocirculation is addressed [early and appropriate primary coronary intervention (PCI)].[10]

Significant ischemia-infarction is not a classically explained supply-demand [poststenotic acute myocardial infarction (AMI)] phenomenon. It is described rather as a lack of coronary flow that leads to consequences not limited to contractile function metabolism and morphology. The effects extend to and more importantly to molecular signaling and rearrangements that have implications for vascular and myocardial repair/remodeling (including stunning).[11]

In PCI era, following reperfusion, microcirculatory deficit is predominant force driving morbidity and mortality and its management is predominantly medical. With adequate reperfusion and ever improving medical and supportive care, mortality has been improving significantly compared to times when delayed presentation, thrombolysis and poor reperfusion were common.

PROPOSED REASONS FOR INTRA-AORTIC BALLOON PUMP FAILURE AS A MECHANICAL CIRCULATORY SUPPORT

- Trial design:
  - Observational studies and their inherent biases
  - Randomized controlled trials (RCTs): Restrictive inclusion, open labeled
- Equipment:
  - Balloon volume: <40 mL
  - Understanding the timing of inflation and deflation to optimize hemodynamics
- Timing:
  - Mostly late or as rescue
  - Scant prophylactic use
- Excessive research for use in single ethology (ACS)
- *Patient factors*: Inclusion of sicker patients and those who underwent cardiopulmonary resuscitation (CPR) into treatment arm.

EVIDENCE-BASED REVIEW FOR FAILURE OF INTRA-AORTIC BALLOON PUMP

- *Intra-aortic balloon pump use in ACS*: ACS [with or without shock; coronary artery bypass grafting (CABG) or PCI group; pre- or postprocedure; with or without re-perfusion] is the main indication for IABP use in clinical practice. Studies showed benefit in IABP use when used in patients who did not undergo reperfusion therapy or those who underwent reperfusion using thrombolysis. There seems to be no such improvement when used in patients who underwent reperfusion through PCI, if one allows for the inequalities of these observational trials. Overall mortality in last 3 decades of IABP use improved consistently and more so after 2003 following increased use of PCI making IABP contribution to mortality benefit less contributory[12] **(Fig. 1)**.
  - Coming to the acute myocardial infarction (AMI) with CS group which formed 20% of IABP use, earlier studies have shown benefit (pre-2003) but over the last decade, more and more studies failed to show similar benefit more so than non-CS group.
  - Primary coronary intervention-lead re-vascularization has become primary treatment modality in AMI and since this process became more and more

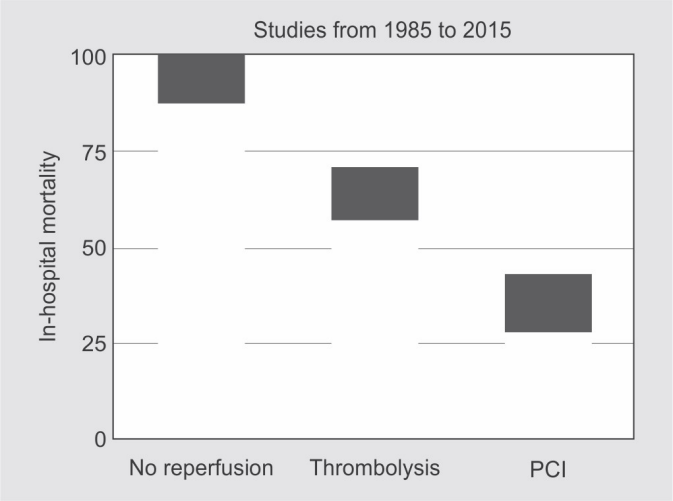


Fig. 1: In-hospital mortality in ACS.

standardized (early and evidence driven), the lesser the mortality in this group of patients.[13] Since this positive change in care which might also improve overall quality of care, mortality continued to improve at a rate not seen prior. This improvement in care discriminated those who were not going to do well and those who will. Those who do not do well and develop or already in CS, the MCS addition does not seem to change the outcome. Be it for IABP or Impella device (both peripherally inserted). This is synonymous with sepsis trials in critically ill where the standard of care has improved to an extent that we are struggling to find benefit with goal-directed therapies, antibiotic choices or when and how organ support is instituted.[14]

- *Intra-aortic balloon pump use in non-ACS cardiogenic shock*: Predominant indication remains to be heart failure with reduced ejection fraction (HFrEF) in CS. Due to non-ACS nature of illness, increased coronary perfusion, myocardial oxygen demand improvement and/or minimal increase in cardiac output cannot explain the suggested improvement. It is hypothesized to be due to preferential or effective afterload reduction in this group of patients compared to ACS. IABP deemed more beneficial in high volume state compared to normal volume for a given reduced contractility.[15,16]

INTERVENTION BIAS

Medical literature and day-to-day clinical practice is filled with acts by healthcare professionals that is deemed intervention bias. It is argued that a clinician would more likely to choose to intervene rather than not, use of such intervention persists even after its benefit is in question and/or also allows for publication bias. When we think of IABP, all above scenarios could easily be met.

INTRA-AORTIC BALLOON PUMP IN INDIA

When literature review is undertaken for IABP use in Indian patients, CS as an indication accounted for 40%.[17] This is significantly higher compared to western literature (~20%). This might be due to preferential use in sicker group of patients, as a rescue therapy and/or as decision based on cost implications. When looked at patients presenting with CS due to AMI undergoing PCI, IABP support is used in excess of 70%.[18] Non-ACS indications remain scant in Indian subset. Coming to cardiac surgical patients, 5–8% of them undergo IABP insertion and majority of them for (80%) for CS (perioperatively).[19,20] During the course of last 2 decades, the use of IABP for AMI-CS has reduced by half.[18] The only significant change is moving from thrombolysis predominant to PCI predominant reperfusion strategy and in turn improved outcomes. Despite the research and an industry push for increased Impella device usage, IABP still remains the main MCS in AMI setting. Even in experienced cardiac and cardiothoracic units that have capacity to offer central MCS devices, IABP remains the main MCS. Given the experience and cost implications with other MCS, IABP will be continued to be used albeit marginally lower compared to 5–10 years ago (Post-IABP-SHOCK trials). Inspired of variable but high usage, published literature in Indian subset remains scant and consisted of retrospective data.

FUTURE UTILITIES

- Continue to use IABP as first-line MCS in LMICs like India.
- As MCS for papillary muscle rupture leading to acute mitral regurgitation with CS (pre- or perioperatively).
- Increase of non-ACS indications.
- Experimental modes in IABP (timing, balloon sizes, combination with other MCS, etc.).

CONCLUSION

Intra-aortic balloon pump is ineffective in altering clinically relevant outcomes when used in patients suffering from CS. This is likely due to poor increment in cardiac output (as MCS), inability to show independent benefit with increased coronary perfusion, and modest after load reduction in majority which is not sufficient to alter clinical course. Finding benefit from IABP in current era is a sign of lacunae in care and point to areas of improvement like early reperfusion strategies, medical management, supportive care, and overall standard of care. With availability of newer MCS, which provides better increment in cardiac output in ACS with CS, IABP may soon be on the receiving end of obituaries like Swan-Ganz catheter. In Indian setting, due to relative ease of availability, cost factor or in some part due to intervention bias, it may still remain in use as MCS of

choice till other devices become affordable (Central devices > peripheral devices).

Its use in CS due to HFrEF in overload state might be another avenue for research and clinical use though, this indication comprises only 2–3% of IABP patients. Experimental modes (mid-systolic and end-systolic counterpulsation) could be part of research to find more benefit out of the device given it might be in clinical use for some time to come.

Although the SHOCK II study fails to demonstrate short-term and long-term mortality benefits with IABP therapy adjunctive to PCI in ST-elevation MI complicated by CS as compared to a medical therapy group, it may be secondary to extensive damage to the heart muscle tissue not able to sustain the cardiac function for an increased period of time despite IABP support. In such patients, IABP may be an option as temporizing hemodynamic support to bridge to the durable mechanical assistance device or heart transplantation. Therefore, early consultation with an interprofessional cardiogenic shock team, including an interventional cardiologist and advanced heart failure specialist, before or at the time of IABP insertion may prove beneficial to devise a plan of care about urgent revascularization. Such a plan can ensure the adequacy of the hemodynamic support and contemplate a long-term plan of care to improve survival outcomes. The interventional cardiologist's role is the decision-making about the initiation of mechanical support devices and placement of the IABP and/or other percutaneous mechanical support devices and revascularization for acute myocardial infarction. Advanced heart failure cardiologist evaluation is essential to assess for the requirement of durable ventricular assist devices (VAD) or heart transplantation, and, if needed, can coordinate for listing the patient for durable VAD and heart transplantation. Additionally, heart failure specialists can provide further recommendations about treatment options for patients with decompensated heart failure complicated by cardiogenic shock. Further, the cardiothoracic surgery team should be promptly involved in patient care if mechanical complications of myocardial infarction, i.e., severe mitral regurgitation due to papillary muscle rupture or ventricle septal rupture, is diagnosed and requires urgent surgical repair. Furthermore, the role of intensivist is imperative in care as patients with cardiogenic shock secondary to myocardial infarction usually experience multi-organ failure, and require intensive care interventions to prevent and treat multi-organ dysfunction and manage the critically ill patients requiring mechanical ventilator support, and prevent and treat malnutrition, delirium, pressure ulcers, and thromboembolism. The intensive care unit physician plays the role of a coordinating physician and serves the responsibilities of diagnosis, triage, activation of subspecialties and additional team members,

TABLE 2: Percutaneous mechanical circulatory devices.

Left ventricle to aorta	*Left atrium to systemic artery*	*Right atrium to systemic artery*	*Right atrium to pulmonary artery*
IABP	Tandem heart	V-A ECMO	Impella RP
Impella device			Adapted tandem heart

and medical management of the cardiogenic shock patients with multi-organ failure. Moreover, an intensivist has a vital role in ensuring the adequate functioning of the IABP and continuous monitoring for early identification of the device-related complication and its management. Intensivist and interventional cardiologists must be cognizant of the patient's goals of care consistently throughout the care. In conditions of refractory cardiogenic shock with an inappropriate response to medical therapy, revascularization, inotropes/vasopressors and IABP support, and further escalation of care to heart transplantation or permanent ventricular assist device is not a goal or deemed futile, and an interprofessional team approach can assist in the transition of care to end of life care/comfort care. In such a condition, consultation of the palliative care/hospice care team to provide comfort care is warranted.

REFERENCES

1. Cohen M, Urban P, Christenson JT, Joseph DL, Freedman RJ Jr, Miller MF, et al.; Benchmark Registry Collaborators. Intra-aortic balloon counterpulsation in US and non-US centres: results of the Benchmark Registry. Eur Heart J. 2003;24(19):1763-70.
2. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al.; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40:87-165.
3. Zheng XY, Wang Y, Chen Y, Wang X, Chen L, Li J, et al. The effectiveness of intra-aortic balloon pump for myocardial infarction in patients with or without cardiogenic shock: a meta-analysis and systematic review. BMC Cardiovasc Disord. 2016;16(1):148.
4. Marik PE. Obituary: pulmonary artery catheter 1970 to 2013. Ann Intensive Care. 2013;3(1):38.
5. Foy AJ, Filippone EJ. The case for intervention bias in the practice of medicine. Yale J Biol Med. 2013;86(2):271-80.
6. Unverzagt S, Buerke M, de Waha A, Haerting J, Pietzner D, Seyfarth M, et al. Intra-aortic balloon pump counterpulsation (IABP) for myocardial infarction complicated by cardiogenic shock. Cochrane Database Syst Rev. 2015;2015(3):CD007398.
7. Krishna M, Zacharowski K. Principles of intra-aortic balloon pump counterpulsation. Cont Edu Anaesth Crit Care Pain. 2009;9(1):24-8.
8. TRIUMPH Investigators, Alexander JH, Reynolds HR, Stebbins AL, Dzavik V, Harrington RA, et al. Effect of tilarginine acetate in patients with acute myocardial infarction and cardiogenic shock: the TRIUMPH randomized controlled trial. JAMA. 2007;297:1657-66.

9. Adjedj J, Picard F, Durand-Viel G, Sigal-Cinqualbre A, Daou D, Diebold B, et al. Coronary microcirculation in acute myocardial ischaemia: From non-invasive to invasive absolute flow assessment. Arch Cardiovasc Dis. 2018;111(4):306-15.
10. Noc M, Erlinge D, Neskovic AN, Kafedzic S, Merkely B, Zima E, et al. COOL AMI EU pilot trial: a multicentre, prospective, randomised controlled trial to assess cooling as an adjunctive therapy to percutaneous intervention in patients with acute myocardial infarction. Euro Intervention. 2017;13(5): e531-9.
11. Heusch G. Myocardial ischemia: lack of coronary blood flow, myocardial oxygen supply-demand imbalance, or what? Am J Physiol Heart Circ Physiol. 2019;316(6):H1439-46.
12. Romeo F, Acconcia MC, Sergi D, Romeo A, Muscoli S, Valente S, et al. The outcome of intra-aortic balloon pump support in acute myocardial infarction complicated by cardiogenic shock according to the type of revascularization: a comprehensive meta-analysis. Am Heart J. 2013;165(5):679-92.
13. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. N Engl J Med. 1999;341:625-34.
14. Kaukonen K, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality Related to Severe Sepsis and Septic Shock Among Critically Ill Patients in Australia and New Zealand, 2000-2012. JAMA. 2014;311(13):1308-16.
15. Fried JA, Nair A, Takeda K, Clerkin K, Topkara VK, Masoumi A, et al. Clinical and hemodynamic effects of intra-aortic balloon pump therapy in chronic heart failure patients with cardiogenic shock. J Heart Lung Transplant. 2018;37(11):1313-21.
16. Kimman JR, Van Mieghem NM, Endeman H, Brugts JJ, Constantinescu AA, Manintveld OC, et al. Mechanical Support in Early Cardiogenic Shock: What Is the Role of Intra-aortic Balloon Counterpulsation? Curr Heart Fail Rep. 2020;17(5):247-60.
17. Kapadia FN, Vadi S, Bajan K, Shukla U. A two years outcome analysis of patients on intra-aortic balloon pump in a tertiary care center. Indian J Crit Care Med. 2004;8(3)157-61.
18. Raja DC, Chopra A, Vijaykumar S, Maharajan R, Anandhan H, Vasu N, et al., Predictors of short-term outcomes in patients undergoing percutaneous coronary intervention in cardiogenic shock complicating STEMI—A tertiary care center experience. Indian Heart J. 2018;70(Suppl 3):S259-64.
19. Kanchi M, Chandran NVA. Intra-aortic Balloon Pump—Current Status. J Card Crit Care TSS. 2018;2:71-8.
20. Murthy PR, Setty HSN, Kamalapurkar G, Nagashetty RK, Manjunath CN. Beneficial effects of pre-operative intra aortic balloon pump support in high risk patients undergoing coronary artery bypass graft surgery. Heart Res Open J. 2017;4(2):23-8.

CHAPTER 49

Sinus Tachycardia in Intensive Care Unit: Should it be Treated?

Mukul Misra, Ashootosh Mall, Lokendra Gupta

INTRODUCTION

Normal sinus rhythm originates from the sinus node at rates between 60 and 100 beats/min. Rate above 100 beats/min is defined as sinus tachycardia (ST). Infants and children generally have faster heart rates compared with adults, both during rest and exercise. In contrast, elderly individuals have slower rates supposedly due to reduction in number of pacemaker cells (*p* cells) in the sinus node as well as due to reduced sympathetic tone. The rate of the sinus rhythm depends upon the inherent automaticity of the sinus node as well as the parasympathetic (vagal) and sympathetic activity, the former reducing and the later enhancing the sinus node discharge rate. The P wave in the electrocardiogram (ECG) leads 1, 2, and augmented vector foot (aVF) is positive while negative in augmented vector right (aVR) and positive in leads V5 and 6. The PR interval is >120 msec with slight variation in heart rate.[1] Slight variations in P wave morphology can occur due to shift in pacemaker site within the sinus node. Besides autonomic activity, other important factors for variation of sinus rhythm rate include age, sex, and physical activity. It is important to pay attention to these features in the 12 lead ECG so that a correct diagnosis of ST is made. Other narrow QRS tachycardias may be encountered which need definitive diagnosis as they have specific management strategies.

Two types of ST deserve mention although they may not be important for patients admitted to ICU. Firstly, inappropriate sinus tachycardia (IST, chronic nonparoxysmal sinus tachycardia), which occurs in settings of no underlying cardiac pathology and without an evident trigger for ST.[2,3] The diagnosis is made by exclusion although not a common condition often encountered in young females and healthcare professionals. The other variety term as postural tachycardia syndrome (POTS) often affects similar population but the symptoms occur on change in posture from recumbency to standing. This may be associated with blood pressure changes as well. IST generally has emotional or physiological triggers.[4]

SINUS TACHYCARDIA IN INTENSIVE CARE UNIT PATIENTS

Coming to the issue of ST in patients admitted to ICUs, it is common but exact prevalence is not known. However, it may be a cause of concern on many occasions. It is an issue which is encountered by every intensivist but the problem is hardly ever discussed. There are no randomized controlled trials and whatever knowledge is there, that is based upon retrospective observational studies. There is a variety of reasons for ST and we will discuss this later. It is arbitrarily defined as mild, moderate, and severe according to rate, viz. 100–110 as mild, >110–120 as moderate, and >120 as severe tachycardia.

It is well known that an increase in heart rate leads to cardiac overload which can be well tolerated by normal hearts but can be harmful for patients with cardiac dysfunction, underlying coronary artery disease, and elderly. Increased heart rates decrease diastolic filling times of the ventricles and reduce stroke volume and adversely affect coronary filling. A recent retrospective study by Masao et al. from Japan (2019) in 476 patients found ICU and in-hospital mortality associated with ST rate and duration. The data showed ICU mortality of 0.9%, 5.6%, and 57.1% and in-hospital mortality of 1.8%, 16.7%, and 85.7% in patients with mild, moderate and severe tachycardia respectively, which, they defined according to heart rate and duration.[5]

Another issue is the duration of tachycardia. The data is scanty and here is no clearly defined duration of ST, which is considered to be harmful. The definitions are arbitrary as have been defined by researchers. One study by Park et al. defined duration of persistent ST >6 hours and a rate increase >20% of baseline value.[6] Thus, both the issues the rate and the duration of tachycardia deserve attention.

Patients admitted to ICU often have other abnormalities such as acid-base and electrolyte abnormalities, and compromised renal function due to variety of reasons that may further aggravate the situation of perturbations produced by increase in sinus rates.

COMMON CAUSES OF SINUS TACHYCARDIA IN INTENSIVE CARE UNIT PATIENTS

Sinus tachycardia is easily identified on monitor and the rhythm is confirmed from a 12-lead ECG. After establishing that the tachycardia under question is indeed sinus, its etiology needs to be found out. Tachycardia can have physiological, pathological, or pharmacological causes. Physiologically, it is commonly associated with catecholaminergic triggers, including exercise, stress, pain, fever, and anxiety.[7] The major causes of ST are shown in **Table 1**.

TABLE 1: Major causes of sinus tachycardia (ST).

Physiologic causes	*Pathologic conditions*	*Pharmacologic*
	Fever	Caffeine
	Substance withdrawal	Nicotine
Exercise	Hyperthyroidism	Atropine
Stress (fight or flight response)	Pulmonary embolism	Dobutamine
Anxiety	Sepsis	Adrenaline
Emotions	Dehydration	Vasopressin
Pain	Chronic anemia or acute blood loss	
	Pheochromocytoma	Theophylline
	Heart failure	Cocaine
		Methamphetamine

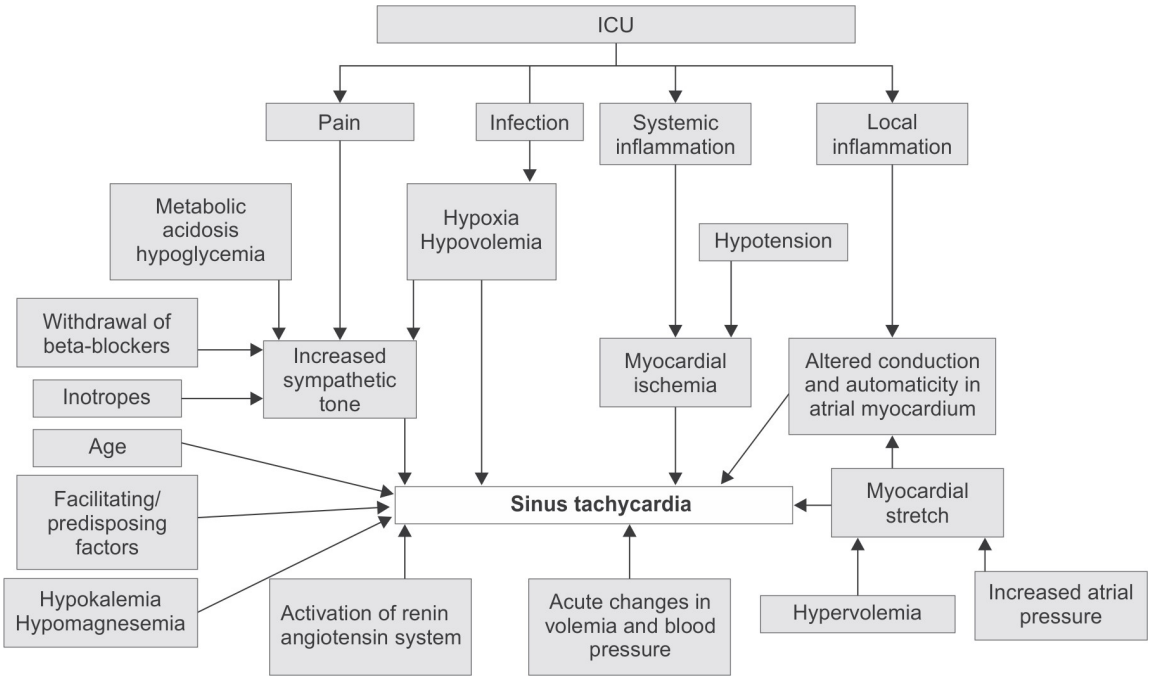
PATHOPHYSIOLOGY

The pathophysiologic processes leading to ST by various triggers are several and the complex process is shown in **Flowchart 1**. There is involvement of adrenergic and renin-angiotensin-system, fluid and electrolyte balance, inflammation and infection, and drugs among others.

DIFFERENTIAL DIAGNOSIS

Sinus tachycardia requires differentiation from other tachycardias of supraventricular origin (narrow QRS), which may mimic ST and creates confusion. For example, an ectopic atrial tachycardia arising in close vicinity of sinus node may have similar ECG configuration as ST but needs differentiation because management lines are different. Such tachycardias have fixed rates often with abrupt onset and offset. Similarly, a sinoatrial (SA) nodal re-entrant tachycardia can closely mimic a ST because of ECG characteristics. However, it has an abrupt onset and offset. Sinus nodal re-entry is the underlying mechanism for such a tachycardia.[8] An atrial flutter (AF) with a fixed 2:1 atrioventricular block (AV) block can mimic ST but a careful look at the 12-lead ECG can clarify the issue with identification of saw-tooth appearance of "p" waves in leads 2, 3, and aVF. Similarly, AF with rapid ventricular rate often can create confusion but absence of clearly defined "p" waves in ECG and irregularity in RR interval identifies the rhythm. AV nodal re-entrant tachycardias are also narrow QRS tachycardias. However, they have faster rates and they lack clearly discernible T waves on surface ECGs and require differentiation from ST.

Flowchart 1: Factors involved in the complex pathophysiology of sinus tachycardia.



A definite diagnosis of ST is important because other mimicking arrhythmias, although may have similar impact on outcome and prognosis, have specific treatment options.

EVALUATION

The evaluation of persistent ST in ICU involves a careful history and examination of the patient. This is to assess that the tachycardia is an appropriate response and then focus on identification of the underlying cause. The common investigations that help in identification of underlying cause include an electrocardiogram, pulse oximetry, echocardiogram, arterial blood gas, serum lactate level, chest X-ray, D-dimer, CT pulmonary angiogram, cardiac enzymes levels, blood sugar, electrolytes, complete blood count, C-reactive protein (CRP), procalcitonin and/or a toxicology screen.

Important features to elicit in history and examination include exposure and at the same time withdrawal of drugs and substances which may be the culprit for tachycardia. Often, it is a neglected issue. Also, measurement of a full set of vital signs, including temperature and pulse oximetry, is of paramount importance.[9] An electrocardiogram is required to confirm the presence of ST and to rule out the presence of other types of tachycardias. It may also give clue to an acute coronary event being the underlying cause of ST. Just by watching all the parameters on monitor can give us a clue about the cause of ST. A simple bedside 2D Doppler echocardiography (echo) can identify pericardial effusion; assess left ventricular function and stroke volume. Arterial blood gas is vital to rule out acid-base and electrolyte abnormalities. A chest X-ray is useful to identify pneumonia, pulmonary edema, or a pneumothorax. D-dimer, CT pulmonary angiogram (CTPA), and ventilation-perfusion scans can determine the presence of a pulmonary embolus.[10] Glucose and ammonia levels can help to identify metabolic derangements.[11]A complete blood count, serum procalcitonin and blood, and other fluid cultures can help to identify the presence of anemia and infection.

APPROACH AND MANAGEMENT

A practical algorithm, easy to remember and follow, has been proposed by Frank Lodeserto in 2018 in his blog posted in *"REBELEM"* which is as follows:

- A: Airway—Obstruction/foreign body
- B: Breathing—Spasm/Infection
- C: Circulation—Hypotension
- D: Drugs administration/withdrawal
- E: Erythrocyte deficiency—Anemia
- F: Fever
- G: Glucose
- H: Hurts Pain—One of the most common symptom in ICU

As already mentioned, ST may be caused by single or multiple factors in an individual. The episodes may not be related to cardiorespiratory instability (CRI). However, significant and/or persistent tachycardia may lead to organ dysfunction. Hence, immediate intervention is more often required.[12] Timely recognition of these early signals of CRI is critical, as even a short period of organ hypoperfusion in ICU can lead to serious adverse outcome including mortality.[13]

TREAT THE UNDERLYING CAUSE

Management is primarily based upon identifying and treating the underlying cause. Patients with ST who have signs and symptoms of shock related to suspected volume depletion, signs of sepsis related to infection, or acute clinical deterioration related to another suspected medical condition (e.g., hypoxia, myocardial ischemia, heart failure, pulmonary embolism etc.) should be treated on priority. Treating the underlying cause is of utmost importance as therapy indicated in ST in some conditions like acute coronary syndrome (beta blocker) may be contraindicated in other conditions (sepsis/hypovolemia).

So far as ST in acute coronary syndrome is concerned triggers may be many ranging from pain, anxiety, hypoxia, or even impending cardiogenic shock. A cautious beta blockade (IV metaprolol/propranolol) is often used to treat ST in these settings.

TREATMENT OF SINUS TACHYCARDIA

The treatment of symptomatic ST is difficult, often with suboptimal results.[4] Prior to beginning treatment, it is important to exclude other etiologies of ST as described above and continue withdrawing any medications that may be contributing to tachycardia. So, once it is decided that the ST has to be treated, the choice of therapy is most often a beta-blocker (BB). It is based on mostly retrospective observational studies. A short-acting BB, esmolol is the one that has been studied more often that too in the setting of ST caused by sepsis. BB has potential protective features during critical illness. It causes reduction in heart rate, decreases cardiac work load and beneficial effects on metabolism, and organ function and inflammation have been reported.

Studies with BB in ICU patients have shown that they reduce mortality in selected group of patients.[14] There are many studies on the role of BB in sepsis patients and data suggests that BB can be beneficial in such patients. Morelli et al. (2013) conducted a randomized controlled trial with esmolol infusion in patients having ST in sepsis.[15] They reported that a continuous esmolol infusion titrated to maintain heart rate between 80 and 94 beats/min in septic shock patients with a heart rate of 95 beats/min or higher and requiring norepinephrine to maintain mean arterial pressure (MAP) of 65 mm Hg, initiated 24 hours after

hemodynamic optimization, was associated with a significant reduction in norepinephrine and fluid requirements and with a decrease in 28-day mortality compared to standard care.

Ivabradine is labeled by the Food and Drug Administration (FDA) (USA) and Drugs Controller General of India (DCGI) (India) for use in patients with systolic heart failure (ejection fraction < 35%) with a resting heart rate above 70 beats/min. It is a pure sinus node rate reducer with no effect on blood pressure and hemodynamics. One landmark trial was SHIFT (Systolic Heart failure treatment with the If inhibitor ivabradine Trial) trial in which Swedberg et al. found beneficial role of ivabradine in heart rate reduction in moderate to severe heart failure.[16] A large randomized study of ivabradine versus placebo in patients with coronary artery disease and left ventricular dysfunction supports the safety and efficacy of ivabradine for lowering heart rates, although these patients did not have inappropriate ST and there are limited data on long-term safety and efficacy.[17] Moreover, ivabradine is available by oral route only. In ICU, most commonly BBs are considered to be drug of choice for ST but they can interfere with the effects of inotropic agents while ivabradine is not active on neurohormonal pathways, thus avoiding any interference with inotropic amines.

Also, there are some retrospective studies in which role of nondihydropyridines (DHP) calcium-channel blocker (CCB) diltiazem was studied. One retrospective chart review study was by Gabrielli et al. in 2001 in which intravenous diltiazem was administered as a slow 10-mg bolus dose (0.1–0.2 mg/kg ideal body weight), and then as infusion started at 5 or 10 mg/h and increased up to 30 mg/h, as needed, to decrease heart rate to <100 beats/min. It was given to patients in whom BBs were either contraindicated or failed.[18]

PROGNOSIS

Persistent ST requires urgent evaluation by an intensivist. Early identification and intervention may result in favorable patient outcomes depending on the underlying etiology.[19] If ST is confirmed and determined to be due to an identifiable cause then the treatment of the cause becomes necessary. Whether heart rate reduction would have had any survival benefit in critically ill patients remains unknown. Further studies are needed to determine whether heart rate reduction contributes to better patient outcomes. In the absence of randomized trials there are no clear cut recommendations for treating ST in ICU patients and choice of agent is clinician's choice. Randomized trials are required with BB, ivabradine or non-DHP CCBs to see whether they may alter outcome in these patients.

CONCLUSION

Sinus tachycardia (ST) is a common problem in ICU patients. The exact prevalence is not known. The etiopathogenesis is complex and multifactorial. There is suggestion that fast heart rates for long duration are related to poor patient outcomes. Commonly used drugs are short-acting BB esmolol, diltiazam, and ivabradine. However, whether heart rate reduction with the use of available agents leads to improved outcomes has not been confirmed in randomized controlled trials. Therefore, randomized trials are needed to assess prevalence, causes and outcomes associated with ST, and the effects of therapy with various available agents in ICU patients.

REFERENCES

1. Goldberger AL, Goldberger Z, Shvillkin A. Goldberger's Clinical Electrocardiography, 9th edition. Elsevier, 2017.
2. Pellegrini CN, Scheinman MM. Epidemiology and definition of inappropriate sinus tachycardia. J Interv Card Electrophysiol. 2016;46(1):29-32.
3. Still AM, Raatikainen P, Ylitalo A, Kauma H, Ikäheimo M, Antero Kesäniemi Y, et al. Prevalence, characteristics and natural course of inappropriate sinus tachycardia. Europace. 2005;7(2):104-12.
4. Sheldon RS, Grubb BP 2nd, Olshansky B, Shen WK, Calkins H, Brignole M, et al. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. Heart Rhythm. 2015;12:e41-e63.
5. Hayashi M, Taniguchi A, Kaku R, Fujimoto S, Isoyama S, Manabe S, et al. Prolonged Tachycardia with Higher Heart Rate Is Associated with Higher ICU and In-hospital Mortality. Acta Med Okayama. 2019;73(2):147-53.
6. Park S, Jung KS, Kim DG, Jang SH, Kang HR, Hwang YI, et al. New onset persistent tachycardia in the intensive care unit. Am J respir crit care med. 2009;179:A1593.
7. Yusuf S, Camm AJ. Deciphering the sinus tachycardias. Clin Cardiol. 2005;28(6):267-76.
8. Yusuf S, Camm AJ. The sinus tachycardias. Nat Clin Pract Cardiovasc Med. 2005;2:44.
9. Page RL, Joglar JA, Caldwell MA, Calkins H, Conti JB, Deal BJ, et al. 2015 ACC/AHA/HRS Guideline for the Management of Adult Patients with Supraventricular Tachycardia: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2016;133:e471-505.
10. Corrigan D, Prucnal C, Kabrhel C. Pulmonary embolism: the diagnosis, risk-stratification, treatment and disposition of emergency department patients. Clin Exp Emerg Med. 2016;3(3):117-25.
11. Reno CM, Daphna-Iken D, Chen YS, VanderWeele J, Jethi K, Fisher SJ. Severe hypoglycemia-induced lethal cardiac arrhythmias are mediated by sympathoadrenal activation. Diabetes. 2013;62(10):3570-81.
12. Mullins CF, Psirides A. Activities of a Medical emergency team: a prospective observational study of 795 calls. Anaesth Intensive Care. 2016;44(1):34-43.
13. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. Anesthesiology. 2013;119(3):507-15.

14. Christensen S, Johansen MB, Tønnesen E, Larsson A, Pedersen L, Lemeshow S, et al. Preadmission beta-blocker use and 30-day mortality among patients in intensive care: a cohort study. Crit Care. 2011;15:R87.
15. Morelli A, Ertmer C, Westphal M, Rehberg S, Kampmeier T, Ligges S, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical ctrial. JAMA. 2013;310:1683-91.
16. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo controlled study. Lancet. 2010;376:9744:875-85.
17. Tendera M, Talajic M, Robertson M, Tardif JC, Ferrari R, Ford I, et al. Safety of ivabradine in patients with coronary artery disease and left ventricular systolic dysfunction (from the BEAUTIFUL Holter Substudy). Am J Cardiol. 2011;107:805-11.
18. Gabrielli A, Gallagher TJ, Caruso LJ, Bennett NT, Layon AJ. Diltiazem to treat sinus tachycardia in critically ill patients: a four-year experience. Crit Care Med. 2001;29(10):1874-9.
19. Armen SB, Freer CV, Showalter JW, Crook T, Whitener CJ, West C, et al. Improving Outcomes in Patients With Sepsis. Am J Med Qual. 2016;31(1):56-63.

SECTION

8

Endocrine and Metabolism

50

CHAPTER

Are Steroids Interchangeable?

Sunil Karanth, Prashant Nasa, Ajith Kumar AK

INTRODUCTION

Steroids are molecules produced in the adrenal cortex, the gonads, and the placenta, which have a variety of staggering roles in human physiology. Steroids produced from adrenal glands (adrenal cortex) can be divided into three functional categories: Glucocorticoids, mineralocorticoids, and androgens. Steroids produced exclusively in adrenal glands include cortisol, 11-deoxycortisol, aldosterone, corticosterone, and 11-deoxycorticosterone. Glucocorticoids are involved in stress response, intermediary metabolism, anti-inflammatory actions, and immunomodulation, while mineralocorticoids play a key role in salt and water balance. Cortisol is the primary glucocorticoid hormone; its production and release are influenced by the adrenocorticotropic hormone (ACTH) of the anterior pituitary. Aldosterone, a major mineralocorticoid hormone, is controlled by the renin–angiotensin–aldosterone system (RASS), which is the key regulator of blood volume and systemic vascular resistance.

Steroids are double-edged weapons. Exogenous steroids are considered potentially life-saving in many indications in the intensive care unit (ICU). Steroids are used in the management of septic shock, acute respiratory distress syndrome (ARDS), acute exacerbations of chronic obstructive pulmonary disease (COPD), unwarranted airway edema, anaphylaxis, and various autoimmune disorders. Steroids are also considered in the management of infections such as tuberculous and bacterial meningitis, extrapulmonary tuberculosis, *Pneumocystis jirovecii* pneumonia (PCP), and community-acquired pneumonia (CAP). Steroids are also considered for regression of vasogenic cerebral edema associated with intracerebral space-occupying lesions or spinal cord injuries. Other steroid use in ICU includes myxedema coma, fetal maturity, thyroid storm, life-threatening hypercalcemia, autoimmune hemolytic anemias, management of brain-dead patients prior to organ donation, and prevention or treatment of transplant rejection. Steroids being a double-edged sword could potentially increase susceptibility to infections and critical illness polyneuromyopathy.

Theoretically, various considerations are needed while deciding the choice of steroids including preparations [oral vs. intravenous (IV)], duration of action, evidence in each setting, and degree of glucocorticoid/mineralocorticoid activity of exogenous steroid **(Table 1)**. To understand the interchangeability of steroids, one needs to be familiar with the equipotency of various preparations and the degree of glucocorticoid/mineralocorticoid activity of a particular compound. In this chapter, we concisely reviewed the evidence on the interchangeability of steroids, mainly focusing on common conditions such as sepsis, ARDS, infections, immunomodulation, and inflammatory emergencies.

SEPTIC SHOCK

Steroids have been advocated in the management of septic shock based on the hypothesis of absolute or relative adrenal insufficiency. The pathophysiology of adrenal insufficiency of septic shock involves multifactorial pathways; stimulation of hypothalamic-pituitary axis (HPA) causing loss of diurnal cortisol variation, and enhanced cortisol release, HPA suppression with hyporesponsiveness of adrenocortical system, and lastly, glucocorticoid resistance. The assessment of the adrenal reserve prior to administration of steroids in septic shock is not routinely advocated because of the unreliability ACTH test to predict responder versus nonresponder.

Annane et al., in their 2002 study, randomized 300 vasopressor dependent septic shock patients and administered steroids as hydrocortisone 50 mg IV 6 hourly plus fludrocortisone 50 μg daily via nasogastric (NG) tube for 7 days in the interventional arm, showing a 28-day mortality benefit (55 vs. 61%), and faster shock reversal (57 vs. 40%) in the steroid arm.[1]

APROCCHHS (activated protein C and corticosteroids for human septic shock) trial randomized 1,241 septic

TABLE 1: Comparison of different steroids based on equivalent dose and action.

	Equivalent dose (mg)	*Anti-inflammatory (glucocorticoid) potency*	*Mineral corticoid potency*	*Duration of action (hours)*
Glucocorticoids				
Short acting:				
Hydrocortisone	20	1	1	8–12
Cortisone	25	0.8	0.8	8–12
Intermediate acting:				
Prednisone	5	4	0.8	12–36
Prednisolone	5	4	0.8	12–36
Methylprednisolone	4	5	0.5	12–36
Triamcinolone	4	5	0	12–36
Long acting:				
Dexamethasone	0.75	30	0	36–54
Betamethasone	0.75	30	0	36–54
Mineralocorticoids				
Long acting:				
Fludrocortisone	Not available	15	150	24–36
Aldosterone	Not available	0	400	Half-life <20 minutes

shock patients (medical as well as surgical) on vasopressors. The treatment arm was administered 200 mg of hydrocortisone daily in divided doses plus fludrocortisone 50 μg per day for 7 days, similar to the study by Annane et al. There was reduced mortality in the steroid group at 90 days (43 vs. 49 %) and 180 days (47 vs. 53 %) and earlier shock reversal (17 vs. 15 days). There was an early ICU discharge, early hospital discharge, and decreased incidence of organ failure in the steroid group.[2]

However, several other large randomized controlled trials (RCTs) such as CORTICUS (Corticosteroid Therapy of Septic Shock), VANISH (Vasopressin vs Norepinephrine as Initial Therapy in Septic Shock), and ADRENAL (Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock) failed to show any benefit of steroids in mortality though faster shock reversal was noted. The HYPRESS (Hydrocortisone for Prevention of Septic Shock) trial which studied severe sepsis patients without shock did not show any preventive benefit of steroid administration. Recent meta-analyses concluded minimal to null mortality benefit with exogenous steroids administration in septic shock though steroids do lessen the duration of septic shock.[3,4]

Hydrocortisone is the most widely used agent in septic shock because of its equipotent glucocorticoid and mineralocorticoid action. Older small trials of the 1980s used high-dose methylprednisolone in septic shock, without any mortality benefit. Surviving Sepsis Campaign (SSC) guidelines removed recommendation on the addition of oral fludrocortisone to IV hydrocortisone, since the latter has significant mineral corticoid activity. Moreover, the absorption and effectiveness of enteral fludrocortisone can be erratic in shock-related splanchnic hypoperfusion. The 2021 SSC guidelines suggest using hydrocortisone to treat septic shock (not sepsis) with an ongoing requirement of vasopressors.[5] Most experts recommend the use of steroids for up to 5–7 days or rapid tapering once the shock has improved with close monitoring. Evidence supporting other steroids in the management of septic shock is lacking.

ACUTE RESPIRATORY DISTRESS SYNDROME

Acute respiratory distress syndrome is a heterogeneous clinical syndrome linked with multifactorial etiologies such as pneumonia, pancreatitis, sepsis, trauma, blood transfusion, and drowning.

Steroids for ARDS management are a matter of ongoing debate, despite many RCTs. In a recent RCT (DEXA-ARDS), from 17 ICUs in Spain, early dexamethasone use in moderate–severe ARDS could reduce the duration of mechanical ventilation {mean difference of 4.8 days [95% confidence interval (CI) 2.57–7.03; $p < 0.0001$]} and mortality [–15.3% (95% CI –25.9 to –4.9; $p = 0{\cdot}0047$)].[6] A large open-label RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial and subsequent meta-analysis based on seven studies in ARDS associated with COVID-19 found significantly lower mortality in patients with steroids.[7] The benefit was only seen in patients on mechanical

ventilation or oxygen without mechanical ventilation. The mortality benefit was independent of the type of steroids used (dexamethasone or hydrocortisone), suggesting a class effect.

Chaudhuri et al. performed a meta-analysis of 18 RCTs (including 2,826 patients) comparing steroids versus placebo or usual care in ARDS (associated with COVID-19 or with other etiology). The use of steroids was associated with lower mortality in ARDS of any etiology [relative risk (RR) 0.82, 95% CI 0.72–0.95, and absolute risk reduction (ARR) 8.0%, 95% CI 2.2–12.5%]. The effect was consistent, irrespective of the type and dosage of steroid.[8]

Hence, evidence supports the use of oral or IV steroids in moderate–severe ARDS (with PaO_2/FiO_2 <200) irrespective of the type of steroids.

INFECTIONS

Steroids have been considered in the management of severe infectious diseases for their potential immunomodulatory or anti-inflammatory properties. The majority of the anti-inflammatory actions of steroids is linked to the glucocorticoid receptor, causing inhibition of transcription of proinflammatory genes, including NF-κB in leukocytes. In addition, steroids regulate the transcription of genes responsible for cytokines, chemokines, and cell adhesion molecules involved in the host inflammatory response.

Meningitis

Steroids in combination with antibiotics can improve outcomes in bacterial meningitis. The anti-inflammatory action of steroids attenuates cytokine-mediated neurotoxicity, resulting from host-microbe interplay. Despite theoretical concerns of decreased penetration of antimicrobials because of steroids effect on blood–brain permeability, studies have reported improved overall outcomes (decreased hearing loss, neurological sequelae or mortality) in certain bacterial meningitis such as *Haemophilus influenzae,* tubercular, and pneumococcal meningitis. First prospective randomized trial on the use of dexamethasone in acute bacterial meningitis showed improved outcome without increased risk of complications.[9] A Cochrane meta-analysis reviewed studies on other steroids (hydrocortisone and prednisone) besides dexamethasone in bacterial meningitis and found no difference in mortality, especially in low-income countries.[10] Recently, another meta-analysis of nine RCTs found no mortality benefit with steroids in meningitis. However, steroids were effective in reducing hearing loss and neurological sequelae.[11]

Tuberculosis

Steroids (dexamethasone, prednisolone, or hydrocortisone) have an established place in managing patients with tuberculous meningitis, pericarditis, pleural tuberculosis, and adrenal insufficiency. The evidence is meagre on the use of hydrocortisone and other glucocorticoids in tuberculosis-related septic shock and ARDS.[12]

Pneumonia

The evidence supporting adjunctive steroids in CAP is mixed. A recent meta-analysis which evaluated different types of steroids in CAP found methylprednisolone or prednisolone to reduce mortality [odds ratio (OR) 0.37, 95% CI 0.19–0.72], whereas hydrocortisone use did not (OR 0.9, 95% CI 0.54–1.49). ICU length of stay and duration of mechanical ventilation was also lower in steroid group.[13] However, divergent results of meta-analyses on the role of corticosteroids led to recent guidelines by the American Thoracic Society and the Infectious Diseases Society of America suggesting against the routine use of corticosteroids in severe CAP except in patients with associated, approved indications (e.g., asthma or COPD, autoimmune conditions or septic shock). Recommendations are against its use in influenza and mild or moderate CAP.

Adjunctive steroids (prednisolone or methylprednisolone) played a crucial role in the management of severe PCP (with hypoxemia) in human immunodeficiency virus (HIV)-infected patients and showed mortality benefits. A recent review of steroids in CAP found insufficient evidence supporting one type over the other and recommended an equivalent dose of any corticosteroid for severe CAP or severe COVID-19.[14]

ANAPHYLAXIS

Despite anaphylaxis being a common emergency, there are no RCTs on the use of steroids. Most of the supporting evidence is either based on observational studies or animal and laboratory studies. A recent meta-analysis by Liyange et al. found that the average rate of steroid use in the emergency room (ER) for severe allergy or anaphylaxis was around 67.99%. Despite lack of evidence, there seems to be a trend to use steroids as one of the mainstay treatment modalities. No evidence showed any benefit in either reducing mortality or revisit to hospital, but it may help reduce the length of stay. It is difficult to comment on the choice of steroids for this emergency with the current level of evidence. Studies have used varying steroid formulations ranging from hydrocortisone, prednisolone to oral methylprednisolone. Thus, it can be concluded that there is not enough evidence for or against the use of steroids in anaphylactic shock, and certainly no data to suggest one type of steroid formulation over the other. For clinical practice, if an individual clinician decides to use steroids in a patient with anaphylaxis, any formulation IV or oral can be used based on his experience with the same.[15]

POSTEXTUBATION STRIDOR

The incidence of postextubation stridor varies from 1.5 to 26.3%. The use of steroids has been a long-established strategy to avoid reintubation in patients after extubation, particularly in high-risk patients. There is a reasonable degree of evidence for its use in pediatric and adult populations. Over the years, different steroids such as methylprednisolone, dexamethasone, and hydrocortisone have been used in studies with reasonably good outcomes. A meta-analysis by Kuriyama et al. showed that administration of prophylactic corticosteroids before elective extubation was associated with significant reductions in the incidence of postextubation airway events such as reintubation, with fewer adverse events.

Among the studies included, five of them used dexamethasone, four used methylprednisolone, and two used hydrocortisone for the test arm.[16] There are no studies comparing the different steroid formulations with each other. Hence, systemic steroids can reduce the risk of postextubation airway events. Based on available evidence, methylprednisolone, dexamethasone, or hydrocortisone can be used interchangeably to achieve this outcome. However, more studies are required comparing different steroid formulations for this indication.

ASTHMA

The early use of systemic steroids remains the mainstay of therapy in acute asthma. When administered within 1 hour for a short course, systemic steroids are known to reduce the rate of relapse and readmission to the ER.[17] There is no difference in the use of a short course of IV or oral steroids for exacerbation of asthma needing admission to the ER. However, if oral steroids cannot be administered or there will be doubt about the compliance or absorption, an equivalent dose of IV steroids for a period of 5–7 days can be used. In children, a single dose of dexamethasone 0.6 mg/kg (maximum 18 mg) was found to be comparable to prednisolone 2 mg/kg/day in two divided doses for 5 days in regards to the resolution of symptoms. The optimal dose for systemic corticosteroids in asthma exacerbations remains to be established. There seems to be no benefit in exceeding doses of 2 mg/kg/day of prednisolone in any of the outcomes, including lung function, rate of hospital admission, or the length of stay. Thus, daily doses of oral steroids equivalent to 50 mg prednisolone as a single morning dose, or 200 mg hydrocortisone in divided doses, are adequate for most patients.[18] In conclusion, oral prednisolone as a single dose of 1–2 mg/kg for 5–7 days or equivalent dose of methylprednisolone or hydrocortisone in divided doses can be used as alternatives in patients with acute severe asthma requiring admission to the ER as recommended by Global Initiative For Asthma (GINA) 2020 guidelines.

EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Exacerbation of COPD is yet another condition often requiring admission to the ICU. As in asthma, there is good evidence supporting the benefit of steroids. However, different studies have used different steroid regimes with equal efficacy. These studies include both ICU and non-ICU patients.[19] Methylprednisolone is the commonly used parenteral steroid in many studies. However, there are studies on oral prednisolone and IV hydrocortisone (followed by oral prednisolone) with similar results. All the studies have shown benefits with the use of systemic steroids in terms of reduced length of stay, delayed relapse, and faster symptom resolution. Though there is limited literature comparing different types of steroids. A meta-analysis by Abroug et al. showed a trend toward better outcomes with most of the steroids compared to placebo.[20] Hence, methylprednisolone, prednisolone, or hydrocortisone followed by oral prednisolone for a period of 5–7 days can be used interchangeably for acute exacerbation of COPD.

RHEUMATOLOGIC EMERGENCIES

At times, rheumatologic diseases present as medical emergencies needing ICU.

- Catastrophic antiphospholipid syndrome (cAPS)
- Pulmonary-renal syndrome
- Central nervous system vasculitis
- Macrophage activation syndrome
- Scleroderma renal crisis
- Septic arthritis

In the case of cAPS, methylprednisolone, along with other modalities of therapies such as plasmapheresis, forms the mainstay of treatment.[21] Methylprednisolone at 1–2 mg/kg is preferred over other parenteral steroids due to the available evidence and pharmacodynamic consideration of its limited first-pass metabolism. In the case of pulmonary-renal syndrome, pulse dosing with methylprednisolone at 15–20 mg/kg followed by maintenance therapy of 1–2 mg/kg is the most commonly administered form of systemic steroids. It is hard to recommend an alternative form of steroids, especially for pulse therapy, due to the limited clinical experience and data. In the case of anti-Ro syndrome or neonatal lupus, a fluorinated glucocorticoid is preferred over other forms of steroids because of its ability to cross the placental barrier. In summary, methylprednisolone is used as a mainstay therapy either alone or adjuvant to other immune-modulating agents in many rheumatologic emergencies. The experience and evidence for other forms of steroids are limited.

POST-TRANSPLANT SETTING

Here again, past experience available is with the use of methylprednisolone or oral prednisolone. In specific

TABLE 2: Evidence and inference on interchangeability of steroids for various conditions.

Conditions	*Evidence on interchangeability*	*Type of steroids*	*Inference*
Septic shock	No	Hydrocortisone	Hydrocortisone is the preferred steroid because of equipotent glucocorticoid and mineralocorticoid action
ARDS	Yes	Methylprednisolone, dexamethasone, or hydrocortisone	Moderate or severe ARDS, and interchangeability of steroids is acceptable
Meningitis	Yes	Dexamethasone, prednisone, or hydrocortisone	Evidence on mortality benefit is conflicting. However, steroids may reduce the neurological sequelae
Tuberculosis	Equivocal		Steroids may be used in tubercular meningitis, pericarditis, pleural tuberculosis, and adrenal insufficiency. The interchangeability of steroids is acceptable
Pneumonia	Yes	Methylprednisolone or prednisone	Against routine use of corticosteroids in severe pneumonia except for indications like asthma, COPD, COVID-19, septic shock, severe PCP, and autoimmune conditions. The interchangeability of steroids is acceptable
Anaphylaxis	No		No data supporting one type of steroid over other
Postextubation stridor	Equivocal	Methylprednisolone, dexamethasone, or hydrocortisone	No data comparing different steroids. Studies used different steroids and the interchangeability of steroids is acceptable
Asthma	Yes	Methylprednisolone, dexamethasone, or hydrocortisone	The interchangeability of steroids is acceptable for management of acute severe asthma
Exacerbation of COPD	Equivocal	Methylprednisolone, prednisone, or hydrocortisone	The interchangeability of steroids is acceptable
Rheumatological emergencies	No	Methylprednisolone	Pulse dose of methylprednisolone is only tested for this indication
Post-transplant	No	Methylprednisolone or prednisone	No evidence for other types of steroids

(ARDS: acute respiratory distress syndrome, COPD: chronic obstructive pulmonary disease, COVID-19: coronavirus disease 2019, PCP: pneumocystis pneumonia)

situations, if a patient develops septic shock, hydrocortisone can be used as an alternative.[22] However, there is no available evidence supporting other types of steroids.

CONCLUSION (TABLE 2)

The evidence comparing different steroids is lacking in various diseases and clinical conditions. The interchangeability of steroids in the management of different diseases depends on the available evidence, pharmacokinetic and pharmacodynamic considerations, and available formulation. The use of a steroid should be based on available evidence in the right dose and duration for a life-threatening emergency. However, in a case of nonavailability or resource-limited setting, an alternative type of steroid can be used in equivalent doses with monitoring.

REFERENCES

1. Annane D, Sébille V, Charpentier C, Bollaert PE, François B, Korach JM, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA. 2002;288(7):862-71.
2. Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot JP, Siami S, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. N Engl J Med. 2018;378(9):809-18.
3. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y, et al. Corticosteroids for treating sepsis in children and adults. Cochrane Database Syst Rev. 2019;12(12):CD002243.
4. Lyu QQ, Chen QH, Zheng RQ, Yu JQ, Gu XH. Effect of low-dose hydrocortisone therapy in adult patients with septic shock: A meta-analysis with trial sequential analysis of randomized controlled trials. J Intensive Care Med. 2020;35(10):97-83.
5. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: a international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47(11):1181-247.
6. Villar J, Ferrando C, Martínez D, Ambrós A, Muñoz T, Soler JA, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med. 2020;8(3):267-76.
7. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: A meta-analysis. JAMA. 2020;324(13):1330-41.

8. Chaudhuri D, Sasaki K, Karkar A, Sharif S, Lewis K, Mammen MJ, et al. Corticosteroids in COVID-19 and non-COVID-19 ARDS: a systematic review and meta-analysis. Intensive Care Med. 2021;47(5):521-37.
9. de Gans J, van de Beek D; European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators. Dexamethasone in adults with bacterial meningitis. N Engl J Med. 2002;347(20):1549-56.
10. Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev. 2015;2015(9):CD004405.
11. Rayanakorn A, Ser HL, Pusparajah P, Chan KG, Goh BH, Khan TM, et al. Comparative efficacy of antibiotic(s) alone or in combination of corticosteroids in adults with acute bacterial meningitis: A systematic review and network meta-analysis. PLoS One. 2020;15(5):e0232947.
12. Chaudhry D, Tyagi D. Tuberculosis in intensive care unit. Indian J Crit Care Med. 2021;25(Suppl 2):S150-4.
13. Huang J, Guo J, Li H, Huang W, Zhang T. Efficacy and safety of adjunctive corticosteroids therapy for patients with severe community-acquired pneumonia. Medicine 2019;98(13):e14636.
14. Martin-Loeches I, Torres A. Corticosteroids for CAP, influenza and COVID-19: when, how and benefits or harm? Eur Respir Rev. 2021;30(159):200346.
15. Liyanage CK, Galappatthy P, Seneviratne SL. Corticosteroids in management of anaphylaxis; a systematic review of evidence. Eur Ann Allergy Clin Immunol. 2017;49(5):196-207.
16. Kuriyama A, Umakoshi N, Rao S. Prophylactic corticosteroids for prevention of post-extubation stridor and reintubation in adults. A systematic review and meta-analysis. Chest. 2017;151(5):1002-10.
17. Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma. Cochrane Database Syst Rev. 2007;(3):CD000195.
18. Global Initiative for Asthma (GINA). (2020) Asthma management and prevention for adults and children older than 5 years. [online] Available from: https://ginasthma.org/wp-content/uploads/2020/04/Main-pocket-guide_2020_04_03-final-wms.pdf. [Last accessed February 2022].
19. Crisafulli E, Barbeta E, Ielpo A, Torres A. Management of severe acute exacerbations of COPD: an updated narrative review. Multidiscip Respir Med. 2018;13:36.
20. Abroug F, Ouanes I, Abroug S, Dachraoui F, Abdallah SB, Hammouda Z, et al. Systemic corticosteroids in acute exacerbation of COPD: a meta-analysis of controlled studies with emphasis on ICU patients. Ann Intensive Care. 2014;4:32.
21. Gutiérrez-González LA. Rheumatologic emergencies. Clin Rheumatol. 2015;34(12):2011-9.
22. Mudge DW. Avoiding or stopping steroids in kidney transplant recipients: sounds good but does it work? Cochrane Database Syst Rev. 2016;8:ED000114.

CHAPTER 51

Interpretation of Cortisol Levels in the Intensive Care Unit

Prakash Jiandani, Gunjan Chanchalani

INTRODUCTION

Critically ill patients are at their physiological extremes, and in a "stress response". Stress response is nothing but a complex neuroendocrine response, mediated by the hypothalamic-pituitary-adrenal (HPA) axis and the sympathoadrenal system, to a variety of insults. Whether this stress response is appropriate for a given condition, or whether a "lesser" or a "higher" response would be more appropriate, is a question largely unanswered.

Critical illness-related corticosteroid insufficiency (CIRCI), a concept that was first introduced in 2008 by Society of Critical Care Medicine (SCCM), is characterized by inadequate intracellular glucocorticoid-mediated anti-inflammatory activity for the severity of the patient's critical illness, which results in dysregulated systemic inflammation.[1] The prevalence of adrenal sufficiency in ICU patients is between 0 and 77%.[2] However, diagnosing adrenal insufficiency and interpretation of cortisol levels in critically ill have remained challenging with limited scientific evidence and poor agreement among the experts in the field.

PHYSIOLOGY

Any stress—infective, trauma, etc. will lead to activation of the HPA axis, resulting in increased secretion of corticotropin releasing hormone (CRH) and arginine vasopressin, from the paraventricular nucleus of the hypothalamus **(Flowchart 1)**. CRH acts on the anterior pituitary and increases the production of adrenocorticotrophic hormone (ACTH), which in turn stimulates the zona fasciculata of the adrenal cortex to release more cortisol.

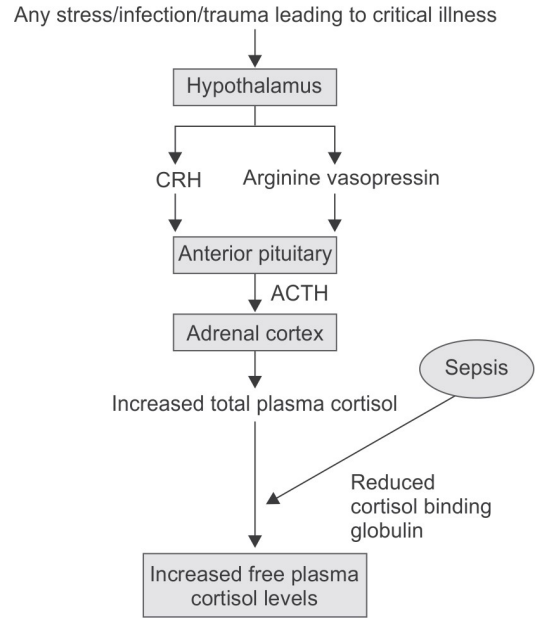
Arginine vasopressin is also a weak ACTH secretagog, which acts synergistically with corticotropin-releasing hormone to stimulate the secretion of ACTH.

Physiologically, ACTH and cortisol are secreted in the cyclical manner over the 24-hour period, with a maximum plasma cortisol level at 8–9 a.m. (110–150 nmol/L), to a minimum plasma level at midnight (<140 nmol/L).[3] Multiple factors increase the production and release of cortisol—stress, cytokines, tissue damage, hypoxia, hypotension, and hypoglycemia. The half-life is 60–90 minutes.

Less than 10% of circulating cortisol is available in the free, biologically active form. More than 90% is bound to corticosteroid-binding globulin, the levels of which fall by 50% in sepsis or any acute illness, thus increasing the amount of free-active cortisol.[4] Also the stress of illness upregulates ACTH secretion, which leads to rise in blood cortisol levels in a few minutes.[4]

This increase in plasma cortisol levels results in multiple effects—metabolic (increased catabolism, increased gluconeogenesis, increased lipolysis, and increase in the blood sugar levels), cardiovascular (increase in the blood pressure), and immune (anti-inflammatory and immune suppressive)—which are aimed at maintaining or restoring homeostasis during stress.[1,5]

Flowchart 1: Hypothalamic-pituitary-adrenal (HPA) axis during critical illness.



(ACTH: adrenocorticotrophic hormone; CRH: corticotropin releasing hormone)

ASSESSMENT OF ADRENAL FUNCTION IN THE CRITICALLY ILL

Adrenal function can be assessed by either assessing basal hormonal levels or by dynamic function tests **(Table 1)**. However, the cut-off values in the critically ill are not well established and often controversial.

Plasma Total Cortisol Levels

How it is done?

Sample is collected at any time of the day for random cortisol levels. Blood samples should be collected at 8 am and 4 pm for evaluating the diurnal variation in cortisol levels.

Interpretation: A number of studies have demonstrated the rise in plasma cortisol levels in the critically ill, ranging from 15 to 50 μg/dL. Since the range of plasma cortisol levels seen in studies is wide, a normal reference range for the critically ill has not been defined.

The maximum plasma cortisol levels of 60 μg/dL have been demonstrated in ICU patients.[6]

There is lack of consensus on the cut-off value of serum cortisol levels for initiation of glucocorticoid therapy. Many authors have proposed a random serum cortisol levels anywhere from 10 μg/dL up to 36 μg/dL as the normal adrenal function.[5,7]

However, a plasma cortisol level below 15 μg/dL has been defined as the cut-off for diagnosing adrenal sufficiency.[8]

In critical illness, patients are highly stressed, multiorgan dysfunction and malnutrition may develop, and the concentrations of corticosteroid-binding globulin and albumin are commonly decreased. Therefore, measured serum total cortisol concentrations can be misleadingly lower than anticipated, resulting in the incorrect conclusion that adrenal function is impaired. Since cortisol binding globulin cannot be measured easily, serum albumin is considered as a surrogate marker of the same.[2]

If albumin level is >2.5 g/dL:[8]

- Serum cortisol > 15 μg/dL = adrenal sufficiency
- Serum cortisol < 10 μg/dL = adrenal insufficiency

If albumin level is <2.5 g/dL:

- Serum cortisol > 11 μg/dL = adrenal sufficiency
- Serum cortisol < 8 μg/dL = adrenal insufficiency

TABLE 1: Biochemical tests for screening for assessing adrenal function in intensive care unit (ICU).

Basal hormonal assays	*Dynamic tests*
• Plasma cortisol levels (timed/random)	• ACTH stimulation test (Cosyntropin test)
• Urine cortisol	• Metyrapone test
• Salivary cortisol levels	• Insulin hypoglycemia test
• Plasma ACTH levels	• CRH stimulation test

(ACTH: adrenocorticotrophic hormone; CRH: corticotropin releasing hormone)

2012 Surviving sepsis guideline recommended a cortisol level cut-off of 18 μg/dL as a possible threshold to initiate glucocorticoid therapy.[9]

Controversy and Confusion in Interpretation

- The plasma levels vary as per the diagnosis and the stress level, severity and duration of the critical illness, hydration levels, and protein levels.[2]
- Also, whether a single random cortisol measurement establishes the 24-hour secretory profile of cortisol in ICU patients, has not been very clear.
- The diurnal variation in cortisol secretion is often disrupted in the ICU patients due to factors such as light, pain, lack of sleep, etc.[10]

  Hence, the optimal time for collection of sample for determining the cortisol levels in ICU is controversial and may require sequential evaluation.
- Different assays used for the interpretation of cortisol levels can give varying results up to 10–12%.[11] And hence establishing reference range can be difficult among different hospitals and laboratories.

Plasma-free Cortisol Levels

Only the free fraction of plasma cortisol is biologically active and of relevance in ICU patients. During critical illness, the cortisol-binding globulin levels drop and hence the free fraction of plasma cortisol is increased, whereas the total levels may remain the same. Similarly, total cortisol levels are low in hypoproteinemic patients, but the serum-free levels are elevated in them.[8]

Thus, most commercial assays which measure only the total plasma cortisol levels may miss the detection of the rise in free-active fraction of plasma cortisol.

Interpretation: A random-free cortisol level of 1.8 μg/dL should be considered as the cut-off value to diagnose patients at risk for adrenal insufficiency in ICU[12] and that the corticotropin-stimulated rise in serum-free cortisol concentration by 3 μg/dL or greater should be interpreted as a normal response in critically ill patients.

Urine Cortisol and Salivary Cortisol Levels

Urine and salivary cortisol levels predominantly reflect the free-cortisol fraction and may be more appropriate to measure in septic and in critically ill patients. So a raised urinary cortisol level suggests an increase in the plasma-free cortisol levels.

Salivary cortisol levels have shown to be reliable and practical method to assess the free cortisol levels during critical illness.[13]

However, collection of salivary sample may be difficult in critically ill patients and collection of urinary sample may be limited in patients with acute kidney injury.

High-dose Cosyntropin Test

The Cosyntropin test has been studied in the critically ill patients and was initially recommended for assessing the cortisol function in this group of patients.

How it is done?

Measure baseline serum cortisol level, and then administer 250 μg of synthetic ACTH. Collect further samples for cortisol level at 30 and 60 minutes after.

Interpretation: A normal response is an increase in serum cortisol levels by 9 μg/dL, or a rise above 18–20 μg/dL.[8]

Controversy and Confusion in Interpretation

- The cut-off values have been extrapolated from studies done in healthy volunteers, and their interpretation in critically ill is not established.
- Many experts believe that this test assesses the adrenal reserve and is not a measurement of adrenal function and its use in determining adrenal insufficiency in the critically ill should be avoided.[14]
- The dose of synthetic ACTH used in the test is much higher than the normal physiological levels, and may over-ride the adrenal resistance to ACTH, thus missing the diagnosis of mild secondary adrenal insufficiency.[14]

The Evidence

Observational studies have demonstrated that patients who have a high baseline plasma cortisol level (>34 μg/dL), with a reduced response to the Cosyntropin test (an increase < 9 μg/dL), had an increased mortality.[15] Other pooled data have suggested that the rise in cortisol levels in Cosyntropin test of <400 nmol/L is associated with increased mortality.[15]

Low-dose Cosyntropin Test

Low-dose Cosyntropin test (use of 1 μg of synthetic ACTH) is more physiological; however, the data for its use in critically ill patients is limited.[14]

How it is done?

Measure baseline serum cortisol level, and then administer 1 μg stimulation dose of synthetic ACTH. Collect further samples for cortisol level at 30 minutes and 60 minutes after injection.

Interpretation: A normal response is an increase in serum cortisol levels by 9 μg/dL.

Controversy and Confusion in Interpretation

Studies have shown that low-dose ACTH test is more sensitive than the high-dose test for diagnosing adrenal insufficiency.[16,17]

Applying the same cortisol criteria to both the low-dose and high-dose ACTH stimulation tests will increase false positive results with the former test.[18]

However, this low-dose test is not yet well-validated in ICU patients, and thus it is not yet recommended for critically ill patients by most experts.

CONCLUSION

Interpretation of cortisol levels during critical illness is very complex and there is total lack of strong evidence for recommendations/cut-off values that fit with all patients. There are multiple caveats in interpretation of cortisol levels in the critically ill population—controversial cut-off values, varying assays, and disruption of diurnal variation. Hence, a single plasma cortisol level should be interpreted with caution and a second value should be checked at 6–12 hours interval. The conventional high-dose ACTH test has its limitations. The low-dose ACTH test, insulin hypoglycemia, and the metyrapone tests have not yet been validated for its use in ICU patients. The plasma-free cortisol levels are more relevant and reflect the adrenal function more closely in the ICU patients; however, due to the technical difficulties in processing the same, its use is currently limited. Further research and studies are needed to appropriately diagnose adrenal insufficiency in the acutely ill population.

REFERENCES

1. Marik PE, Pastores SM, Annane D, Meduri GU, Sprung CL, Arlt W, et al. American College of Critical Care Medicine. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med. 2008;36(6):1937-49.
2. Sosa S, Danilowicz K, Rizzo LFL. Adrenal axis in critical illness. Medicina (Buenos Aires). 2021;81:69-75.
3. Weitzman ED, Fukushima D, Nogeire C, Roffwarg H, Gallagher TF, Hellman L. Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. J Clin Endocrinol Metab. 1971;33:14-22.
4. Carrasco GA, Van de Kar LD. Neuroendocrine pharmacology of stress. Eur J Pharmacol. 2003;463:235-72.
5. Marik PE, Zaloga GP. Adrenal Insufficiency in the critically ill: A new look at an old problem. Chest. 2002;122:1784-96.
6. Annane D, Bellissant E, Sebille V, Lesieur O, Mathieu B, Raphael JC, et al. Impaired pressor sensitivity to noradrenaline in septic shock patients with and without impaired adrenal function reserve. Br J Clin Pharmacol. 1998;46:589-97.
7. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. N Engl J Med. 2003;348:727-34.
8. Hamrahian AH, Oseni TS, Arafah BM. Measurements of Serum Free Cortisol in Critically Ill Patients. N Engl J Med. 2004;350:1629-38.
9. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Crit Care Med. 2013;41(2):580-637.

10. Meyer TJ, Eveloff SE, Bauer MS, Schwartz WA, Hill NS, Millman RP. Adverse environmental conditions in the respiratory and medical ICU settings. Chest. 1994;105:1211-6.
11. Clark PM, Neylon I, Raggatt PR, Sheppard MC, Stewart PM. Defining the normal cortisol response to the short Synacthen test: implications for the investigation of hypothalamic-pituitary disorders. Clin Endocrinol. 1998;49: 287-92.
12. Arafah BM. Review: Hypothalamic pituitary adrenal functions during critical illness: Limitations of current assessment methods. J Clin Endocrinol Metab. 2006;91:3725-45.
13. Arafah BM, Nishiyama FJ, Tlaygeh H, Hejal R. Measurement of Salivary Cortisol Concentration in the Assessment of Adrenal Function in Critically Ill Subjects: A Surrogate Marker of the Circulating Free Cortisol. J Clin Endocrinol Metabol. 2007;92(8):2965-71.
14. Dickstein GE, Arad, Shechner C. Low dose ACTH stimulation test. Endocrinologist. 1997;7:285-93.
15. Annane D, Sebille V, Troche G, Raphael JC, Gajdos P, Bellissant E. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA. 2000;283:1038-45.
16. Mayenknecht J, Diedderich S, Bahr V, Plockinger U, Oelkers M. Comparison of low-dose and high-dose corticotropin tests in patients with pituitary disease. J Clin Endocrinol Metab. 1998;83:1558-62.
17. Siraux V, De Becker D, Yalavatti G, Mélot C, Gervy C, Mockel J, et al. Relative adrenal insufficiency in patients with septic shock: comparison of the low-dose and conventional corticotropin tests. Crit Care Med. 2005;33:2479-86.
18. Loriaux DL, Fleseriu M. Relative adrenal insufficiency. Curr Opin Endocrinol Diab Obes. 2009;16:392-400.

SECTION 9

Trauma Burns

CHAPTER 52

Disaster Preparedness

Simant Kumar Jha, K Swarna Deepak, Sanjay Shah

INTRODUCTION

Millions of people are getting affected each year at local (personal and business) or national level. Golden rule for successfully managing disaster at all levels is to increase awareness and by developing action plans and practice them. Definition of disaster preparedness by UNISDR (United Nations Interventional Strategy and Disaster Reduction, 2009) is the knowledge, capabilities, and actions of governments, organizations, community, groups, and individuals to effectively anticipate, respond to, and recover from impacts of likely, imminent, or current hazards, events, or conditions. Basically preparedness is group activity including individual level activity (such as first aid training, stock piling of equipment, and supplies), community efforts (training and field exercises), government strategies (public information dissemination, evacuation rate, early warning system, and contagious plans.[1]

Disaster is an unplanned event in which available resources are always less compared to the needs of affected community.

CLASSIFICATION OF DISASTER

- Natural disaster, e.g., hurricane, flood, fire, and earthquake.
- Manmade disaster, e.g., acts of terrorism, war, riots, economic blows and collapse (hyperinflation, depression, and recession), and manmade environmental disasters (such as COVID-19 from Wuhan, China).
- Hybrid disasters.

GOALS OF DISASTER PREPAREDNESS

- To reduce damage and deaths
- Reduce personal sufferings
- Speedy and effective recovery

In other words, goals are prevention, protection, mitigation, response, and recovery.

What disaster management aims?
Main aim is to give prompt assistance to victims of disaster and further reducing and avoiding potential losses from hazards.

What is mitigation?
It is building codes and zoning, vulnerability analysis, and public education.

What is preparedness?
It is basically making a plan how to respond. Examples are emergency exercises and preparedness plan along with training and warning system.

What is vulnerability?
The extent of damage likely to be suffered during the disaster on account of various hazard prone features.

Define multiple casualty incidents.
They are situations in which hospital resources are not overwhelmed but strained.

Define mass casualty events.
Disasters are large enough to overwhelm the existing hospital resources.

What is response?
Efforts to minimize the hazards created by a disaster. Examples are search, rescue, and emergency relief.

What is recovery?
Returning the community to normal. Examples are temporary housing, grants, and medical care.

State and local administration has to plan specifically with coordination, training the resources along with regular exercises of plan. There should be a continuous evaluation which provides an opportunity for correction of plan. This should be continuum happening both predisaster and during disaster.

Managers of facilities and security should follow these steps during planning for emergencies. The key five steps that facility and security managers can use to help guide emergency planning are as follows:

1. *Know your risks*: Potential emergencies should be listed first and they should be ranked in order. It is must to know what has to be done and what resources to be utilized? Identification of areas which need investment of resources is important for which risk matrix helps.
2. *Build a team*: Every individual in the organization should be given role of first responder. Inclusive team should be comprising of experts from different departments for making emergency plans.
3. *Make critical information quickly accessible*: Concise plan should be made as per threat and risk. In case of emergency users want to know what is the emergency and what is to be done during emergency? Users want information to be easily accessible and quickly read.
4. *Update your alert and response procedures*: Plans are being made with involvement of everyone knowing what is going to happen and what has to be done? There should be specific plans which can be implanted promptly. Notification tools in form of email, voice, and text blasts are to be used. Whatever language is being used should be clear and easily understood. Notification process will be identified after action and is to be used as a valuable tool for evaluating the plan.
5. *Test the plan*: A series of table tops, drills, and exercises designed are organized what people are expected to know. Two methods are most cost-effective methods.

The first one is lectures and response sessions are meant for educating the personnel so that they can act in case of emergency.

Table tops are good for not only getting information and response action in front of audience but also it is good for stimulating the response from audience and for simulation.

Apex body for managing disaster is National Disaster Management Authority (NDMA) and is headed by the Prime Minister of India. It has five major divisions, viz. policy and plans, mitigation, operations and communications and information and technology, administration, and finance.

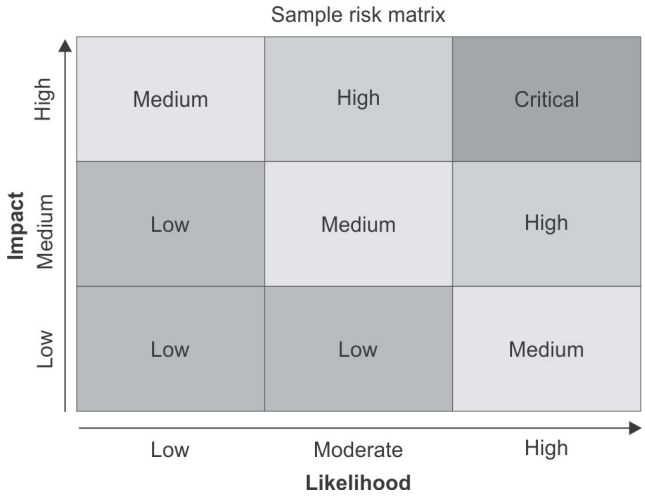


Fig. 1: Sample risk matrix.

The following are the tips suggested by the national institute of health for disaster preparedness:

- Disaster preparedness tips:
  - Preparation of emergency kits is necessary at least 3 days before that includes battery-operated radio or television, medicines, batteries, first aid kit, money, seasonal clothing, and sanitation supplies, flashlight, nonperishable food, and water.
  - Practice drills should be conducted to know the safe location in your house. For any type of emergencies, it should be decided where to reunite again in case of separation. Out of state friends or relatives should be contacted by separated family members to report their whereabouts and condition.
  - First aid and cardiopulmonary resuscitation (CPR) should be learnt from your local Red Cross chapter or other community organizations.
  - In case the lines are damaged, everybody should know how to shut off gas, water, and electricity. Insurance coverage should be up-to-date and should be reflecting present property values. Flood insurance should be checked.
  - Inventory of home contents should be compiled.

  Pictures and/or videos should be made. Safe areas for storage have to be identified.
  - Secure your water heater and major appliances, as well as tall, heavy furniture, hanging plants, picture frames, and mirrors (especially those over beds).
  - Arrangements for pets should be made.
  - Self-sufficient after a disaster is the key thing.

ASPECTS OF PREHOSPITAL PHASE

It can be divided into the following:

- Basic prehospital trauma care
- Advanced prehospital trauma care.

All modern emergency medical services (EMS) system will follow the early ideas of either bringing the patient to physician or bringing physician to patients.

First physician-based EMS was developed in Heidelberg, Germany. The first ground based paramedic system in the USA are often attributed to an article from Irelay in 1967 by Frank Pantridse and John Geddes.

What happens in most EMS system?

- Basic medical provider rush to the patient
- Later more skilled and trained persons arrive.

What first responders do?

- Chest compression
- Automatic defibrillation
- Basic airway management.

Advanced physicians/paramedics can do advanced interventions such as laryngeal mask airway (LMA) insertions. All EMS systems are undergoing changes

over years. In USA, they mostly send paramedics at the scene to do basic procedures.

What are the recent devices for airway management?

- Eschmann elastic bougie
- Supraglottic devices.

Recent development of video-assisted laryngoscopes such as glidescope and CMAC video laryngoscope are being used by prehospital care provider in Netherlands.

What are the new changes?

- Low volume resuscitation
- Revival of tourniquets
- Blood stopping garments.

Circulation

Central venous system has been used in some prehospital system.

ACUTE STRESS REACTION AND POST-TRAUMATIC STRESS DISORDER

Prehospital providers are group of people who are at greater risk of post-traumatic stress disorder (PTSD). EMS system has developed critical incident stress debriefing or meeting. These intervals are meant to manage stress to accelerate the recovering process and to mitigate the impact of traumatic events during debriefing reason. Open climate of communications are vitals along with acknowledgement. All the workers at risk should be identified and should be given early treatment.

DISASTER MITIGATION

Measures that are aimed at reducing the impact of natural or man-made disasters are called disaster mitigation.

Disaster preparedness is an integral part of reducing the impact of the disaster. It aims at measures which need to be adopted by government, organizations, societies, or individuals to respond rapidly and effectively to disaster situations.[2] It includes disaster plans, coordination, training, and optimum utilization of resources. The success of a disaster management depends on how well you are prepared.

Disaster plan should envisage proper coordination between the organizations, local bodies, and government.

Hospitals play a key role in disaster management as they have the primary responsibility of saving lives. When a disaster strikes, the resources in a hospital can get overwhelmed and contingency measures are required to control the event. Also hospitals have to continue with their essential work and return back to normal as early as possible.

Hospital emergency plan is unique to each hospital as it depends on their bed strength, staff, and other resources.[3] Disasters and mass causalities can cause great chaos and inefficiency in hospitals unless properly prepared. In India, small scale hospitals and primary health centers provide primary care while tertiary care is provided at large teaching hospitals. Private sector plays a larger role in tertiary care and a private public partnership is essential in optimum utilization of resources during a disaster. When a disaster strikes, majority of victims will be the walking wounded category, whose care can be delivered at the community health centers and primary care hospitals. This will help in unloading the stress on tertiary care centers. Networking between healthcare centers is essential for a better outcome.

HOSPITAL NETWORKING

Hospital networking means a coordination between various healthcare facilities in a geographical area for optimum utilization of available resources. Hospitals have to be networked for information, materials, manpower, and training.[3]

Components of Hospital Networking

District authorities should take the lead in networking hospitals in a disaster.

A disaster management plan should have two components: (1) Prehospital and (2) Hospital.

1. *Prehospital*: Responsibilities include triaging at the site, providing first aid, and ambulance services.
2. Hospital services should involve primary, secondary, and tertiary care.

The hospital should plan not only for disasters occurring at remote centers but also when the hospital itself is affected by disasters such as flood, earthquake, and fire.

In case of incidents not affecting the hospital, the goals should be to:

- Increase the surge capacity
- Providing care to patients being received
- Ensure proper ongoing treatment for all those who are already inpatients
- Providing adequate medications, dressing material, and medical equipment.

The disaster plan should clearly mention the roles, responsibilities, and limitations of each team, and a proper hierarchy should be followed. Hospitals should have a written document as policy.

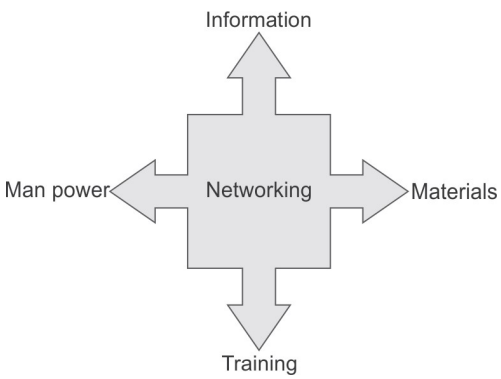


Fig. 2: Hospital networking.

Planning Phase/Predisaster Phase: Components

- *To create a disaster management committee*: To create a new centralized emergency/disaster tackling committee. If there is a pre-existing command center in hospital, it has to be used effectively.

Staffing of the committee should be adequate.

- Defining roles of each healthcare personnel and creation of job cards.
- Command control system creation:
  - Can be closed down once the emergency time is over.
  - Creates a predictable chain of command.
  - Creates a flexible and prioritized response to emergencies.
- Identification of specific treatment areas and creation of a mean arterial pressure (MAP) with locations and capacity of each area.
  - Central command office
  - Office for communications
  - External and internal security office
  - Reception and triage area
  - Area for decontamination
  - Place for handling minor injuries
  - Emergency room (ER) (for acute care of casualties)
  - Definitive treatment areas (operation theaters and wards)
  - Intensive care unit (ICU) and high-dependency unit (HDU) areas for managing critical patients
  - Mortuary
  - Area for relatives of casualties
  - Media briefing area
  - Grieving/counseling area.

If the capacity of the area is more than required, the color of area should be changed.

- *Support services such as laboratory and radiology*: Need for extra resources both in the form of skilled persons, equipment etc., has to be anticipated.
  Respective head of the services has to be the leader and will report the hospital medical head.
- Nursing services
- Logistics (dietary service, sanitation, transport, electricity, water supply).
- Security and crowd management
- *Media and public relations center*: Only a specific spokesperson has to address the media on behalf of the hospital.
- Documentation
- Mortuary:
  - Disaster tag should be attached to all the victims who are dead on arrival.
  - Details of all the bodies are to be meticulously maintained and relayed back regularly.
- Personnel planning:
  - *Medical staff*: Clinical, pre-, and paraclinical staff details and duty roster have to be maintained at medical head's and nursing head's office.
  - *Ancillary staff*: Duty roster of ancillary staff in laboratories, blood bank, housekeeping, etc., should be available with hospital operations head.
  - *Volunteers and reserved staff*: Details and possible skills of the volunteers, reserve staff have to be maintained in case of major disasters.
- Education and training staff:
  - Training in basic resuscitation skills
  - Training and regular drills in disaster management plan of the hospital
  - Training in roles and responsibilities as well as knowing their job card description.
- Disaster drills:
  Regular conduction of disaster drills in hospital's staff builds up confidence in the staff and avoids confusion when the actual disaster strikes.

Disaster Phase

- *Activation plan*: Notification of emergency and activation of chain of command.

Incident Command System and Incident Commander

Incident commander need not be a medical person but anyone who has the leadership qualities to coordinate and command multiple departments of hospital during disaster.

Incident commander is the most competent person in the hospital and reports directly to the hospital administration.

Incident Staff

Incident staff consists of seven positions who provide the manpower and resources to incident commander during disaster.

- *Operations chief*: Heading all patient care services such as medical care, ancillary care, and human services.
- *Logistics chief*: Heads all support services such as communication, transportation, food/beverage, sanitation, water, and electricity.
- *Planning chief*: Heads the medical, nursing, and allied staff planning.
- *Public relations officer*: Heads the external communication with relatives, media, and government.
- Fire and security chief
- Finance chief
- *Liaison chief*: Coordinates between police, defense, ambulance services, other hospitals, and blood banks.

Operational Phase

Tackling emergencies in mass casualty events according to pre-existent disaster plan.

Different Types of Hospital's Responses

- *Intrahospital response phase*: Minor multicasualty incident, which can be managed at regular ER by mobilizing internal resources.
- *Out of hospital phase*: Major casualty event where hospital space and resources are overwhelmed. Needs opening up of new areas as well as extra staff. Creates a strain on the regular workflow.
- *Catastrophic disorder*: Hundreds of casualties start to arrive after events such as earthquakes and bombings, where government and external resource's help needs to be taken.

Deactivation Plan (Phase of Demobilization)

Activated once the incident command center in hospital is satisfied that the disaster is subsided. Deactivation should be very meticulous as once the disaster plan is deactivated, it is very difficult to reactivate it.

HAZARD IDENTIFICATION

Hazard identification involves determining the specific risks a particular geographical area or healthcare provider is prone to. This ensures a realistic and relevant approach targeted to the specific area.

Hazard vulnerability analysis (HVA) provides a systematic approach to estimate the demand healthcare provider is subjected to in case of a disaster and their ability to provide it.

Disaster planning starts with HVA to assess the most probable hazards for a hospital.

A comprehensive disaster plan should consider all hazards.

Early warning systems to forecast and predict a hazard are the first component of disaster management.

A disaster can occur at any time and the response has to be implemented as per the plan built earlier.

When a disaster alert is received by the hospital, a designated person should have the responsibility to trigger the incident response system. It should be considered that when a disaster strikes the hospital is already running in its full capacity and should be able to accommodate the patients over and above its normal capacity.

Surge capacity: It is the ability of a hospital to expand beyond capacity to provide services for the increased demand. It should be addressed early in the planning.[4]

An *emergency operation center (EOC)* has to be established and the policies and procedure on incident response system has to be implemented.[5] EOC should actively coordinate the emergency operations. Clear, accurate, and timely communication should be maintained and systems should be in place to support the information exchange among authorized personnel.

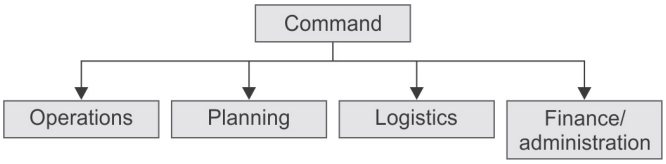


Fig. 3: Organizational structure of incident command system.[5]

A senior person who preferably has an experience in managing a disaster should be the incident commander.

SAFETY AND SECURITY

Designated security team should be in place. Identify areas which are more vulnerable. Ensure the control of patient, relatives, vehicle flow, parking, and crowd control. System should be in place to secure the valuable items which the patients might have. Ensure that policies on hospital evacuation are clearly defined.

TRIAGE

Triage is defined as process of sorting out and it is actually a *dynamic* decision-making process for the management of maximum number of patients with available resources. It is the quite important and challenging aspect of disaster management, both in the prehospital and hospital phases. Disaster triage is significantly different from conventional triage on daily basis of emergency department. The objective and challenge of disaster triage is to screen the *small minority* of patients who require urgent lifesaving intervention including damage control surgery, from the larger majority of noncritical casualties. Immediate priority is given to critical patients with greatest chance of survival with least resources and time. Literature shows that among the victims, up to 15–25% patients are injured critically. Under triage and over triage are triage errors which will always be present in the chaotic atmosphere of mass casualty events.[6] Under triage is finding the critically injured victims who require immediate care to a delayed category which in turn leads to delayed treatment with higher mortality and morbidity. Over triage is finding the noncritical survivors with almost no life-threatening injuries to immediate or urgent care. With increasing incidence of over triage, the medical system will be more overwhelmed with resulting increase in mortality and morbidity. It is very controversial that how much is the acceptable level of over/under triage in a disaster and what is the best method for evaluation of triage effectiveness.

Levels of Triage

There are three levels of triage for medical disaster and the level of disaster triage used at any phase of the disaster usually depends on the ratio of victims to capabilities. Many disasters or mass casualty incident (MCI) will have multiple levels of triage as patients move from actual disaster scene to definitive medical care.

Field triage (level 1) is process of identifying patients who potentially require immediate care at disaster scene. Victims are divided in two categories as "acute" or "nonacute." In most of settings, color coding is being used.

Medical triage (level 2) is the process of identifying patients by senior most or experienced healthcare provider at entry point or collection site which may be fixed or mobile site.

Patients are classified into the following categories:

- *Red (urgent)*: Who requires lifesaving interventions (airway, breathing, and circulation) are required.
- *Yellow (delayed):* Who have potential life-threatening injury and can deteriorate if timely treatment not given.
- *Green (minor)*: Who has minor injury (walking wounded) with minimal or no medical care or psychological support.
- *Black*: Deceased victims
- *Gray/blue*: It is defined for the "expectant" category of patients which is unique to MCIs. These are not expected to survive due to the severity of injuries or underlying comorbidities and they eat away significant resources. Classification of the expectant category of disaster victims remains controversial and in most of centers, it has been proposed based on severity of injury, age, underlying diseases, and hemodynamic stability of victims at scene.

Evacuation triage (level 3) is usually a neglected area of disaster preparedness. Using same color coding classification, priorities for transfer to hospital facilities are assigned to disaster victims.

HUMAN RESOURCES

Effective human resource management is essential during a disaster.

LOGISTICS

A system should be in place to ensure continuous supply of medicines, dressing materials, and equipment by agreement with vendors. Adequate stores of linen, medical, and surgical items should be stored in causality marked as disaster store and should be opened only when disaster alert is activated. All nonessential services might need to be postponed.[7]

Disaster plans should be made in close association with the financial advisors of the hospital to make it cost effective.

Postdisaster recovery plan can help mitigate the impact on continuity of business and should be a part of disaster preparedness.

Disaster preparedness should have drills including table top ones to identify opportunities for improvement.[8]

CONCLUSION

All hospitals should have an emergency response plan which should be reviewed on a regular basis with practice drills. Planning, resource utilization, and allocation are vital to successful management of disasters.

Adequate preparedness and community awareness before the striking of the disaster will reduce its impact and many lives can be saved during the initial hours after the disaster has occurred.

REFERENCES

1. Elizabeth F, Cecep S, Duncan T. Effect of natural disaster on mortality risks over the longer term. Nat Sustain. 2020;3:614-9.
2. Government of Kerala. (2018). Hospital Disaster Management Guidelines, DHS. [online] Available from: https://dhs.kerala.gov.in/wp-content/uploads/2020/08/hdmg_18082018.pdf. [Last accessed February 2022].
3. Government of India. Guidelines for hospital emergency preparedness planning GOI- UNDP DRM programme 2002-2008. [online] Available from: http://asdma.gov.in/pdf/publication/undp/guidelines_hospital_emergency.pdf. [Last accessed February 2022].
4. World Health Organization. Hospital Emergency Response Checklist, WHO Manual 2011. [online] Available from: https://www.who.int/docs/default-source/documents/publications/hospital-emergency-response-checklist.pdf. [Last accessed February 2022].
5. Queensland government disaster management guidelines 2021. [online] Available from: https://www.disaster.qld.gov.au/dmg/Documents/QLD-Disaster-Management-Guideline.pdf. [Last accessed February 2022].
6. The Capacity Project. (2011). Human resources for healthcare action frame work. [online] Available from: https://www.capacityproject.org/framework/. [Last accessed February 2022].
7. World Health Organization. (2006). Handbook of supply management at first level healthcare facilities. [online] Available from: https://www.who.int/management/resources/procurement/handbookforsupplymanagement.pdf?ua=1. [Last accessed February 2022].
8. Briggs SM. Advanced Disaster Medical Response Manual for Providers, 2nd edition. Woodbury, CT: Cine-Med Publishing, Inc; 2014.

CHAPTER 53

Severe Head Trauma

HR Rajathadri, Sulagna Bhattacharjee, Raymond Dominic Savio

INTRODUCTION

Traumatic brain injury (TBI) is one of the leading causes of morbidity and mortality globally. It leads to severe disability and escalating cost of care. Treatment goals largely focus on prevention of secondary injury, and need to be individualized and multimodal. Increasing age at presentation, frailty, comorbidities, and non-neurological complications add intricacy to the care of these patients.

DEFINITION

Traumatic brain injury is defined as a disruption in the normal function of the brain that can be caused by a bump, blow, or jolt to the head, or a penetrating head injury.[1]

EPIDEMIOLOGY

India has the highest rate of head injury and attributable mortality in the world, according to data from Indian Head Injury Foundation. 60% of head injuries are from road accidents. Fall from height accounts for 20–25% and violence, 1% of TBIs. The incidence is underestimated in low- and middle-income countries (LMIC) due to paucity of data. The mean age of patients with TBI is lower in LMIC compared to high-income countries (HIC), leading to higher disability adjusted life years (DALYs).

CLASSIFICATION

Traumatic brain injury is traditionally classified based on Glasgow coma scale (GCS) into mild (13–15), moderate (9–12), and severe (≤8) **(Table 1)**. However, GCS is affected by factors such as sedation, intoxication, intubation, and facial injury affecting eye opening, despite being well validated in TBI. The Full Outline Responsiveness Score (FOUR SCORE) can be used to overcome the confounding issues with GCS in trauma **(Table 2)**.[2] The GCS-P **(Table 3)**, which incorporates pupillary assessment, has also been shown to be useful in gauging mortality.[3] The morphological classification of TBI is outlined in **Flowchart 1**.

PATHOPHYSIOLOGY

The pathophysiology revolves around primary and secondary injuries.

Primary Injury

Primary injury happens from the external force causing disruption of intracranial contents.

Secondary Injury

Secondary injury follows primary injury and leads to further brain damage, morbidity, and mortality **(Table 4)**.

TABLE 1: Glasgow coma scale.

	Not testable (NT)	***1***	***2***	***3***	***4***	***5***	***6***
Eye opening	For example, severe trauma to the eyes	Does not open eyes	Opens eyes in response to pain	Opens eyes in response to voice	Opens eyes spontaneously	N/A	N/A
Verbal response	For example, intubation	Makes no sounds	Makes sounds	Words	Confused, disoriented	Oriented, converses normally	N/A
Motor response	For example, neuromuscular paralysis	Makes no movements	Extension to painful stimuli	Abnormal flexion to painful stimuli	Flexion/ withdrawal to painful stimuli	Localizes painful stimuli	Obeys command

TABLE 2: Full outline responsiveness score (FOUR SCORE).

Points	*Eye response*	*Motor response*	*Brainstem reflexes*	*Respiration*
4	Eyelids open or opened, tracking, or blinking to command	Thumbs-up, fist, or peace sign	Pupil and corneal reflexes present	Not intubated, regular breathing pattern
3	Eyelids open but not tracking	Localizing to pain	One pupil wide and fixed	Not intubated, Cheyne–Stokes breathing pattern
2	Eyelids closed but open to loud voice	Flexion response to pain	Pupil or corneal reflexes absent	Not intubated, irregular breathing
1	Eyelids closed but open to pain	Extension response to pain	Pupil and corneal reflexes absent	Breathes above ventilator rate
0	Eyelids remain closed with pain	No response to pain or generalized myoclonus status	Absent pupil, corneal, and cough reflex	Breathes at ventilator rate or apnea

TABLE 3: GCS (Glasgow Coma Scale)-P.

GCS-P = GCS – PRS (Pupil reactivity score)	
Pupils unreactive to light	***Pupil reactivity score***
Both pupils	2
One pupil	1
Neither pupil	0

TABLE 4: Common causes of secondary brain injury.

S. no.	*Secondary brain insult*
1	Edema and elevated intracranial pressure
2	Loss of cerebral autoregulation, increasing vulnerability to hypotension or hypertension
3	Seizures
4	Vasospasm
5	Paroxysmal sympathetic hyperactivity as a driver of fever and autonomic instability

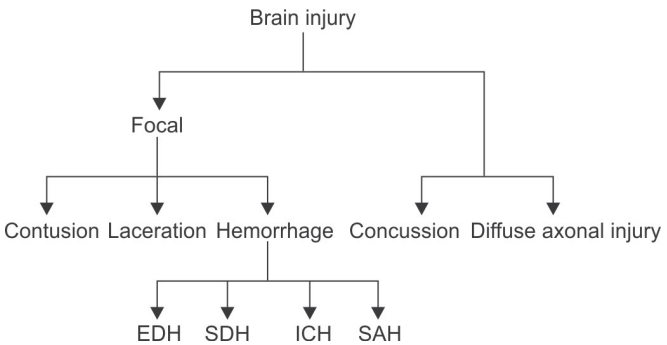
Management strategies typically focus on prevention and management of secondary brain injury.

CEREBRAL AUTOREGULATION

Three mechanisms **(Fig. 1)** control brain autoregulation which are as follows:

- *Neurogenic*: Cerebral vasculature is extensively innervated. The autonomic nervous system controls cerebral blood flow (CBF) by altering the tone of vessels.
- *Myogenic*: This maintains CBF irrespective of blood pressure, between a mean arterial pressure (MAP) range of 70–150 mm Hg. Increase in MAP produces cerebral vasoconstriction and vice versa.
- *Chemical*: Cerebral metabolic rate (CMR), PaO_2 and $PaCO_2$ have direct relationships affecting the CBF. An increase in CMR and $PaCO_2$ or a decrease in PaO_2 cause increase in CBF and vice versa. These mechanisms however have an operational threshold range. Changes in CBF directly alter the intracranial pressure (ICP).

Flowchart 1: Morphological classification of traumatic brain injury (TBI).



(EDH: epidural hematoma; ICH: intracerebral hemorrhage; SAH: subarachnoid hemorrhage; SDH: subdural hematoma)

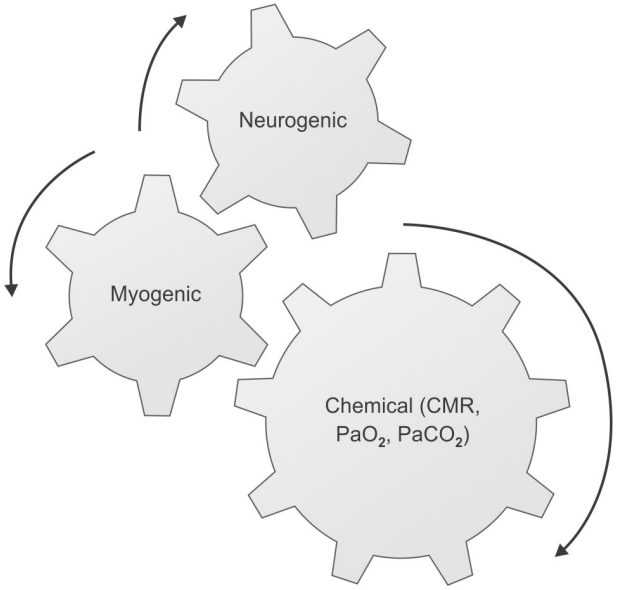


Fig. 1: Mechanisms regulating cerebral blood flow. (CMR: cerebral metabolic rate)

Moreover, this relation is time-dependent and gets attenuated after 12–14 hours due to changes in pH of the brain.[4]

INITIAL EVALUATION AND MANAGEMENT

Prehospital Management

This includes prevention and treatment of common insults that could trigger secondary brain damage, notably, hypoxia, hypotension, and spine destabilization. Standard protocols are to be deployed in the management of airway, breathing, and circulation with frequent monitoring for signs of red alert. Care should be taken to avoid hypo/hyperventilation. 0.9% saline is preferred for volume resuscitation. All patients should have cervical spines stabilized with a hard cervical collar until cervical spine injury is ruled out.

Emergency Department Management

Initial Management

The advanced trauma life support (ATLS) protocol for assessment and stabilization of trauma victims[5] is to be followed **(Table 5)**. Further elaboration on this content is beyond the scope of this document.

Antifibrinolytic Therapy

Use of tranexamic acid within 3 hours of injury in the CRASH-3 trial was associated with a mortality benefit in patients of moderate TBI, but not severe TBI. A dose of 1 g over 10 minutes followed by 1 g administered over 8 hours is therefore to be considered, as it is inexpensive and evidence based.[6]

Neuroimaging

Noncontrast computed tomography (CT) scan is the preferred modality for initial neuroimaging in TBI. This can ascertain the type of injury and need for life-saving surgical interventions.

TABLE 5: Advanced trauma life support (ATLS) elements for initial assessment.[5]

S. no.	Elements
1	Preparation
2	Triage
3	Primary survey (ABCDE) with immediate resuscitation of patients with life-threatening injuries
4	Adjuncts to primary survey and resuscitation
5	Consideration of the need for patient transfer
6	Secondary survey (head-to-toe evaluation and patient history)
7	Adjuncts to the secondary survey
8	Continued postresuscitation monitoring and re-evaluation
9	Definitive care

INTENSIVE CARE MANAGEMENT

Hemodynamic Management

- *Blood pressure*: Target systolic blood pressure (SBP) of ≥100 mm Hg for patients 50–69 years of age and ≥110 mm Hg for patients 15–49 and >70 years of age is recommended by Brain Trauma Foundation (BTF) guidelines.[7] This can be achieved using vasopressors and/or fluid resuscitation. However, a more rationale target would be the cerebral perfusion pressure (CPP).
- *Fluids*: 0.9% saline is recommended for patients with TBI. Other balanced salt solutions are relatively hypotonic and can increase cerebral edema. Potential harm from use of other balanced salt solutions was observed in the TBI subgroup of BASICS trial.[8] Similarly, albumin is contraindicated in patients with TBI as it was shown to increase mortality in SAFE trial.[9]
- *CPP*: A target CPP between 60 and 70 mm Hg is recommended by the BTF guidelines. Targeting a higher CPP >70 mm Hg has been associated with a higher risk of acute respiratory distress syndrome (ARDS).[7] In patients with TBI, autoregulatory capacity for maintaining CPP is compromised. Therefore, it becomes prudent to reduce raised ICP in order to optimize CPP rather than targeting a higher MAP, as this could worsen cerebral edema.[10]

Ventilatory Management

It is imperative to target normoxia and normocapnia. Both, high and low levels of PaO_2 and $PaCO_2$ are detrimental. Hyperventilation for control of ICP is recommended only for a short duration of time. Observational studies have shown that lung protective ventilation (LPV) is safe in TBI and there is no significant impact of high or low positive end-expiratory pressure (PEEP) on ICP. Very small observational reports of TBI patients with ARDS undergoing prone position ventilation have documented an improvement in CPP despite an increase in ICP.[11]

Antiseizure Prophylaxis

Brain Trauma Foundation guidelines recommend prophylaxis for early seizures (within 7 days of TBI) but not for late seizures (beyond 7 days from TBI).[7] Albeit levetiracetam is not superior to phenytoin for this purpose,[12] it is emerging as a preferred choice based on evidence for better long-term outcomes compared to phenytoin. **Table 6** enumerates the risk factors for seizures in TBI.

Anticoagulant Management

Therapeutic anticoagulation should be reversed using appropriate blood products, antidotes, or chelating agents.

TABLE 6: Risk factors for seizures in traumatic brain injury (TBI).

Early seizures (≤7 days)	*Late seizures (>7 days)*
Intracranial hematoma	Intracranial hematoma
Focal neurological signs	Early seizures, especially when delayed
Post-traumatic amnesia >24 hours	Post-traumatic amnesia >24 hours
Any neurological signs	At least one nonreactive pupil
Depressed skull fracture	Depressed skull fracture
Subarachnoid hemorrhage	Dural penetration
Injury before 5 years of age	Injury after 16 years of age
Linear skull fracture	Glasgow Coma Scale score of 3–8
	Time to following commands of a week or more

While traditional platelet count target is ≥80,000 cells/cu mm, a recent trial showed a higher risk of hematoma expansion with counts ≤135,000 cells/cu mm.[13] There is no role for routine platelet transfusion in patients consuming antiplatelet drugs.[14] Thromboelastogram (TEG) can be used to optimize transfusion practice.

Thromboprophylaxis

Mechanical thromboprophylaxis should be initiated in all patients in the absence of significant limb trauma. Pharmacoprophylaxis can be initiated after 24 hours in the absence of contraindications or hematoma expansion.[15]

Temperature Management

Hypothermia and hyperthermia should be avoided. BTF guidelines recommend avoiding prophylactic hypothermia to reduce ICP. The Eurotherm trial demonstrated higher mortality and more harm in survivors who underwent hypothermia.[16] Also, the POLAR trial did not demonstrate any significant difference in improved neurological outcomes with institution of prophylactic hypothermia in severe TBI patients.[17]

Nutrition

Brain Trauma Foundation guidelines recommend achieving target caloric requirement by days 5–7 post injury.

Steroids

Contraindication to steroids for TBI is the only level 1 recommendation in BTF guidelines based on the CRASH trial.[18]

Infection Prophylaxis

Brain Trauma Foundation guidelines suggest early tracheostomy and antibiotic impregnated external ventricular drain (EVD) catheters to reduce risk of nosocomial infections.

TABLE 7: Standard protocols for raised intracranial pressure (ICP).

S. no.	*Protocol*
1	Head end elevation of bed
2	Neck in neutral position
3	Avoiding tight collars for the neck
4	Analgesia to decrease pain
5	Sedation to decrease ICP
6	Endotracheal intubation and ventilation
7	Normocapnia and avoiding hypoxia
8	Avoiding hyponatremia

Intracranial Pressure Management

Standard protocols for patients with high ICP are listed in **Table 7**.

Impending Herniation

Patients with signs of impending herniation such as anisocoria, irregular respiration, or Cushing triad should undergo emergent re-evaluation with neuroimaging and other standard protocols together with osmotherapy/surgical intervention where appropriate. The Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC) management algorithm for patients with ICP monitoring is outlined in **Flowchart 2**.

Intracranial Pressure and Cerebral Perfusion Pressure Monitoring

For reasons discussed earlier, it is prudent to reduce ICP rather than increase MAP to optimize CPP, in a setting of raised ICP. This therefore warrants measuring ICP and CPP in all patients with severe TBI to improve outcome. While the gold standard for ICP monitoring is through an EVD, this is associated with a risk of bleeding and infection. Nonetheless, it carries the therapeutic advantage of CSF drainage for reducing ICP. Other means of ICP monitoring include intraparenchymal catheters, subdural bolt, and epidural bolt with their individual advantages and limitations.

Despite the BEST TRIP randomized controlled trial (RCT)[20] showing no difference in mortality between groups where ICP was either measured or clinically judged, the BTF guidelines recommend ICP monitoring based on observational studies which demonstrated benefit.

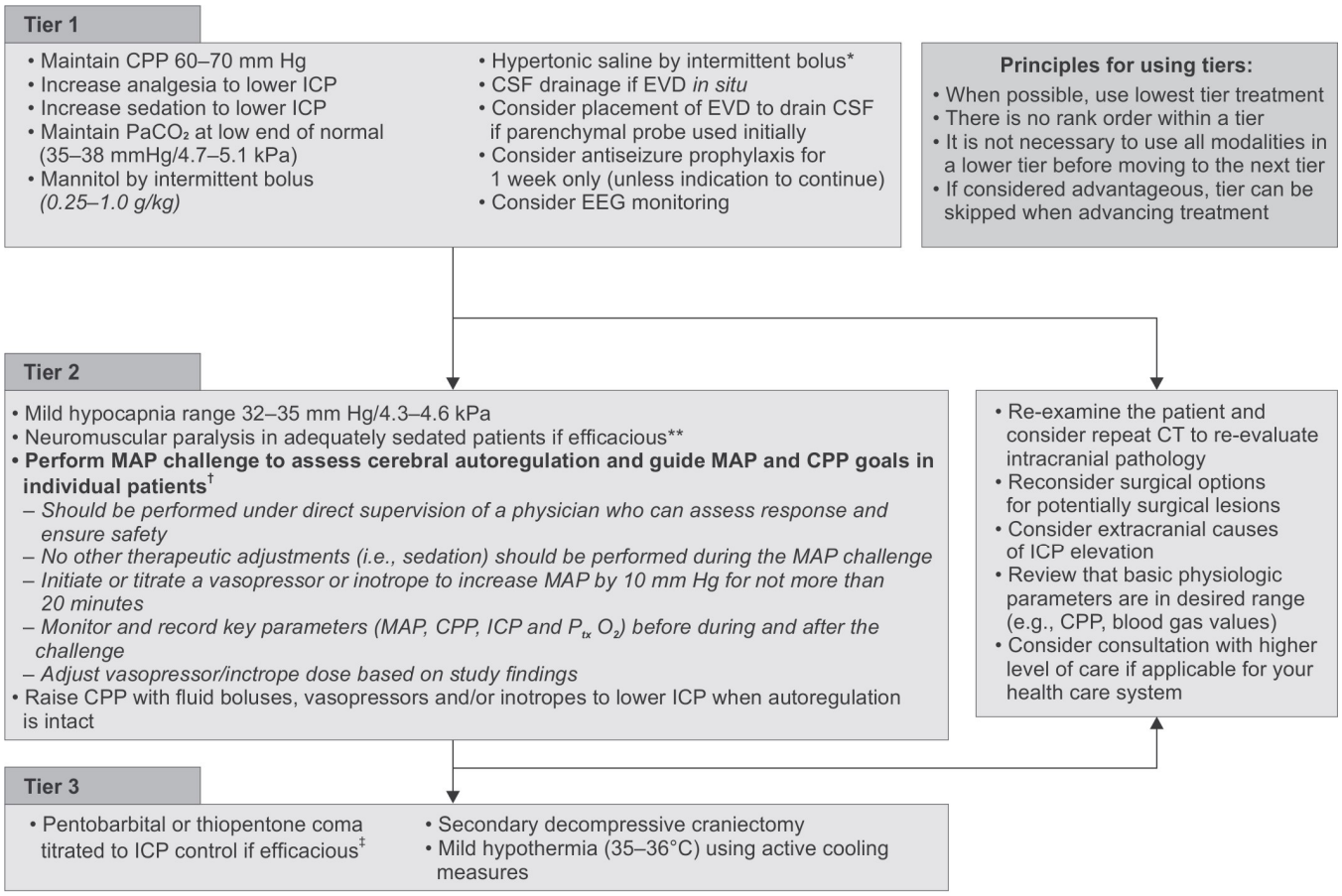
Cerebrospinal Fluid Drainage

Using an EVD, CSF can be drained to control ICP. Continuous drainage is preferred over intermittent drainage.[7]

Analgesia and Sedation

Adequate analgesia and sedation is crucial to prevent and treat raised ICP, in the face of pain from concomitant injuries

Flowchart 2: Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC) management algorithm for patients with intracranial pressure (ICP) monitoring.[19]



* We recommend using sodium and osmolality limits of 155 mEq/L and of 320 mEq/L respectively as administration limits for both mannitol and hypertonic saline

** We recommend a trial dose of neuromuscular paralysis and only proceeding to a continuous infusion when efficacy is demonstrated

† Rosenthal G. et al 2011

‡ Barbiturate administration should only be continued when a beneficial effect on ICP is demonstrated
Titrate barbiturate to achieve ICP control but not exceed the dose which achieves burst suppression
Hypotension must be avoided when barbiturates are administered

(CPP: cerebral perfusion pressure; CSF: cerebrospinal fluid; CT: computed tomography; EEG: electroencephalogram; ICP: intracranial pressure; EVD: external ventricular drain; MAP: mean arterial pressure)

and interventions. A careful choice of agent such as opioid analgesic, general anesthetic, or α2-agonist with meticulous titration to desired end-points and watchful attention to hemodynamic and other adverse effects is vital to successful management. Neuromuscular paralysis can be considered as a tier-2 strategy for control of refractory ICP.[7]

Osmotherapy

Mannitol and hypertonic saline (HS), when infused, increase serum osmolality and dehydrate the brain, causing a reduction in ICP. There is no evidence for superiority of one over the other. When administered at equal osmotic loads, both reduce ICP to a similar magnitude.

Mannitol is dosed at 0.5–1 g/kg/dose (infused over 30 minutes and repeated q 6–8 hours if needed) with a target osmolality not greater than 320 mOsm/L. There is a theoretical risk of mannitol extravasation inside brain tissue and aggravation of cerebral edema, as its reflection coefficient is 0.9, compared to HS. Cardiac, renal, and pulmonary functions and fluid-electrolyte status are to be carefully monitored during therapy.

Hypertonic saline infusion should target a serum sodium not exceeding 155 mEq/L. Common side effects include hypernatremia and normal anion gap metabolic acidosis. Unlike mannitol, it does not cause hemodynamic disturbance and can be used in patients with hemodynamic instability and renal dysfunction.

Hypothermia

Hypothermia can be considered as a tier-3 therapy for refractory ICP. There is however insufficient evidence for the benefit of hypothermia in TBI.

Decompressive Craniectomy

This is to be considered as a last resort to control refractory ICP. Large bifrontal decompressive craniectomy is recommended over small decompressive craniectomy.[7] The DECRA and RESCUEicp trials for decompressive craniectomy demonstrated more unfavorable outcomes and higher rates of vegetative state respectively despite reducing ICP.[21,22]

Minimally Invasive Surgery

There is growing experience in the field of minimally invasive surgery (MIS) for conditions such as supratentorial intracerebral hemorrhage (ICH) using stereotactic and endoscopic approaches. Careful selection of patients has the potential for improving outcomes.

Multimodality and Advanced Monitoring in Traumatic Brain Injury

Considering the lack of high-quality evidence for ICP monitoring and given the physiological benefits of an ICP-driven strategy, the concept of multimodal monitoring (MM) and integration of data to arrive at treatment plan has surfaced.[23] Some of the parameters included in MM are as follows:

- *Clinical monitoring*: Using GCS and FOUR score to assess brain function.
- *ICP monitoring*: Using invasive techniques.
- *Cerebral autoregulation monitoring*: This is assessed by observing the variation of ICP with MAP. Pearson's correlation coefficient is used to obtain the pressure reactivity index (PRI) which varies between –1 and +1. In normalcy, the coefficient and PRI have a negative value, indicating an inverse relation between MAP and ICP. Plotting the PRI against CPP results in a U-shaped curve in many patients, and the point where the PRI is most negative, corresponds to the optimal CPP. This helps estimate the CPP range at which autoregulatory capacity is most preserved in that injured brain.
- *Transcranial Doppler (TCD)*: While primarily used in SAH to monitor CBF and detect vasospasm, it is also useful to monitor blood flow in TBI. Treatment response, CO_2 reactivity and pressure reactivity can be assessed by observing the trend in CBF. Although it is noninvasive, inexpensive, and can be done at the bedside, it has a high interobserver variability.
- *Jugular venous oximetry*: A vascular catheter placed in a retrograde manner, with the tip of the catheter lying in the jugular bulb, is used for this purpose. The tip has a sensor which measures real-time oxygen saturation. This can be used as a surrogate measure for global CBF. The normal range is between 55 and 75% and a decrease in saturation is associated with worse prognosis.
- *Brain tissue oxygen partial pressure ($PbtO_2$)*: This consists of focal tissue oxygen content measurement using a probe placed in the subcortical white matter of the brain. Normal value ranges between 20 and 40 mm Hg. $PbtO_2$ <20 mm Hg is considered ischemia of the brain and is associated with poor prognosis in observational studies.
- *Cerebral microdialysis*: The concentrations of clinically relevant molecules are measured using a catheter with semipermeable membrane inserted into the brain parenchyma. A high lactate:pyruvate ratio is used as a marker for cerebral ischemia in the presence of low pyruvate levels. This can also be used as an endpoint for optimizing cerebral perfusion. Similarly, a high glutamate level measured through microdialysis catheter is a marker of excitotoxicity and hypoxia/ischemia.
- *Electroencephalogram (EEG)*: There is a high incidence of nonconvulsive seizures in patients with TBI and EEG aids in its detection, and optimization of anticonvulsant therapy. It is a resource intensive monitoring, requiring specialized equipment and personnel. Invasive EEG is sometimes done using subdural electrodes to monitor seizures that are not seen with scalp electrodes.
- *Automated infrared pupillometry (AIP)*: This modality uses an infrared light-emitting diode and allows for magnified view of the pupils and accurate assessment of variables such as size, latency, constriction velocity, and dilation velocity. These measurements are compared against a normative model of pupil reaction to light and automatically graded to provide a neurological pupil index (NPI) on a scale of 0–5 (<3 is considered abnormal).[24] The need for additional equipment and infrastructure precludes its routine use.
- *Ultrasonography (USG)*: Bedside USG finds several applications in the noninvasive assessment of ICP such as optic nerve sheath diameter (ONSD) estimation, pupillary assessment especially when the eyelids cannot be opened, two-dimensional (2D) brain USG, cerebral midline shift measurement, and TCD. The ONSD estimation in particular has shown great correlation with ICP and treatment changes.[24]

BIOMARKERS IN TRAUMATIC BRAIN INJURY

Calcium-binding protein S-100β, glial fibrillary acid protein, and ubiquitin C-terminal hydrolase-L1 are among the most studied biomarkers in TBI for prognostication. Direct measurement from parenchyma or CSF will result in better assessment of biomarkers; however, this is cumbersome and does not allow for serial measurements. Therefore, serum levels of the above markers are measured. The utility of absolute levels, time from injury, and serial values to predict severity of injury and the need for

TABLE 8: Summary of pivotal trials in traumatic brain injury (TBI).

Trial name	*Total number of patients*	*Intervention(n)*	*Control (n)*	*Intervention mortality*	*Control mortality*	*Outcome measure (95% CI)*	*Conclusion*
CRASH-3[6]	10,127	Tranexamic acid (TA)	Placebo	18.5%	19.8%	RR 0.94 (0.86–1.02)	TA within 3 hours of TBI reduces mortality
CRASH[18]	3,020	Methylprednisolone	Placebo	21.1%	17.9%	RR 1.18 (1.09–1.27)	Steroids should not be used to TBI
EUROTHERM[16]	2,498	Hypothermia (32–35°C)	Standard treatment	34.9%	26.6%	RR 1.45 (1.01–2.10)	Therapeutic hypothermia did not result in better outcome in TBI
POLAR[17]	500	Hypothermia (35°C)	Normothermia (36.5–37.5°C)	21.1% (at 6 months)	18.1% (at 6 months)	RR 1.15 (0.80–1.64) P = 0.45	Primary outcome favorable Glasgow Outcome Score Extended (GOSE) 5–8 not significantly different
BEST TRIP[20]	324	Intraparenchymal ICP monitor guided treatment	Clinical and image-guided treatment	56%	53%	OR 1.09 (0.74–1.58)	ICP monitoring guided treatment did not result in better outcome
DECRA[21]	155	Decompressive craniectomy (DC)	Standard treatment	19.1%	18.29%	Risk of unfavorable outcome OR 2.21 (1.14–4.26)	Early bifrontal DC reduced ICP and ICU LOS but with increased unfavorable outcomes
RESCUE ICP[22]	409	DC	Standard treatment	26.9%	48.9%	Absolute difference −22.1 (−31.5 to −12.7)	DC resulted in lesser mortality but with higher vegetative state

(CI: confidence interval; ICP: intracranial pressure; ICU: intensive care unit; LOS: length of stay; OR: odds ratio; RR: relative risk; TA: total anesthesia; TBI: traumatic brain injury)

surgical intervention are under research. The high cost and nonavailability of these biomarker tests, and the lack of evidence confer upon them only an experimental role at present.[25]

A summary of the landmark trials concerning severe traumatic brain injury has been given in **(Table 8)**.

NON-NEUROLOGICAL COMPLICATIONS IN TRAUMATIC BRAIN INJURY

Several non-neurological complications associated with TBI often aggravate the course of stay in ICU. These include, and are not limited to sepsis, acute kidney injury (AKI), ARDS, bleeding or coagulation abnormalities, electrolyte disturbances, shock requiring vasopressors, stress cardiomyopathy, dysautonomia, hypothalamic–pituitary–adrenal (HPA) axis dysfunction, etc. All precautions are to be taken to foresee and avoid such complications as they are expected to adversely impact the course of TBI. The description of careful choice of auxiliary treatment strategies such as continuous renal replacement therapy (CRRT) over intermittent modalities and antibiotics with a low seizure profile is beyond the scope of this document and needs to be borne in mind.

REHABILITATION AFTER TRAUMATIC BRAIN INJURY

There is enormous focus lately, on the importance of early rehabilitation of the critically ill patient with TBI. While there could be several impediments including care-provider's attitude, every effort must be taken to identify the suitable patient at the optimal time for the appropriate strategy. Preliminary observations have established the feasibility of early mobilization using simple maneuvers such as chair sitting to the more resource consuming techniques such as the standard and ERIGO tilt table.[26] Spasticity is another long-term complication which can be prevented by the use of baclofen, botulinum toxin injection, serial casting etc. where appropriate.

CONCLUSION

Traumatic brain injury presents several unique challenges to the patient, clinician, and the society. A careful understanding of pathophysiology and ethical application of evidence-based practice is paramount to improving meaningful outcomes. The future beholds several promises in terms of better evidence, newer monitoring modalities, and artificial intelligence. Nonetheless, one may also imagine the complexity of the disease to compound!

REFERENCES

1. Pervez M, Kitagawa RS, Chang TR. Definition of traumatic brain injury, neurosurgery, trauma orthopedics, neuroimaging, psychology, and psychiatry in mild traumatic brain injury. Neuroimaging Clin North Am. 2018;28(1):1-13.
2. Wijdicks EF, Bamlet WR, Maramattom BV, Manno EM, McClelland RL. Validation of a new coma scale: The FOUR score. Ann Neurol. 2005;58(4):585-93.
3. Jain S, Iverson LM. Glasgow Coma Scale. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021.
4. Patel PM. Cerebral physiology and the effects of anesthetic drugs. In: Ronald D. Miller (Eds) Miller's Anesthesia, 8th edition. Philadelphia: Elsevier Saunders; 2015. pp. 387-419.
5. Galvagno SM Jr, Nahmias JT, Young DA. Advanced Trauma Life Support® Update 2019: Management and applications for adults and special populations. Anesthesiol Clin. 2019;37(1):13-32.
6. CRASH-3 Trial Collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. Lancet. 2019;394(10210):1713-23.
7. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GWJ, Bell MJ, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. Neurosurgery. 2017;80(1):6-15.
8. Zampieri FG, Machado FR, Biondi RS, Freitas FGR, Veiga VC, Figueiredo RC, et al. BaSICS investigators and the BRICNet members. Effect of intravenous fluid treatment with a balanced solution vs 0.9% saline solution on mortality in critically ill patients: The BaSICS Randomized Clinical Trial. JAMA. 2021;326(9):e2111684.
9. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350(22):2247-56.
10. Howells T, Elf K, Jones PA, Ronne-Engström E, Piper I, Nilsson P, et al. Pressure reactivity as a guide in the treatment of cerebral perfusion pressure in patients with brain trauma. J Neurosurg. 2005;102(2):311-7.
11. Piran P, Stevens RD. Lung-protective ventilation and adjunctive strategies to manage respiratory failure: are they safe in the neurological patient? Curr Opin Crit Care. 2021;27(2):115-9.
12. Yang Y, Zheng F, Xu X, Wang X. Levetiracetam versus phenytoin for seizure prophylaxis following traumatic brain injury: A systematic review and meta-analysis. CNS Drugs. 2016;30(8):677-88.
13. Joseph B, Pandit V, Meyer D, Butvidas L, Kulvatunyou N, Khalil M, et al. The significance of platelet count in traumatic brain injury patients on antiplatelet therapy. J Trauma Acute Care Surg. 2014;77(3):417-21.
14. Holzmacher JL, Reynolds C, Patel M, Maluso P, Holland S, Gamsky N, et al. Platelet transfusion does not improve outcomes in patients with brain injury on antiplatelet therapy. Brain Inj. 2018;32(3):325-30.
15. Margolick J, Dandurand C, Duncan K, Chen W, Evans DC, Sekhon MS, et al. A systematic review of the risks and benefits of venous thromboembolism prophylaxis in traumatic brain injury. Can J Neurol Sci. 2018;45(4):432-44.
16. Andrews PJ, Sinclair HL, Rodriguez A, Harris BA, Battison CG, Rhodes JKJ, et al; Eurotherm3235 Trial Collaborators. Hypothermia for intracranial hypertension after traumatic brain injury. N Engl J Med. 2015;373(25):2403-12.
17. Cooper DJ, Nichol AD, Bailey M, Bernard S, Cameron PA, Pili-Floury S, et al. Effect of early sustained prophylactic hypothermia on neurologic outcomes among patients with severe traumatic brain injury: The POLAR Randomized Clinical Trial. JAMA. 2018;320(21):2211-20.
18. The CRASH trial management group; The CRASH trial collaborators. The CRASH trial protocol (Corticosteroid randomisation after significant head injury) [ISRCTN74459797]. BMC Emerg Med. 2001;1(1):1.
19. Hawryluk GWJ, Aguilera S, Buki A, Bulger E, Citerio G, Cooper DJ, et al. A management algorithm for patients with intracranial pressure monitoring: the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC). Intensive Care Med. 2019;45(12):1783-94.
20. Le Roux P. Intracranial pressure after the BEST TRIP trial: a call for more monitoring. Curr Opin Crit Care. 2014;20(2):141-7.
21. Cooper DJ, Rosenfeld JV, Murray L, Arabi YM, Davies AR, D'Urso P, et al. Decompressive craniectomy in diffuse traumatic brain injury. N Engl J Med. 2011;364(16):1493-502.
22. Hutchinson PJ, Kolias AG, Timofeev IS, Corteen EA, Czosnyka M, Timothy J, et al. Trial of decompressive craniectomy for traumatic intracranial hypertension. N Engl J Med. 2016;375(12):1119-30.
23. Smith M. Multimodality neuromonitoring in adult traumatic brain injury: a narrative review. Anesthesiology. 2018;128(2):401-15.
24. Romagnosi F, Bongiovanni F, Oddo M. Eyeing up the injured brain: automated pupillometry and optic nerve sheath diameter. Curr Opin Crit Care. 2020;26(2):115-21.
25. Mendoza DA, López KD, Echeverri RA, Pastor L, Rueda S, Fernández, LL, et al. Utility of biomarkers in traumatic brain injury: a narrative review. Colomb J Anesthesiol. 2020;48(3):155-61.
26. Hernandez S, Kittelty K, Hodgson CL. Rehabilitating the neurological patient in the ICU: what is important? Curr Opin Crit Care. 2021;27:120-30.

CHAPTER

54

Challenges of Managing Polytrauma in Accidental COVID Positive Patient

Ritesh Shah, Vikas Sikri, Saswati Sinha

INTRODUCTION

Polytrauma in itself is challenging to handle in any tertiary care center, but in the COVID era, it becomes a humongous task to handle such patients. Ideally, each patient being admitted through emergency needs COVID testing, rapid screening test followed by reverse transcription polymerase chain reaction (RT-PCR), if necessary. Triage is necessary from the moment patient enters the emergency department. Not every hospital is equipped with infrastructure to handle COVID patients, that too with polytrauma. So, understanding limitations and setting up a specific area to handle COVID patients, is of utmost importance.

PRIMARY GOAL

Safety of patient by providing high quality standard care as per guidelines and at the same time, safety of healthcare workers and other patients by avoiding cross-transmission of COVID infection.

GENERAL PRINCIPLES/REQUIREMENTS

- Segregated area in triage to keep suspected and confirmed COVID patients has to be earmarked.
- Dedicated radiological unit if possible to image such patients.
- *Intrahospital transport*: A separate corridor/lift for transport of COVID patients to subjective COVID ward/ intensive care unit (ICU), preferably a negative isolation.

ASSESSMENT IN TRIAGE

The goal in any trauma patient is to prevent death and disability in injured patient. Assessing the trauma patients in emergency is a challenge as the patient can be either asymptomatic or not in position to give the history himself/ herself if the injuries are grave. Sometimes, the trauma victims are brought in by by-standers with no relevant history available at all. In the COVID era, it is prudent to assume all patients as positive unless proven otherwise. Such patients should be managed in the separate designated area in triage earmarked for suspected/confirmed COVID patients. A rapid COVID test should be sent immediately on arrival. Proper examination may not be possible in PPE (personal protective equipment) by the medical professionals, radiological examination could be more reliable in such scenario.

PRIMARY SURVEY[1]

Primary survey involves rapid assessment and treatment of life-threatening injuries.

A: Airway management with cervical cord protection
B: Breathing and ventilation
C: Circulation with hemorrhage control
D: Disability
E: Exposure and environmental control

Airway

Airway management is the key component in polytrauma patients. The objective is to diagnose any obstruction or a potential obstruction and remove it, so as to keep the airway patent. In COVID patients, it poses the risk of aerosol transmission of the virus as the airway handler is too close to the patient's oronasal cavity. It should always be remembered that personal protection is the priority. Level 3 precautions must be followed while intubating this subset of patients, including proper donning of appropriate respiratory equipment, tightly fitting N-95 mask, gloves, and face shield. Preferably, a senior person should intubate as it takes lesser time, thus minimizing the risk of exposure. Care should be taken to avoid neck injury, proper in-line neck mobilization should be performed while intubating. Proper doffing should also be done in order to prevent self-contamination.[2]

All the airway equipment, preferably disposable, should be kept in designated area to avoid last minute glitches. Careful handling of disposables should also be taken care of as per national COVID protocols developed to manage such biological waste.

Breathing and Ventilation

Breathing management can vary from requirement of simple oxygen to mechanical ventilation. Clinical examination of chest and respiratory system must be carried out in detail to look for pneumothorax, hemothorax, or any other open chest wound. Even in the patients with no chest injury, COVID lung can be difficult to ventilate. Ensure a filter at the end of expiratory limb in order to minimize contaminated aerosol entering ambient environment. Standard acute respiratory distress syndrome (ARDS) ventilation protocols, and lung protective ventilation should be followed while ventilating such patients.

Circulation and Hemorrhage Control

Examine for skin color, weak pulses, and look for blood pressure measurements. Any obvious hemorrhage should be controlled with direct pressure. Ensure an extra pair of gloves to prevent self-contamination. Take two large bore peripheral cannula and start fluid resuscitation and send blood tests. Alert the laboratory and blood bank. Be careful about blood splash.

Disability

A quick look at the patient's consciousness and Glasgow Coma Scale (GCS) should be done.

Exposure and Environment

Hypothermia, burns, and exposure to chemicals should be evaluated.

SECONDARY SURVEY

After adequate hemodynamic resuscitation, secondary survey should be done. The purpose of secondary survey is to examine from head to toe and not miss out any significant injury. Vital signs need to be monitored closely so as not to miss out any early warning signs. Physical examination can be difficult in COVID patients as the examiner, in full PPE kit, can have difficulty maneuvering the patient and parts such as palpation and percussion could not always be feasible. One has to rely on vital signs and gross examination skills.

After secondary survey, all the diagnostics should be ordered meticulously including a throat swab for COVID RT-PCR, relevant consultations should be sought early as the concerned specialty doctor has to don appropriately before examination and this can consume precious time and intervention.

DIAGNOSTIC CHALLENGES IN A POLYTRAUMA PATIENT

Any trauma patient presenting to the hospital during the pandemic times is challenging as far as further investigation and diagnosis of injuries are concerned.

Challenges and Suggestions

- Upon arrival to the emergency room, all polytrauma victims should be considered COVID-19 positive unless proven otherwise and all precautions implemented—no delay in investigation and management should occur in an attempt to rule out COVID infection.[3]
- Blood collection on arrival and for daily monitoring may be challenging for phlebotomist in PPE.
- Screening for COVID-19 should focus on symptoms (fever, cough, and shortness of breath) but it may be challenging as patient may not be in the condition to provide proper history and there may not be any family member available.
- Nasopharyngeal swabs or lower respiratory samples should urgently be sent for diagnosis of SARS-CoV-2—either RT-PCR or geneXpert (CB-NAAT) or Tru-NAT (micro-RT-PCR) to try and streamline the location where the patient should be treated.
- As per Advanced Trauma Life Support (ATLS) guidelines, X-ray, and Focused Assessment with Sonography for Trauma (FAST) may be more useful as clinical examination with personal protective equipment becomes more challenging. Having dedicated X-ray machines and a portable ultrasound might be of great benefit but availability might vary. Disinfection of the equipment needs to be ensured as per infection control protocol.
- Since RT-PCR has a limited sensitivity and turnaround time is varied, many trauma centers across several countries have included chest ultrasound or computed tomography (CT) scans to expedite diagnosis of COVID-19 infection. Studies comparing sensitivity of RT-PCR with chest CT scans have demonstrated a higher sensitivity of CT scans (98 vs. 71%).[4]
- Wherever feasible, a dedicated CT scanner should be available near the trauma triage area for critically ill trauma victims to limit transport of COVID patients through other hospital areas to reduce exposure.
- CT manifestations of COVID-19 infection needs to be closely looked for especially in situations where concomitant chest trauma might coexist. While bilateral ground glass opacities in the subpleural areas, which later may progress to consolidation, are common features in COVID pneumonia, pulmonary contusions are usually seen as focal nonsegmental areas of parenchymal consolidation. However, differentiation may be challenging and the radiologist needs to be alerted to look for the same.[5] Shadows which appear later on as ventilator-associated pneumonia also need to be differentiated from worsening of COVID-19 infection.
- Many patients with trauma may have elevated markers of inflammation such as C-reactive protein (CRP), lactate dehydrogenase (LDH), IL-6, and ferritin, which

are routinely used to monitor COVID patients. These markers are difficult to interpret and less specific for diagnosis and monitoring of trauma patients.

- There should be a low threshold of a whole body CT scan for polytrauma victims considering the challenges of clinical examination and routine investigations and an attempt to minimize repeated transport and exposure in these patients.

MANAGEMENT OF POLYTRAUMA IN COVID-19 POSITIVE PATIENTS

Majority of trauma patients do not arrive at the hospital with COVID-19 positive status. During pandemic times, each and every patient who arrives at trauma, we need to take all precautions as suspected or positive patient for COVID-19.

As we face triage and diagnostic challenges, management of polytrauma patients is the greatest challenge. At any point of time during hospital course, the primary approach of A-B-C (airway-breathing-circulation) remains challenging.

After initial stabilization and investigations, we need to plan further intervention. We can divide patients into three categories:[1,6]

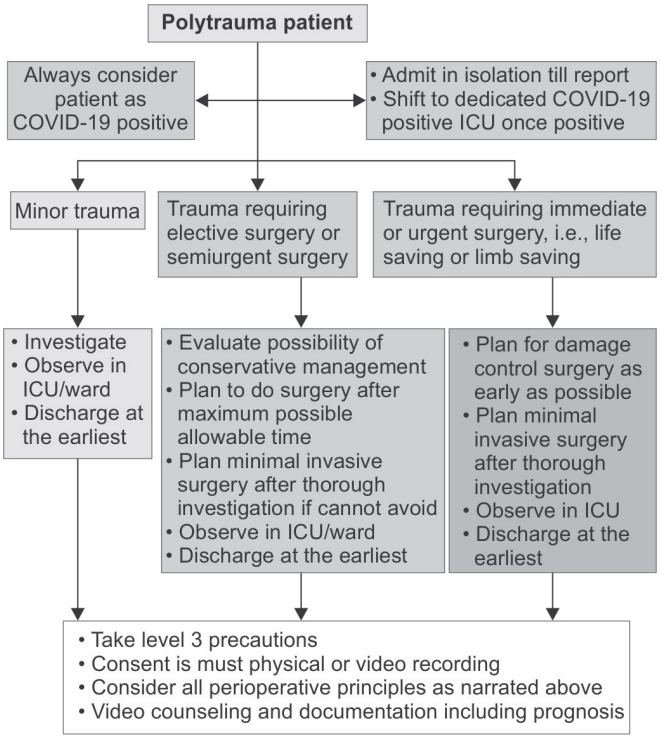
1. Patients who do not require surgical intervention at all
2. Patients who do not require immediate surgical intervention
3. Patients who require immediate or urgent surgical intervention.

The surgery should be done for salvaging a limb or saving a life, hemorrhage control, contamination abatement, or compartment pressure relief.

If patient requires surgery, patient should be transferred to the operating room (OR) with predetermined transport route including dedicated pathways and elevators should be designed in such a way to shortening the outdoor distance, minimize the exposure to others, and limiting the time in suspected or positive areas.

An algorithmic approach to manage polytrauma in COVID-19 positive patient is shown in **Flowchart 1**.

Flowchart 1: Approach to polytrauma patients with COVID-19 positive status.



(ICU: intensive care unit)

SURGERY[1,6-10]

Challenges

- Exposure to healthcare workers, especially surgical team
- Difficult to perform surgery because of unusual surgical wear which include additional PPE
- Increased duration of surgery
- There might be trauma-induced coagulopathy
- Blood and blood product availability may be an issue
- High risk of perioperative complications.

Challenges for the Surgeon

- The excessive protective suits decrease surgeon's tactile, auditory and visual sensitivity, which may reduce surgical precision, and increase duration of surgery
- The PPE can cause:
  - Excessive and recurrent fogging on the face shield or goggles
  - Decrease the visual field
  - Discomfort due to perspiration
  - Breathing difficulties
  - Double or triple gloves restrict the movement or flexibility.

The general principles to be followed for surgical intervention:

- Conservative approach is always better.
- Separate donning and doffing areas.
- Threshold for surgery should be higher.
- Dedicated OR is necessary, preferably negative pressure OR. Surgery can be done when the pressure is between –10 and –5 pa. If it is not available, an isolated OR with an independent purification system is an alternative. The purification system should be shut down during the surgery.
- Minimally invasive technique is preferred.
- Efforts should be made to minimize surgical time.
- Two surgeons are preferred to minimize surgical time.
- Level 3 precautions need to be taken.

- Surgeon should stay out of the OR while induction of anesthesia and intubation.
- Experienced surgeon and dedicated staff should be available to minimize surgical duration and reduce postoperative complications.
- Damage control surgery with minimum duration and manipulation should be done. Strategies such as packing homeostasis, temporary abdominal closure, and external fixation rather than definitive internal fixation can be used to minimize the duration and aerosol generation. If possible, avoid alternate surgical intervention to canal instrumentation.
- Gentle movement to avoid contamination by spattering of blood, fluid, or bone debris.
- Rinsing and drainage of fluid should be minimized. Syringe wash should be preferred over direct and pulsed lavage.
- Excessive negative pressure suction should be avoided.
- Use of electrical cautery should be minimized or use with lower power.
- Smoke should be suctioned immediately and continuously.
- Fix up the staff. Avoid in and out movement while surgery. Frequency of door opening should be strictly minimized.
- Maximum eight persons should be allowed inside OR including surgeon, anesthetist, nurse, technician, and other support staff.
- Use more and more disposable items. Items once enter the OR should not be taken out.
- Dedicated instruments and equipment including C-arm should be allotted.
- Two suction apparatus should be there, one for surgeon and one for anesthesiologist.
- Cleaning of instruments/equipment and infection control protocols should be followed strictly.
- The biomedical waste disposal practices should be strictly and cautiously followed. All material should be treated as infective and should be disposed off in dedicated yellow bags.
- There should be 30 minutes gap to start cleaning up OR after surgery to allow aerosols to settle.
- Keep 1–4 hours between two surgeries in the same OR for infection control and cleaning of OR.
- In orthopedic surgery, hammering of the implants should be carried out only after covering the area with absorbent linen.

ANESTHESIA[1,6-10]

Challenges

- Exposure to healthcare workers
- Aerosolization
- Intubation
- Ventilation issues in case of pulmonary involvement of COVID-19.

Trauma patients need either emergency or urgent surgery. The type of anesthesia depends on type of injury, type of surgery, patient's hemodynamic status, coagulation profile as well as probable duration of surgery.

Aerosolization is one of the biggest risk factors for transmission of virus. Aerosols are solid or liquid granular substances suspended in the air through dust, smoke, fog, microorganisms, etc. During surgery or anesthesia, procedures which can generate and spread aerosols need to be avoided.

General Principles to be Followed during Anesthesia

- Regional anesthesia is preferred.
- Level 3 precautions to carry out.
- Minimize aerosolization:
  - Avoid bag-mask ventilation.
  - Adequate muscle relaxant and rapid induction to avoid any coughing during intubation.
  - Do not perform sputum aspiration before intubation.
  - Protect anesthesia machine or breathing circuit by placing viral filter at end-expiratory port.
  - Avoid noninvasive ventilation.
  - Avoid nebulization.
  - Extubation under sedation/analgesia if patient's condition permits to avoid violent coughing.
  - The negative pressure aspirator, if available, should be immediately placed on patient's face once the patient enters the OR.
- Remote intubation using video laryngoscope is preferred to avoid proximity to patient.
- Supraglottic airway device such as laryngeal mask airway (LMA) can be used to assist endotracheal intubation.
- Intubation should be done by experienced anesthetist or by the dedicated "Intubation team".
- Use end-tidal CO_2 to confirm proper placement rather than by auscultation.
- Use lung protective ventilation even during intraoperative ventilation.

POSTOPERATIVE PERIOD[1,6-10]

Challenges

- High risk of developing postoperative pulmonary complications and thrombotic complications
- Chances of infection are high
- Difficult to differentiate between trauma-related complications and COVID-19-related complications
- Shortage of manpower and difficulties for rehabilitation.

Postoperative Care

- Patient should be transferred to a dedicated COVID-19 ICU.
- Anticoagulation as per coagulation status. Balance between probability of thrombotic complications because of COVID-19 and bleeding complications because of trauma-induced coagulopathy. All patients should get at least prophylactic anticoagulation if not contraindicated.
- Get lower limb duplex ultrasound in case of minimal suspicion especially in major lower limb trauma or surgery.
- Conservative fluid management as far as possible.
- Medications to take care of PONV (postoperative nausea and vomiting).
- Nutritional support should be optimized.
- Prevention of stress ulcer, gastrointestinal bleeding, and infection.
- Keep high index of suspicion for infection.
- Rehabilitation is the key.
- Continue all COVID-19-related medications at scheduled time.
- Never forget about medications related to comorbidities.
- Psychological support.
- Discharge at the earliest once clinical condition permits.
- Follow-up on teleconsultation except requirement of would inspection/major dressing/infection. Otherwise can provide home care.

CONCLUSION

Polytrauma patients with COVID-19 positive status remain a big challenge right from arrival to hospital, triaging, diagnosis as well as management. They are at high risk of developing perioperative complications. The safety of healthcare workers and other patients should be assured while managing these patients as per standard guidelines. Level 3 precautions need to be taken meticulously. Follow the same trauma guidelines, i.e., primary survey and secondary survey with additional precautions and special requirements. Conservative approach, minimal invasive and damage control surgical intervention, minimize duration of surgery and prevent aerosol generating procedures, etc., are the key principles to be followed. Postoperative rehabilitation and follow-up with teleconsultation should be encouraged.

REFERENCES

1. Li Y, Zeng L, Li Z, Mao Q, Liu D, Zhang L, et al. Emergency trauma care during the outbreak of corona virus disease 2019 (COVID-19) in China. World J Emerg Surg. 2020;15(1):33.
2. Orser BA. Recommendations for endotracheal intubation of COVID-19 patients. Anesth Analg. 2020;130(5):1109-10.
3. Gok AFK, Eryılmaz M, Ozmen MM, Alimoglu O, Ertekin C, Kurtoglu MH. Recommendations for trauma and emergency general surgery practice during COVID-19 pandemic. Ulus Travma Acil Cerrahi Derg. 2020;26(3):335-42.
4. Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang P, et al. Sensitivity of chest CT for COVID-19: comparison to RT-PCR. Radiology. 2020:200432.
5. Revel MP, Parkar AP, Prosch H, Silva M, Sverzellati N, Gleeson F, et al. COVID-19 patients and the radiology department: advice from the European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). Eur Radiol. 2020:1-7.
6. Sawhney C, Singh Y, Jain K, Sawhney R, Trikha A. Trauma care and COVID-19 pandemic. J Anaesthesiol Clin Pharmacol. 2020;36(Suppl 1):S115-20.
7. D'Angelo F, Monestier L, De Falco G, Mazzacane M, Stissi P. Management of traumatology patients during the coronavirus (COVID-19) pandemic: experience in a hub trauma hospital in Northern Italy. Indian J Orthop. 2020;54(Suppl 2):S397-402.
8. Jain VK, Lal H, Patralekh MK, Vaishya R. Fracture management during COVID-19 pandemic: a systematic review. J Clin Orthop Trauma. 2020;11(Suppl 1):S431-41.
9. Dabas V, Bhatia N, Goel A, Yadav V, Bajaj V, Kumar V. management of orthopaedic accidental emergencies amidst COVID-19 pandemic: our experience in preparing to live with corona. Indian J Orthop. 2020;54(Suppl 2):S380-5.
10. Al-Humadi SM, Tantone R, Nazemi AK, Hays T, Pawlak A, Komatsu DE, Namm JD. Outcomes of orthopaedic trauma surgery in COVID-19 positive patients. OTA Int. 2021;4(2):e129.

55

CHAPTER

Whole Blood in Trauma

AK Singh, Nikhil Kothari, Ankur Sharma, Aditya Shukla

INTRODUCTION

Hemorrhage is one of the leading causes of death among road traffic accident patients, and most of these deaths are preventable if timely intervened. Polytrauma with hemorrhagic shock is a common presentation in the emergency department. In these patients, the cause of shock is uncontrolled bleeding which can be concealed internal bleeding or can be a visible external bleeding, which accounts for 30–40% of total trauma deaths. Trauma is a major cause of death in young population across the globe.[1,2] Blood loss after trauma is mostly responsible for these deaths, second only to traumatic brain injury. All these deaths due to trauma are potentially preventable deaths, if timely intervened. The recent development of Advanced Trauma Life Support (ATLS) protocols and improvement in prehospital care and development of appropriate resuscitation guidelines have drastically changed the clinical outcomes of severely injured trauma patients. As per the data available, more than eleven hundred lakh units of packed red blood cells (RBCs) are being transfused each year across United States of America, out of which >40% is used during emergency, while 15% is used during management of trauma patients.[3] In injured patients who are hemodynamically stable, unwarranted blood transfusion may lead to significant complications. The transfusion-related acquired coagulopathy is responsible for a majority of deaths in trauma patients.

The transfusion practices have evolved a lot since 19th century. Warm fresh whole blood (WFWB) was extensively used during the Second World War. During early 70s, with the advancement of the technology, more stress was laid on the component therapy. The evolution started from transfusing whole blood to recent guidelines of component therapy. These changes occurred without much evidence of comparing the risks versus benefits of transfusing the components specifically for patients with shock due to excessive blood loss during trauma.[4-6] These guidelines were based upon the expert's opinion or based on the trials done during elective cardiac surgery. As a consequence of these trials, whole blood units are no longer freely available. Recently, few trauma communities suggested to adapt a change in transfusion practices while managing a patient with hemorrhagic shock. Transfusion of WFWB came back into practice during recent Afghanistan war due to logistic issues and massive requirements. The practice to transfuse the whole blood is now being reintroduced while managing mass casualties during road traffic accidents, with good surgical outcomes. Furthermore, the Joint Trauma System clinical practice guidelines recommend the use of WFWB as the preferred therapy in the out-of-hospital treatment of hemorrhagic shock.[7,8] This approach recommends the rapid control of bleeding from the site of injury by transfusion of blood components including RBCs, plasma, and platelets in the ratio 1:1:1. Patients with hemorrhagic shock due to trauma often require a balance between the transfused blood products comprising of RBCs, plasma, and the platelets. Nowadays the use of whole blood for resuscitation is becoming a common practice, especially during military wars and disaster management. The use of WFWB has also been advocated by United States armed forces during combat operations in Afghanistan and Iraq, supporting the use of whole blood during damage control resuscitation at remote locations.[9,10] Theoretically, the WFWB may have several advantages for patients having hemorrhagic shock when compared with the component therapy in terms of improving the RBCs and platelet functions and also limiting the adverse effects of the stored packed cells.

FACTS ABOUT BLOOD TRANSFUSION

- Transfusion of whole blood provides the advantage of overcoming logistic errors of component transfusion and allowing transfusion of young healthy blood cells.
- Since ages, the overall experience with transfusion of whole blood is well documented and appears safe.
- Use of whole blood was not associated with an increase in transfusion reactions as compared with component transfusion.

- Though the practice of component transfusion is widespread as transfusion of whole blood was not associated with better survival or decreases utilization of blood products.

TRAUMA RESUSCITATION

The American College of Surgeons has defined the ATLS protocol to replace every milliliter of blood with 3 mL of balanced solutions or crystalloids. Before starting the fluid resuscitation, the site of bleeding should be identified as the unidentified source can potentiate the blood loss after fluid resuscitation. Aggressive fluid resuscitation may lead to hemodilution-induced coagulopathy which can be detrimental. This principle is based on the concept that the blood loss from the injury site is further increased if a patient is over enthusiastically resuscitated with balanced crystalloid solution in order to maintain intravascular volume and systolic blood pressure, as it results in dilutional coagulopathy. In order to overcome the coagulopathy due to excessive fluid resuscitation, few hospitals have adopted the policy of hypotensive resuscitation in actively bleeding patients.[11,12]

Massive transfusion protocols prove to be life-saving in trauma patients who are bleeding profusely. These transfusions should be done using blood components and based on coagulation parameters. In life-threatening hemorrhagic shock, the transfusion of WFWB or stored whole blood product is performed empirically in order to save a life. This practice is not guided by laboratory tests and component therapy, but based on clinical findings, which is at times also known as "blind" transfusion.[13]

GENERAL CRITICAL CARE RESUSCITATION

Transfusion of whole blood or blood components should be decided on case-to-case basis in critical care as well as in patients undergoing major surgery. Blood loss up to 30% of blood volume is usually well tolerated without any significant clinical sign and symptoms, which can be effectively managed with crystalloids resuscitation. In healthy young adults, blood loss up to 40% of blood volume (approximately 2 L of blood loss) can be resuscitated by balanced crystalloids. Beyond 40% of acute blood loss, resuscitation with crystalloids may result in dilutional coagulopathy along with normovolemic anemia, which can be life-threatening. In cases of chronic blood loss in otherwise healthy adults, tissue oxygen delivery is maintained up to hemoglobin levels of 6 g/dL.[14] Transfusion of blood or blood components should be strongly considered in critically ill trauma patients if hemoglobin is below 6 g/dL, even if the patient is hemodynamically stable after adequate fluid resuscitation. Antifibrinolytic agents such as tranexamic acid may be considered in trauma or surgical patients with ongoing blood loss.

A systematic review and meta-analysis was published by Crowe et al. in 2020 on whole blood transfusion versus component therapy in trauma resuscitation.[15] The authors searched 1,759 citations and identified 12 studies (reporting 8,431 patients) to meet the eligibility criteria for the systematic review. They revealed a wide heterogeneity in the protocol designs of the included studies. They observed that the whole blood was widely used in each of the included study. The definitions of whole blood in each study were also variable, few people classified the whole blood as WFWB, while others considered the mixture of blood component such as packed RBCs, platelets, and plasma as whole blood. Given the extent of heterogeneity across the included studies, their meta-analysis was considered as inappropriate by few societies. While others considered the meta-analysis by Crowe et al. as an alarming literature, highlighting the lack of awareness and wide variation in practices of blood transfusion across the globe.

Transfusion of WFWB is seen as a common practice in army and during combat settings. If the objective is to evaluate whole blood transfusion practices during road traffic accidents, then there is a need to plan large scale randomized trials in trauma settings where the outcomes of transfusing whole blood during road accidents should be studied. The selection of patients should include people who met with road traffic accidents and suffered from either blunt or penetrating injuries due to trauma as well as the females of childbearing age group. Such studies must also identify the outcomes of transfusing WFWB, stored whole blood, including the type of whole blood used, use of irradiated blood along with the application of leukoreduction and the methods of storage. In these studies, the protocols should be made to decide upon the minimum amount of whole blood transfused, which constitutes the whole blood group, including the type and number of component transfusion to be allowed before receiving the whole blood. The end point of these large scale trials might include not only the in-hospital mortality but also early mortality. While transfusing the fresh whole blood, coagulation studies such as thromboelastography should be done in order to observe the physiologic effects of transfusing fresh whole blood.

The most convincing aspect of transfusing whole blood is that its use helps in managing the logistics of blood transfusion during trauma in resource constraint settings. During disaster management or in cases of mass casualties, it is always easier to give one single unit of whole blood rather than the separate units of packed RBCs, plasma, and platelets while managing several patients at a given time. In certain resource constraint settings, the preparation and storage of the fresh whole blood may be less costly than as compared to similar amounts of component therapy. It also reduces the risk of administrative errors. Thus, the cost-effectiveness in resource constraint settings provides better outcomes of transfusion of fresh warm whole blood.

COMPOSITION OF WHOLE BLOOD

A bag of whole blood contains 450 mL of whole blood with 63 mL of anticoagulant-preservative solution added. The hemoglobin content of a unit of whole blood is 1.2 g/dL with hematocrit (Hct) of 35–45% when stored at +2°C to +6°C.[16]

Indications of Whole Blood Transfusion

Red cell replacement to manage acute blood loss with hypovolemia in trauma or during surgeries. It can also be used during exchange transfusion. Similar to packed cell unit, the unit of whole blood needs to be transfused within 4 hours of release from the blood bank.

Contraindications

Risk of volume overload in patients with cardiac failure, chronic anemia, or chronic kidney disease patients, who are not on dialysis.

Infection Risk

The unit of whole blood is capable of transmitting blood borne infections such as human immunodeficiency virus (HIV), hepatitis B and C, syphilis, and malaria.

Storage

The unit of whole blood needs to be stored at a temperature between +2°C and +6°C in a refrigerator having inbuilt temperature regulated alarms.

Age of Blood

Transfusion of fresh blood results in lesser complications. A study published by Koch et al. in New England Journal of Medicine in the year 2008 showed a single center experience of >6,000 patients posted for cardiac surgery, in which the incidence of complications was less in the group of patients who received the blood stored for <14 days. The cause of the complications was thought to be the changes, which occurs in the stored blood unit. Another multicentric study done in 1,098 cardiac surgery patients in North America showed no difference in the incidence of complications in patients receiving the 10 days old stored blood.

Cross-matching of Blood

It is mandatory to do blood grouping and cross-matching prior to blood transfusion. Unless there is an urgent need for blood transfusion due to massive blood loss, the blood unit should be compatible with the antibodies present in the recipient's plasma. The unit must be serologically or electronically cross-matched to confirm its compatibility. Only exception to this rule is life-threatening blood loss, where group specific uncross-matched blood can be transfused, outweighing the harm from a potential hemolytic reaction.

SIDE EFFECTS OF WHOLE BLOOD AND BLOOD COMPONENTS TRANSFUSION

These side effects are mainly classified as immunologic and nonimmunologic complications.

Immunologic Complications

- Hemolytic transfusion reactions, leading to the destruction of RBCs. It is mainly due to generation of alloantibodies in the recipient in response to human leukocyte antigen (HLA)-specific antigens on the transfused RBCs.[17]
- Nonhemolytic febrile reactions are manifested as rise in body temperature for >2°F, either during blood transfusion or shortly after blood transfusion in the absence of any septic focus. The febrile reaction occurs due to action of antibodies present in the transfused blood against the recipient white blood cells. These febrile episodes also occur due to cytokines either present in the transfused blood or generated by the recipient body in response to the transfused blood. The incidence of the febrile episodes is less in leukodepleted blood (<1%), such blood units are commonly used in postorgan transplant patients. The febrile reactions can be managed by simple antipyretic drugs.
- In few cases, mild allergic reactions self-limiting urticaria or wheezing may happen after blood transfusion, which usually respond to antihistaminics.
- Severe anaphylactic reactions such as tachycardia, nausea, vomiting, abdominal pain, diarrhea, laryngospasm, bronchospasm, or even hypotension are rare but dangerous complications requiring immediate treatment with epinephrine.
- Transfusion-related acute lung injury (TRALI) is characterized by the rapid onset of respiratory distress and pulmonary edema of noncardiac origin, occurring within 4–6 hours of transfusion of blood or blood products in the absence of circulatory overload. The antibodies which are produced against the white blood cells in the donor's body (antileukocyte antibody), either during pregnancy or due to prior transfusions, when enter into the recipient along with the transfused blood cause acute lung injury resulting in TRALI. These stimuli usually trigger a systemic inflammatory response leading to activation of neutrophils, which results in injury to the alveolar capillary membrane. This membrane injury causes increased permeability of alveolar capillary membrane resulting in pulmonary edema. The preferential use of blood collected from healthy male donors may help in reduction of TRALI cases.[18]

Immunologic Complications, Delayed

- Rarely after 7–10 days of blood transfusion, few patients develop thrombocytopenia termed as post-transfusion purpura (PTP). It is of sudden onset and self-limited,

prior exposure to antigens either during pregnancy or previous transfusions is responsible for PTP. If the thrombocytopenia is severe, then high-dose steroids or high-dose intravenous immunoglobulin (IVIg) may be tried.

- The incidence of transfusion-associated graft-versus-host disease (TA-GVHD) is low but it is an extremely fatal condition. In this reaction, the recipient body is not able to recognize and destruct the donor T cells and these T lymphocytes present in the donor blood attack the recipient's tissue particularly in the skin, bone marrow, and the gastrointestinal tract, resulting in widespread tissue destruction. The people living with HIV-AIDS (acquired immunodeficiency syndrome) (PLHA) and organ transplant recipient are at risk of developing TA-GVHD. Use of irradiated blood unit is the only means to prevent this reaction. The irradiation of the blood unit makes the donor T lymphocytes incapable of proliferation inside the recipient body.[19]

Nonimmunologic Complications

- Besides immunologic reactions, transfusion of whole blood or blood components is also associated with transmission of several infections such as cytomegalovirus, bacteria leading sepsis, malaria parasites, Creutzfeldt–Jakob disease (CJD) agent, viral hepatitis, and syphilis.
- Rapid transfusion of large volumes of cold blood may result in hypothermia, which may cause cardiac arrhythmias and coagulopathy. A blood warming device should be considered for warming the unit instead of warming the blood unit by keeping close to patient's/relative's body as it may cause hemolysis due to frequent handling of the unit.
- In patients with poor left ventricular function or decrease urine output, rapid transfusion of large volumes of blood may result in transfusion-associated circulatory overload (TACO) causing cardiogenic (hydrostatic) pulmonary edema.
- Citrate anticoagulant used for storage of blood units can chelate the circulatory ionic calcium which may result in post-transfusion tetany. Regular monitoring of ionized calcium using arterial blood gas analysis should be considered while transfusing multiple blood units.

CONCLUSION

Transfusion of WFWB is the preferred product for trauma resuscitation in case of severe hemorrhagic shock. It contains all essential elements of blood that are necessary for oxygen delivery and hemostasis, in nearly physiologic ratios and concentrations. Whole blood of group "O" which contains low titers of anti-A and anti-B antibodies is considered as universal blood unit which can be even transfused to patients of unknown blood group during life-threatening hemorrhagic shock. The maximum storage period for the whole blood is up to 35 days during which time it retains acceptable hemostatic functions, though supplementation with specific blood components including coagulation factors may be at time necessary in some patients. Available clinical data suggests that the whole blood is at least equivalent if not superior to component therapy in the resuscitation of life-threatening hemorrhage. Low titer group O whole blood can be considered the standard of care in resuscitation of major hemorrhage.[20]

REFERENCES

1. Spahn DR, Bouillon B, Cerny V, Duranteau J, Filipescu D, Hunt BJ, et al. The European guideline on management of major bleeding and coagulopathy following trauma: 5th edition. Crit Care. 2019;23(1):98.
2. Neal MD, Hoffman MK, Cuschieri J, Minei JP, Maier RV, Harbrecht BG, et al. Crystalloid to packed red blood cell transfusion ratio in the massively transfused patient: when a little goes a long way. J Trauma Acute Care Surg. 2012;72(4):892-8.
3. Duchesne JC, Heaney J, Guidry C, McSwain Jr N, Meade P, Cohen M, et al. Diluting the benefits of hemostatic resuscitation: a multi-institutional analysis. J Trauma Acute Care Surg. 2013;75(1):76-82.
4. Ley EJ, Clond MA, Srour MK, Barnajian M, Mirocha J, Margulies DR, et al. Emergency department crystalloid resuscitation of 1.5 L or more is associated with increased mortality in elderly and nonelderly trauma patients. J Trauma. 2011;70(2):398-400.
5. Tran A, Yates J, Lau A, Lampron J, Matar M. Permissive hypotension versus conventional resuscitation strategies in adult trauma patients with hemorrhagic shock: a systematic review and meta-analysis of randomized controlled trials. J Trauma Acute Care Surg. 2018;84(5):802-8.
6. Schreiber MA, Meier EN, Tisherman SA, Kerby JD, Newgard CD, Brasel K, et al. A controlled resuscitation strategy is feasible and safe in hypotensive trauma patients: results of a prospective randomized pilot trial. J Trauma Acute Care Surg. 2015;78(4):687-95.
7. Shih AW, Al Khan S, Wang AY, Dawe P, Young PY, Greene A, et al. Systematic reviews of scores and predictors to trigger activation of massive transfusion protocols. J Trauma Acute Care Surg. 2019;87(3):717-29.
8. Moore EE, Moore HB, Chapman MP, Gonzalez E, Sauaia A. Goal-directed haemostatic resuscitation for trauma induced coagulopathy: maintaining homeostasis. J Trauma Acute Care Surg. 2018;84(6S Suppl 1):S35-40.
9. Cannon JW, Khan MA, Raja AS, Cohen MJ, Como JJ, Cotton BA, et al. Damage control resuscitation in patients with severe traumatic haemorrhage: a practice management guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg. 2017;82(3):605-17.
10. Holcomb JB, Caruso J, McMullin NR, Caruso J, Wade CE, Oetjen-Gerdes L, et al. Causes of death in US special operations forces on themodern battlefield: 2001–2004. Ann Surg. 2007;245(6):986-91.

11. Brohi K, Cohen MJ, Ganter MT, Schultz MJ, Levi M, Mackersie RC, et al. Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. J Trauma. 2008;64(5):1211-17. discussion 1217.
12. McLaughlin DF, Niles SE, Salinas J, Perkins JG, Cox ED, Wade CE, et al. A predictive model for massive transfusion in combat casualty patients. J Trauma. 2008;64(2 suppl):S57–63. discussion S63.
13. Repine TB, Perkins JG, Kauvar DS, Blackborne L. The use of fresh whole blood in massive transfusion. J Trauma. 2006;60 (6 suppl):S59-69.
14. Beekley AC. Damage control resuscitation: a sensible approach to the exsanguinating surgical patient. Crit Care Med. 2008;36(7 Suppl):S267-74.
15. Crowe E, DeSantis SM, Bonnette A, Jansen JO, Yamal JM, Holcomb JB, et al. Whole blood transfusion versus component therapy in trauma resuscitation: a systematic review and meta-analysis. J Am College of Emergency Physicians 2020.29;1(4):633-41.
16. Holcomb JB, Jenkins D, Rhee P, Johannigman J, Mahoney P, Mehta S, et al. Damage control resuscitation: directly addressing the earlycoagulopathy of trauma. J Trauma. 2007;62(2):307-10.
17. Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma. 2007;63:805-13.
18. Maegele M, Lefering R, Paffrath T, Tjardes T, Simanski C, Bouillon B, et al. Red blood cell to plasma ratios transfused during massive transfusion are associated with mortality in severe multiply injury: a retrospective analysis from the Trauma Registry of the Deutsche Gesellschaft fur Unfallchirurgie. Vox Sang. 2008;95(2):112-9.
19. Sondeen J, Prince MD, Dubick MA, Holcomb JB. Fresh whole blood is the best 24 hourhypotensive resuscitation fluid in severe hemorrhagic shock. Shock. 2006;25:S121.
20. Armand R, Hess JR. Treating coagulopathy in trauma patients. Transfus Med Rev. 2003;17(3):223-31.

CHAPTER 56

Coagulopathies and Reversal Agents

Babu Abraham

INTRODUCTION

Uncontrolled hemorrhage following trauma was thought to occur, later into the injury, from factors such as aggressive fluid resuscitation, use of unbalanced blood products, hypothermia, and acidosis.[1] This "iatrogenic coagulopathy" is still a major cause of bleeding and preventable death in trauma. Coagulopathy following trauma that happens early, even before significant fluid is administered, is well recognized and hemorrhagic deaths can occur as early as within 3–6 hours following injury.[2] This has generated the concept of "trauma-induced coagulopathy" (TIC).

TRAUMA-INDUCED COAGULOPATHY[2]

Trauma-induced coagulopathy manifests as a spectrum of phenotypes. At one end of the spectrum is the "early TIC" and the other is the "late TIC." These are not mutually exclusive and in between there are various presentations that have the mixed features. The transition between the two is very variable and unpredictable, taking anywhere from minutes, hours, or days to happen. Older individuals are more vulnerable than the younger adults, while children develop it less frequently, later into the injury and typically in association with traumatic brain injury (TBI). Risk factors for their development and severity have been identified **(Boxes 1 and 2)**.

Early Trauma-induced Coagulopathy

Early TIC generally happens within 6 hours of injury and is characterized by hypocoagulability. Severe cases would have hyperfibrinolysis. Clinically it presents as uncontrolled hemorrhage with protracted shock.

Late Trauma-induced Coagulopathy

Late TIC usually happens after 24 hours of injury and is characterized by hypercoagulability. Patients who recover from severe early TIC usually move from a hypocoagulable to a hypercoagulable state within 24 hours.[3] Clinically, it manifests as deep venous thrombosis, pulmonary embolism, acute respiratory distress syndrome, and multiorgan failure. This phase is antifibrinolytic and systemically prothrombotic. It is a distinct entity from trauma-induced disseminated intravascular coagulation.

Pathophysiology[2]

Cell Based Model of Hemostasis

The classical coagulation cascade **(Fig. 1)** was an in vivo model of coagulation that does not reflect physiology.[4] The goal of hemostasis is to seal the site of injury with a platelet and fibrin plug. The concept of "cell based model of hemostasis"[4] has evolved from the observation that coagulation reactions are localized to cell surfaces. In this model, cells actively regulate and localize coagulation. The two most important cell lines are platelets and endothelial cells. A failure of this mechanism leads to hemostasis failure even when the levels of coagulation proteins are normal. The production of thrombin in this model occurs in a stepwise fashion.

- *Initiation phase*: In the initiation phase, two things happen, first the subendothelial cells that bear tissue

BOX 1: Risk factors for developing trauma-induced coagulopathy (TIC).

- Severe tissue injury
- Hypoperfusion/shock
- Metabolic acidosis
- Hypothermia
- Penetrating injury

BOX 2: Factors associated with trauma-induced coagulopathy (TIC) severity.

- Hypoperfusion/shock
- Long prehospital time
- Prehospital treatment with intravenous crystalloid solution
- Severe TBI
- Hypocalcemia

(TBI: traumatic brain injury)

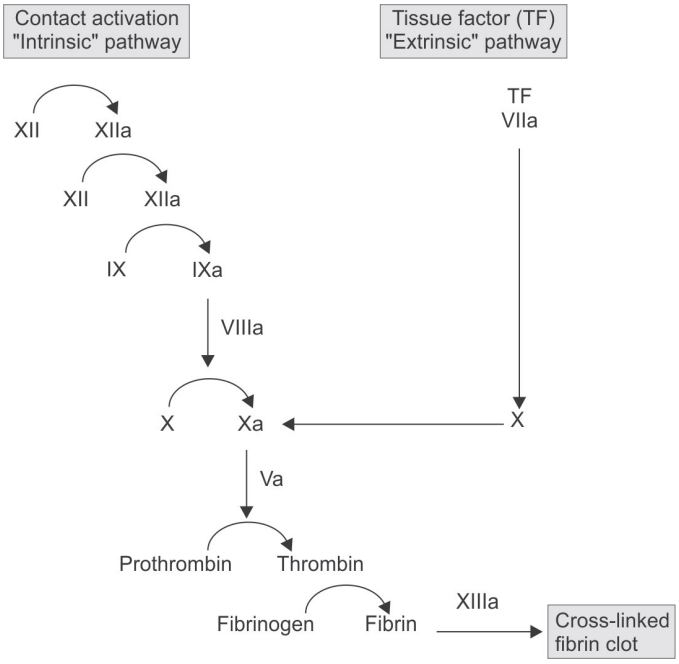


Fig. 1: Coagulation cascade.

factor, on getting exposed to blood at the site of injury, trigger formation of small amount of thrombin, through the extrinsic pathway ("priming thrombus"). Second, there is also formation of small amounts of thrombin on the surface of platelets that adhere to the site of injury.

- *Amplification phase*: This phase utilizes the priming amount of thrombus generated to create a larger burst of thrombin activity on the platelet surfaces by a three-step process consisting of platelet plug formation, platelet activation, and thrombin-related positive feedback, which ensures that primary hemostasis is achieved and a highly procoagulant environment is set up.
- *Propagation phase*: This phase acts through the intrinsic pathway. The activated platelets become the primary surface for generation of large amounts of thrombin ("thrombin burst"). This then becomes the basis for stabilization of the hemostatic clot.

The burst of thrombin produced on the platelets makes the clot stronger, but this needs to be reinforced with fibrin network for it to become strong and stable. Fibrin formation begins early in the process of thrombin burst.

The initiation, amplification, and propagation phases are interdependent and act as an overlapping continuum of events. The traditional coagulation pathway is not redundant. In fact, the cell-based model incorporates both the extrinsic and intrinsic pathways.

Pathogenesis of Trauma-induced Coagulopathy

There are multiple factors that have been implicated in the pathogenesis of TIC. They interact to determine the final clinical phenotype of TIC.

BOX 3: Mechanisms by which metabolic acidosis causes coagulopathy.

- Decrease in FV and FIX activity
- Decrease in platelet number and aggregation
- Increase in fibrinogen consumption
- Decrease in thrombin generation
- Decrease in maximum clot strength

(FIX: Factor IX; FV: Factor V)

- *Hemorrhagic shock*: Early TIC has been attributed to shock leading to decreased oxygen delivery, metabolic acidosis, and hypothermia. Metabolic acidosis causes coagulopathy by various mechanisms **(Box 3)**. Hypothermia decreases the activities of both platelets and coagulation enzymes. Shock has also been shown to cause autodilution of the blood. With the progression of hemorrhagic shock, prothrombotic changes and fibrinolysis failure sets in causing "hypercoagulopathy." This leads to microvascular occlusion by thrombi and multiorgan failure.
- *Tissue injury*: Tissue injury has been implicated in both early hypocoagulable and late hypercoagulable TIC. Severity of tissue injury, extend of tissue injury, and degree of shock have all been identified as risk factors for TIC. Tissue injury has also been implicated in fibrinolysis shut down.
- *Endothelial dysfunction*: Endothelial cell surface is a physiologically active network that regulates coagulation, inflammation, microcirculation, and barrier function. Trauma-associated damage to this network is called "endotheliopathy of trauma" (EOT). It is still unclear whether EOT is the cause or effect of TIC.
- *Platelet dysfunction*: Platelets play an active role in hemostasis, endothelial health, and immune function. Platelet functions get affected in multiple ways in trauma. In early TIC, there is a failure of primary hemostatic function that leads to hemorrhage and in late TIC, there is secondary immunoregulatory dysfunction, leading to hypercoagulopathy. In addition, there is consumptive and dilutional thrombocytopenia. Another feature of TIC is the presence of "platelet exhaustion," where the platelet count is preserved with a pool of exhausted activated platelets that cannot contribute to primary hemostasis.
- *Inappropriate thrombin generation*: A balance between thrombin generation and inhibition is required for hemostasis to be achieved. Dilution of coagulation factors, reduction in the levels of multiple clotting factors, and poor thrombin generation following injury are the possible causes of TIC.
- *Fibrinogen depletion*: Fibrinogen is the most abundant coagulation factor in blood. It is also the first coagulation factor to reach critically low levels in severe bleeding **(Box 4)**. Low fibrinogen level on admission has been

BOX 4: Causes for hypofibrinogenemia in major trauma.

- Hemodilution
- Severe blood loss
- Consumption in clot formation
- Hypothermia impairing synthesis
- Acidosis causing increased degradation of clot

associated with increase in severity of injury, need for transfusion, and increased mortality.

- *Dysregulated fibrinolysis*: Majority of severe trauma patients initially develop depressed fibrinolytic state. Those who retain this beyond 24 hours has been noticed to have an increased mortality. Three dysregulated fibrinolytic problems—hyperfibrinolysis, fibrinolysis shut down, and hypofibrinolysis have been identified in trauma.

Diagnosis

The diagnosis of TIC is based on laboratory-based assays:

- *Early TIC*: The aim of investigations is to identify patients with severe trauma who are at risk of requiring massive blood transfusion and developing early TIC.
  - Conventional coagulation assays (CCAs) such as prothrombin time (PT)/international normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen levels, and platelet count are the most widely used tests for the diagnosis of early TIC. However, the exact diagnosis based on these assays remain debatable, with no clear cut off threshold for PT, INR, or aPTT. They cannot be used as a bench mark for diagnosis of TIC.
  - *Viscoelastic hemostatic assays (VHAs)*: Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are the two common VHA available. They assess the whole blood clot formation and degradation in real time. The benefit that VHA has is that it is able to give several measurements in a single read out, which have been shown to correspond better to the requirements for specific blood component products than CCA.[5] However, there is no evidence to suggest that VHA-guided resuscitation is superior to resuscitation guided by CCA.[6] VHA seems to be the best test at the moment to identify hyperfibrinolysis.
  - *Scoring systems*: Scoring systems –such as The Trauma Associated Severe Hemorrhage Score,[7] The McLaughlin Score,[8] and The Assessment of Blood Consumption Score[9] help to predict the need for massive transfusion but do not diagnose TIC.
- *Late TIC*: Laboratory tests that define late TIC are yet to be developed. A VHA showing increased clot strength and fibrinolysis shut down has been observed to be a risk factor for venous thromboembolism (VTE). Performing repeated VHA may help in picking up patients progressing into late TIC.[10]

Management

Management of TIC can be broadly discussed based upon the site where patients are being treated.

- Care in prehospital setting:
  - *Arresting the bleed*: Arresting the bleed takes priority in out of hospital settings and for this public awareness on stopping the bleed becomes essential. Strategies that mechanically arrest bleeding are being taught to the public by programs such as "STOP THE BLEED" consortium education program.[11]
  - *Initiation of resuscitation*: Resuscitation to restore circulating volumes, achieve homeostasis, and to prevent/reverse hypovolemic shock is usually done by using a combination of fluid and blood products.
    - *Fluid resuscitation*: High volume crystalloid infusion has been associated with hyperfibrinolysis and increased morbidity. "Permissive hypotensive resuscitation," using low volume crystalloids, until hemorrhage control has been achieved has gained acceptance.[12] However, instituting this to all forms of traumatic bleed should be done with caution. The optimal level of hypotension, that can be safely instituted in patients with nonpenetrating injuries, especially in those with TBI, is yet to be defined.
    - *Blood product transfusion*: There is evidence for early use of blood product transfusion in the prehospital setting. Prehospital use of plasma resuscitation in patients who required prolonged transport time to reach definitive care has decreased mortality.[6]
  - Tranexamic acid (TXA): TXA, an antifibrinolytic agent, when used early in the prehospital setting has shown to decrease mortality.[13] The recommended regimen is 1 g intravenous, as a loading dose over 10 minutes, administered within 3 hours of injury followed by an infusion of 1 g over 8 hours. Even though this has become a part of many prehospital recommendations its use varies widely. There exists a concern for VTE and fibrinolysis shut down with its use, even though the large randomized studies of TXA did not show any increase in VTE incidence.[13,14]
- *Care in the hospital*: Prompt cessation of anatomic causes of bleed should be the main focus of in hospital care. Guidelines generally stress upon restricted use of crystalloids, pressive hypotensive resuscitation until active bleeding is controlled, except in the setting of TBI[15] and goal-directed balanced hemostatic resuscitation using higher ratios of plasma to packed red blood cells (PRBCs) with antifibrinolytics once laboratory tests are available.
  - *Balanced product resuscitation*: Even though multiple strategies for the use of blood products have been studied, at the moment the ideal ratio of

blood product transfusion is not clear. Ultimately the clinical status of the patient determines the need for empirical transfusion.

- *High ratio of plasma:PRBC transfusion strategy*[16]: The exact ratio has not been clearly defined. A minimum of 1:2 is suggested and there is no clear benefit of using 1:1 ratio. There is some suggestion that use of platelet transfusion early can improve outcomes. When >4 units of PRBC has been used, transfusion of fibrinogen or cryoprecipitate and platelets has been suggested. These recommendations are only for those who require massive transfusions and it may cause harm if implemented in others.
- *High ratio of fibrinogen/cryoprecipitate:PRBC transfusion strategy*[17]: This strategy has also been suggested to decrease trauma-related mortality but more evidence would be required before it can be recommended.
- *Whole blood transfusion strategy*[18]: Low anti-A and anti-B titer group O whole blood (LTOWB) used to be the standard resuscitation product. It has been shown to be safe and associated with benefits.

- *Goal-directed hemostatic resuscitation*: The new paradigm in trauma resuscitation is "goal-directed hemostatic resuscitation." In this approach, laboratory assays, VHA, or CCA, are done in a serial fashion to guide blood product and adjunct therapy in real time. Goal-directed hemostatic resuscitation targets patients' specific coagulation phenotype, prevents use of excessive blood products, achieves a balanced coagulation profile, and is associated with better outcomes.[19] This strategy could help choosing the appropriate hemostatic agent based on the patients' coagulation phenotype.
- *Pharmacological adjuncts*: In addition to TXA, there are several pharmacological agents that are being studied and have the potential to be efficacious in the treatment of TIC.
  - *Fibrinogen concentrate (FC)*: TIC is associated with fibrinogen deficit. Administration of cryoprecipitate has improved mortality.[20] European guidelines[21] in trauma suggests the use of FC at an initial dose of 3–4 g if fibrinogen levels are <1.5–2 g/L. The subsequent dosing is to be guided by VHA or CCA.
  - *Prothrombin complex concentrate (PCC)*: PCC has been used for nonwarfarin-induced coagulopathy. Retrospective studies in TIC, especially in TBI has shown promise. At this moment, there is not enough data to recommend its use.
  - *Recombinant factor VII (rFVIIa)*: rFVIIa failed to show any benefit in trials and there is a concern that it could cause increased VTE events.

CONCLUSION

Uncontrolled hemorrhage from coagulopathy is a major cause of death following trauma. Over the years, with the improvement in the understanding of TIC—its phenotypes, their pathophysiology, and risk factors—so has the management of the condition moved on to early hemorrhage control, permissive hypotensive resuscitation, and goal-directed hemostatic resuscitation. Despite these developments, there is no clarity in the clinical definition of TIC, no tests sensitive enough to precisely distinguish between the early hypocoagulable and late hypercoagulable states, and there is not enough understanding of the multiple phenotypes seen clinically. With the volume of on-going active research in these fields this is a space that requires constant monitoring.

REFERENCES

1. Hess JR, Brohi K, Dutton RP, Hauser CJ, Holcomb JB, Kluger Y, et al. The coagulopathy of trauma: A review of mechanisms. J Trauma. 2008;65(4):748-54.
2. Moore EE, Moore HB, Kornblith LZ, Neal MD, Hoffman M, Mutch NJ, et al. Trauma-induced coagulopathy. Nat Rev Dis Primers. 2021;7(1):30.
3. Moore HB, Moore EE. Temporal changes in fibrinolysis following injury. Semin Thromb Hemost. 2020;46(2):189-98.
4. Hoffman M, Cichon LJH. Practical coagulation for the blood banker. Transfusion. 2013;53(7):1594-602.
5. Barrett CD, Moore HB, Vigneshwar N, Dhara S, Chandler J, Chapman MP, et al. Plasmin thromboelastography rapidly identifies trauma patients at risk for massive transfusion, mortality, and hyperfibrinolysis: A diagnostic tool to resolve an international debate on tranexamic acid? J Trauma Acute Care Surg. 2020;89(6):991-8.
6. Baksaas-Aasen K, Gall LS, Stensballe J, Juffermans NP, Curry N, Maegele M, et al. Viscoelastic haemostatic assay augmented protocols for major trauma haemorrhage (ITACTIC): a randomized, controlled trial. Intensive Care Medicine. 2021;47(1):49-59.
7. Yücel N, Lefering R, Maegele M, Vorweg M, Tjardes T, Ruchholtz S, et al. Trauma Associated Severe Hemorrhage (TASH)-score: Probability of mass transfusion as surrogate for life threatening hemorrhage after multiple trauma. J Trauma. 2006;60(6):1228-36.
8. McLaughlin DF, Niles SE, Salinas J, Perkins JG, Cox ED, Wade CE, et al. A predictive model for massive transfusion in combat casualty patients. J Trauma. 2008;64(2 Suppl):57-63.
9. Nunez TC, Voskresensky IV, Dossett LA, Shinall R, Dutton WD, Cotton BA. Early prediction of massive transfusion in trauma: Simple as ABC (Assessment of Blood Consumption)? J Trauma. 2009;66(2):346-52.
10. Leeper CM, Neal MD, McKenna CJ, Gaines BA. Trending fibrinolytic dysregulation: fibrinolysis shutdown in the days after injury is associated with poor outcome in severely injured children. Ann Surg. 2017;266(3):508-15.
11. Goolsby C, Jacobs L, Hunt RC, Goralnick E, Singletary EM, Levy MJ, et al. Stop the Bleed Education Consortium: Education program content and delivery recommendations. J Trauma Acute Care Surg. 2018;84(1):205-10.

12. Bickell WH, Wall MJ Jr, Pepe PE, Martin RR, Ginger VF, Allen MK, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso Injuries. N Engl J Med. 1994;331(17):1105-9.
13. CRASH -2 Trial Collaborators; Shakur H, Roberts I, Bautista R, Caballero J, Coats T, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010;376(9734):23-32.
14. The CRASH-3 trial collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. Lancet. 2019;394(10210):1713-23.
15. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GWJ, Bell MJ, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. Neurosurgery. 2017;80(1):6-15.
16. Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma. 2007;63(4):805-13.
17. Itagaki Y, Hayakawa M, Maekawa K, Saito T, Kodate A, Honma Y, et al. Early administration of fibrinogen concentrate is associated with improved survival among severe trauma patients: A single-centre propensity score-matched analysis. World J of Emerg Surg. 2020;15(1):1–10.
18. Black JA, Pierce VS, Kerby JD, Holcomb JB. The evolution of blood transfusion in the trauma patient: Whole blood has come full circle. Seminars in Thrombosis and Hemostasis. 2020;46(2):215-20.
19. Moore HB, Moore EE, Liras IN, Wade C, Huebner BR, Burlew CC, et al. Targeting resuscitation to normalization of coagulating status: Hyper and hypocoagulability after severe injury are both associated with increased mortality. Am J Surg. 2017;214(6):1041-5.
20. Rourke C, Curry N, Khan S, Taylor R, Raza I, Davenport R, et al. Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. J Thromb Haemost. 2012;10(7):1342-51.
21. Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernández-Mondéjar E, et al. The European guideline on management of major bleeding and coagulopathy following trauma: Fourth edition. Crit Care. 2016;20(1):1-55.

CHAPTER 57

New Chemical Burns

K Swarna Deepak, Shyamsunder Tipparaju, Ajit Kumar

INTRODUCTION

A huge number of chemicals are being used in industries and at home for various purposes. These can cause various injuries to skin, eyes, as well multiple systemic effects. There are also growing incidences of chemicals being used for domestic violence and with criminal intent.[1,2] They may represent small percentage (up to 3%) of overall burn but carry significant morbidity (55%) and mortality (30%).[3] Chemical burns on create difficulty to clinicians as it is difficult to assess the depth and extent of burns initially. This article is a small review of common etiologies, pathophysiology, and management of chemical burns.

DEFINITION

Any burn caused externally or internally to the body organs secondary to a strong alkali or acid in the form of caustic or corrosive chemical substance is called as chemical burn. They usually occur secondary to accidents in industries and sometimes at home, work, etc.

Irritant contact dermatitis is caused by very mild chemical exposure. The term caustic burn is used for chemical burn secondary to strong alkali or acid.

PATHOPHYSIOLOGY

Protein denaturation is the common mechanism behind all burns whereas some differences occur with respect to chemical burns.

As opposed to the thermal burns which are usually due to brief exposure to intense heat, chemical burns occur secondary to exposure over longer times and continue in emergency room. In chemical burns, three-dimensional structure of the proteins is destroyed secondary to hydrolysis which may continue over prolonged periods as long as traces of chemical are present in tissues. The severity of injury depends on mechanism of action, duration of contact, amount of substance, and penetration.

MECHANISM OF ACTION[4]

- *Corrosion*: White phosphorus, phenols, and sodium hypochlorite. Denaturation of proteins occurs upon contact with chemical substance.
- *Desiccants*: Concentrated hydrochloric acid and sulfuric acid. Produce exothermic reactions causing damage due to heat and dehydration.
- *Vesicants*: Lewisite, mustard gas, dimethyl sulfoxide, etc. Produce ischemia secondary to anoxic necrosis. Blisters on skin are characteristic.
- *Reduction*: Nitric acid, hydrochloric acid, etc. Free electrons generate heat and tissue damage after the chemical reaction with tissue proteins.
- *Oxidation*: Chromic acid, potassium permanganate, and sodium hypochlorite. Oxygen, sulfur, or halogen causes oxidative stress and damage.
- *Protoplasmic toxins*: Damage is secondary to formation of esters with proteins (e.g., acetic and formic acids) or inhibition of calcium or other organic ions (e.g., oxalic acid, hydrofluoric acids, etc.).

CLINICAL SYMPTOMS AND SIGNS OF CHEMICAL BURN

- Multiple factors play role in clinical presentation of a chemical burn
- pH of the substance
- Chemical substance's concentration
- Duration of contact with substance
- Volume of the substance
- Physical form of chemical substance
- Area of chemical exposure in body
- Route of exposure to chemical substance
- Breakage of skin barrier

The importance of above factors can be understood by two examples:

1. Concentrated forms of some bases and acids create huge thermal energy when diluted causing a chemical as well as thermal burn.
2. *Ingestion of an alkaline battery:* As the battery stays in stomach for prolonged time, severe burn injuries of gastric mucosa are sustained.

Cautious history and examination should be performed in children presenting with chemical burns to rule out possible abuse and/or neglect.

Dermal Exposure

The following are to be considered in case of skin exposure to a chemical—type of substance, site, extent, depth, and presence of circumferential burns.

Symptoms

Burning sensation, irritation, redness, numbness, or pain at the contact site.

Eschar formation occurs due to denaturation of proteins secondary to coagulation necrosis especially with acids.

Alkali burns cause deep injury to skin tissue where denaturation of proteins occurs secondary to liquefactive necrosis.

Ocular Exposure

Loss of vision either partial or complete.

Ingestion

Systemic symptoms can occur when the chemical substance is either inhaled, swallowed, and subsequently gets absorbed into blood after severe burn.

Systemic Symptoms and Signs

- *Cough or shortness of breath:* Dyspnea or cough
- *Low blood pressure:* Hypotension
- *Faintness, weakness, dizziness:* Presyncope, syncope
- Headache
- Muscle twitching or seizures
- Cardiac arrhythmias and cardiac arrest

COMPLICATIONS

Skin

Poor wound healing, secondary infection, and scarring may occur with skin exposure to chemicals. Subsequent skin grafting may be required.

Eyes

Cataract, various degree of ocular injuries including complete visual loss.

Gastrointestinal system: Gastrointestinal bleed, perforation and long-term risk of stricture formation.

Respiratory system: Dysphagia, stridor, wheezing, dyspnea, and tachypnea which may progress to respiratory failure and strictures in future.

MANAGEMENT OF A CHEMICAL BURN[5] (TABLES 1 AND 2)

The ABC principles of trauma care including primary, secondary assessment, as well all principles of burn care apply in case of a patient with chemical burn.

Prompt and thorough history should be taken and management should be started at the earliest. In the

TABLE 1: Principles of management of chemical burns.[5]

Chemical removal	Particulate debris and dry chemical removal
To dilute the chemical exposure	Tap water shower for at least 20–30 minutes at high density. Avoid immersing in water
Burn examination	The depth of the burn is usually more than external appearance. Early involvement of plastic surgeon
Systemic symptoms/signs	Watch for the development of systemic toxicity
Ocular exposure	Continuous lavage with water. Early involvement of ophthalmologist
Inhalational exposure	Oxygen support, airway protection, bronchoscopy if required

TABLE 2: Exceptions in treatment of chemical burns.[5]

Phenol: 50% polyethylene glycol sponges can be used to wipe before lavage *Sulfuric acid*: Soap wash or soda lime *Chlorox*: Egg white, milk or 1% sodium thiosulfate wash followed by irrigation	Irrigation with water *should not* be done
Hydrofluoric acid: To inject 10% calcium gluconate beneath the eschar up to 0.5 mL/cm^2 to relieve pain *White phosphorus*: Lavage with 1–2% copper sulfate	Antidotes

background of accidents at work, material safety data sheets (MSDS) are very useful and to be referred.

Removal of Chemical Substance

Immediate removal of the agent is very important as continuous damage occurs as long as the contact with chemical continues.[6]

Irrigation with Water

It forms an integral part of initial chemical burn management. When done within 10 minutes of exposure to chemical, it has been proved to reduce the morbidity and mortality. Area should be washed with profuse amounts of water at least for 20 minutes. Care should be taken to avoid running off over unaffected areas.

Monitoring for the effectiveness of lavage can be done through checking pH of lavage fluid. pH should be maintained between 5 and 11 and is achieved by a minimum of lavage lasting for 30 minutes to 2 hours.

The standards advised for emergency water decontamination of eyes and skin is ANSI Z-358.1-1998 standard.[7] Irrigation removes and dilutes the chemical agent in contact with the skin. It minimizes the hygroscopic effects of certain agents on tissues. The water irrigation essentially dilutes the agent and removes it from skin.

Neutralizing Substances

The concept of using a specific neutralizing agent is theoretically promising but has been controversial as many authors have proven that dilution rather than neutralization is more beneficial.[8]

Possible dangers with it being exothermic reactions generate heat and generating in further damage to tissues.

Use can be sometimes considered following initial decontamination with water and has to be again followed up by water irrigation.

Diphoterine

Water-soluble powder to be dissolved in water for use. Recently, it has been shown to decrease the pain, chances of admission to burns unit, morbidity, and mortality.[9] It is hypertonic, amphoteric, and polyvalent chelating compound of various chemicals.

The basic principles of managing burns are to monitor wound, to keep them clean, avoid infections, and using topical antiseptics such as 10% mafenide acetate, silver nitrate 0.5%, and 1% silver sulfadiazine.

Management of Systemic Toxicity

Treating should be aware this possibilities. Chemicals like hydrofluoric acid toxicity can cause ventricular fibrillation secondary to hypocalcemia. Formic acid can produce hemolysis, necrotizing pancreatitis, and renal dysfunction. Organic agents can cause liver failure. Inhalational chemical injuries can produce respiratory failure secondary acute respiratory distress syndrome (ARDS). The management remains standard and prognosis remains poor in patients with rapid progression of ARDS.[5]

SPECIFIC MANAGEMENT

Apart from standard practice of management common to all chemical burns, clinicians should have knowledge of some specific agents.

Cement Burns

Predominant component is calcium oxide which acts as an alkali and desiccates the cell. Various types of damage include:

- *Abrasions*: Due to granules in mixture
- *Allergic dermatitis*: Secondary to chromate ions, sand, and gravel
- *Chemical burns*: Alkaline nature of cement causes severe burns which can be insidious and very deep in nature. Removal of cement-soaked clothing, irrigation, and excision followed by skin grating is the management.[10]

Hydrochloric Acid/Muriatic Acid

Quickly denatures into chloride salt and injures skin and tissue deeply. Water irrigation forms the mainstay of initial treatment. Significant lung damage is possible upon inhalation of fumes.

Hydrofluoric Acid

It is used both in industrial and household settings. It is extremely dangerous chemical which can cause severe systemic and local toxicity.

Superficial burns: These occur due to hydrogen ions.

Deep burns and systemic toxicity: Due to free fluoride ions which react with calcium and magnesium ions and produce neutralizing salts resulting in liquefactive necrosis of local tissue. They also cause hypomagnesemia and hypocalcemia. Electrolyte shifts at nerve endings result in severe pain associated hydrofluoric acid. National Institutes of Health (NIH)-Industrial Hygiene's Classification based on concentration:[11]

- Concentration > 50%—causes immediate pain and tissue destruction
- Concentration between 20 and 50%—tissue destruction starts within few hours after exposure
- Concentration < 20%—will take up to 24 hours for damage.

Management

Cardiac arrhythmias occurring are usually very resistant to treatment and preceded by prolonged QTc interval.

Hemodialysis or cation-exchange resins are used to remove fluoride ions.

- Copious irrigation with water
- *Topical treatments*:
  - *Magnesium compounds*: Obsolete now. Poor permeability.
  - *Quaternary compounds*: Zephran or Hyamine 1622. Decrease surface tension. Create nonionized compounds with fluoride in the form of iced solutions.
  - *Calcium gel*: Needs large quantities. Leaves stain. Nonpermeability into skin can be overcome by infiltration.
  - *Calcium gluconate infiltration*: Up to 0.5 mL of 10% injection can be injected beneath nail bed.
- *Intra-arterial infusion*: Improves the delivery of calcium ion to peripheral tissues.

Phosphorus

It usually occurs in setting of military warfare. White phosphorus ignites on exposure to air and irrigation with water forms the most integral part of management in order to remove clusters of chemical.

0.5% copper sulfate is the specific antidote which makes the particles blacker and easier to remove. Side effects being cardiac changes and dyselectrolytemias (calcium and phosphorus).

Strong Alkali

Potassium hydroxide, sodium hydroxide, and lime are examples of strong alkalis. Deep penetration and extended tissue destruction are characteristic of alkali burns. Ocular injury is devastating due to corneal penetration and perforation.

Mechanism: Destruction of lipid barrier occurs secondary to saponification of fat. This is secondary to exothermic reaction generating significant heat. Extensive cell death occurs due to resulting desiccation. Further, the proteins get dissolved by alkalis due to hydroxyl ions resulting in liquefactive necrosis.

Management: Removal of clothes, wiping off chemical, copious irrigation with water. Irrigation with water has multiple beneficial effects such as elimination and dilution of agent and attenuation of increase in tissue metabolism. It also has some anti-inflammatory action and can bring the skin pH to normal level.[12]

Sulfuric Acid

It is frequently seen in the setting of home accidents and quarrels. It is strong acid which creates heat and causes injury by desiccation. Coagulative necrosis and thrombus formation occurs at the injury site.[4] Copious immediate irrigation and early excision are the standard of care.

Nitric acid burn clinical features and management are almost similar except that the burns look deceptively superficial.

Vesicant Chemical Warfare Agents

Ability to produce deep burns and can delayed injury to the tissue up to 24 hours. The rate of healing is also significantly slower due to damage of dermis and examples of chemicals being lewisite and sulfur mustard.[2] Patients usually suffer from multiple sites of burns with severity depending on temperature, moisture level on skin, dose, and length of exposure to the agent. Management consists of aspiration/deroofing of blister, debridement, irrigation, antibiotics, and dressing.

CONCLUSION

Even though they represent a minority of total burn cases, learning about chemical burns is extremely important due to their huge impact on morbidity and mortality. The mainstay of treatment still remains irrigation with water but the knowledge of specific neutralizing agents is also needed in some circumstances.

REFERENCES

1. Sawhney CP, Kaushish R. Acid and alkali: considerations in management. Burns. 1989;15:132-4.
2. Sandford AP, Herndon DN. Chemical burns. In: Herndon DN (Ed). Total Burn Care, 2nd edition. Philadelphia: WB Saunders Company; 2002. pp. 475-80.
3. Robson MC, Smith DJ Jr. Care of thermally injured victim. In: Jurkiewicz MJ, Krizek TJ, Mathes SJ, Ariyan S (Eds). Plastic Surgery: Principles and Practice. St Louis: CV Mosby; 1990. pp. 1355-410.
4. Jelenko C 3rd. Chemicals that "burn". J Trauma. 1974;14:65-72.
5. Carlotto RC, Peters WJ, Neligan PC, Douglas LG, Beeston J. Chemical burns. Can J Surg. 1996;39:205-11.
6. Sykes RA, Mani MM, Hiebert JM. Chemical burns: retrospective review. The J Burn Care Rehab. 1986;7:343-7.
7. Bollas C, Coffey J. In case of emergency. Occup Health Saf. 1998;67(5):50-2.
8. Saydjari R, Abston S, Desai MH. Herndon DN chemical burns. J Burn Care Rehabil. 1986;7:404-8.
9. Hall AH, Blomet J, Mathieu L. Diphoterine for emergent eye/skin chemical splash decontamination: a review. Vet Hum Toxicol. 2002;44(4):228-31.
10. Lewis PM, Ennis O, Kashif A, Dickson WA. Wet cement remains a poorly recognised cause of full-thickness skin burns. Injury. 2004;35:982-5.
11. Edelman P. Hydrofluoric acid buns. Occup Med. 1986;1:89-103.
12. Leonard LG, Scheulen JJ, Munster AM. Chemical burns: effect of prompt first aid. J Trauma. 1982;22:420-3.

CHAPTER 58

Infection Control in Burn Patients

Simant Kumar Jha, Yash Javeri, Ashutosh Bhardwaj

INTRODUCTION

Infections in burn patients not only impact the healing of burned tissue but also conversely have severe systemic complications. After the first 3 days of a major burn, infections are the most common cause of death. Burns lead to a phase of immunosuppression enhancing the risk to acquire infections. Mortality and morbidity are mainly because of infection even though the incidence of wound infections is low. More than half of mortality in a modern burn unit is attributed to sepsis with the majority of episodes within 2 weeks of burns.[1]

Nosocomial infections are the major killer in such patients accounting for more than half of the deaths. Infectious complications are the leading cause of morbidity and mortality in such patients. The burned patient is at a higher risk for a myriad set of infections. Frequent infectious complications occurring in the burn patient are pneumonia, urinary tract infection (UTI), and cellulitis, folliculitis, burn wound infections, and bloodstream infections. Infectious complications are because of bloodstream infections and subsequent sepsis. Based on infection syndrome, it is possible to infer the common etiological agents and their sensitivity trends.

Healthcare-associated pneumonia is the most important infection in this subset. The risk of infections caused by multidrug-resistant (MDR) organisms increases with hospital length of stay. Burn unit patients are among the highest risk groups for blood-borne fungal infections. Nosocomial infections with MDR organisms and fungi contribute to burn wound infections, sepsis, and associated death. Burn patients can develop sepsis from wound infection directly or secondary to pneumonia, catheter-related bloodstream infection (CRBSI), UTI, and suppurative thrombophlebitis.

Patients with major burns have higher rates of healthcare-associated pneumonia than other critical illnesses. Pneumonia is a major cause of morbidity and mortality in burn patients. The estimated prevalence of nosocomial pneumonia ranges from 10 to 65%, with a death rate above 25%.[2]

Burn patients develop UTI commonly because of prolonged urinary catheterization. Though to be a benign infection, it is associated with bacteremia, sepsis, and poor outcomes in burns at a higher rate compared to other critical illnesses.

Burn patients are at higher risk of infective complications with various devices, especially vascular access devices. About 8–57% of burn patients are associated with catheter-associated infection. These infections are a common cause of sepsis. Severe burn injury patients who are hospitalized can have suppurative thrombophlebitis in 5–10% of cases. Even the patients who receive prompt treatment with >20% total body surface area (TBSA), mortality can be as high as 60%.[2]

Stringent infection prevention and burn wound care protocols have grossly curtailed the rates of invasive burn wound infection, altered the microbiological etiology, expanded the timelines between burns and secondary infections, and this all has helped to improve outcomes and survival rates. Severe burn injury is a major challenge for burn physicians. There is a 50% probability of death in sepsis-related burns. In the deceased group of sepsis-accompanying burns, about three-quarters of the patients were infected by gram-negative bacteria. *Pseudomonas aeruginosa* remains the main culprit of septic burn-related mortality.[3]

EPIDEMIOLOGY OF INFECTION

The development of infection is governed by three conditions, first one is a source of organisms followed by mode of transmission; and the susceptibility of the patient.

Sources of Organisms

Burn wounds may be infected by gram-positive bacteria, gram-negative bacteria, or yeasts/fungi. Source of these organisms are in the patient's own endogenous (normal) flora and may be from the hospital environment (exogenous sources).

Within a week the first organism to colonize is gram-positive organism followed by antibiotic susceptible gram-negative organisms. If wound closure is not done in time and broad-spectrum antibiotics are used, in that case the patient becomes infected and these flora may be replaced by yeasts, fungi, and antibiotic-resistant bacteria.

Methicillin-resistant *Staphylococcus aureus* (MRSA), enterococci, group A β-hemolytic *Streptococcus*, and coagulase negative *Staphylococcus* are the main gram-positive organisms.

Vancomycin-resistant enterococci (VRE) is of main concern because of rampant use of vancomycin. VRE may infect patients with H/O use of vancomycin, use of third-generation cephalosporins, and antibiotics active against anaerobes, a critically ill patient with severe underlying disease or immunosuppression, and a prolonged hospital stay.

Gram-negative organisms can cause serious infection in burn patients. Gram-negative bacteremia can cause 50% increase in predicted mortality for patients with bacteremia compared to those without bacteremia.

Serious infections in burn patients can be caused by *Candida* species and fungi such as *Aspergillus*, *Mucor*, and *Rhizopus*. *Candida* colonization appears to be primarily from endogenous sources. True fungi are ubiquitous in the environment and can be found in air handling and ventilation systems, plants, and soil.

Mode of Transmission

Contact, droplet, and airborne spread with direct or indirect contact remains the main mode of transmission, either through the hands of the personnel or from contact with inappropriately decontaminated equipment. Larger burn area will disperse greater volume of organisms in the environment.

Patient Susceptibility

Changes in physical, specific, and nonspecific immune responses determine the patient's susceptibility to infection.

INCIDENCE OF INFECTION

In the acute period following burn injury, infection of wound remains can cause potential serious complications. Children and elderly can have worst clinical outcome following burn injury. More so, obese adults and patients with comorbidities, such as diabetes, are at higher risk of morbidity and mortality.[4]

Number of studies over decades have shown that 42–65% of deaths in burn victims are because of infection. Additionally, burn patients who develop infections are susceptible to twice the mortality rate when compared with uninfected patients.

The 2016 National Burn Repository Report revealed that pneumonia, UTI, and cellulitis are the most prevalent infection that cause most common complications in burn. The most likely cause of this association being prolonged hospital stay and common use of Foley catheters.

Committee on the Organization and Delivery of Burn Care of the American Burn Association issued a consensus statement proposing a definition for e-classification of burn wound infections:

- Burn wound impetigo
- Opened burn-related surgical wound infection
- Burn wound cellulitis
- Invasive infection in unexcised burn wounds. Besides the common pathogens involved in burn patients with infection **(Table 1)**, some pathogens requiring specific concern are MDR strains of *Klebsiella pneumoniae*, MRSA, *P. aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*
- One should not ignore the possibility of carbapenem-resistant *Enterobacteriaceae outbreaks* in burn units.[5]

TABLE 1: Microorganisms causing invasive burn wound infections.

Group	*Species*
Gram-positive organisms	*Staphylococcus aureus*
	Methicillin-resistant *S. aureus*
	Coagulase-negative staphylococci
	Enterococcus spp.
	Vancomycin-resistant enterococci
Gram-negative organisms	*Pseudomonas aeruginosa*
	Escherichia coli
	Klebsiella pneumoniae
	Serratia marcescens
	Enterobacter spp.
	Proteus spp.
	Acinetobacter spp.
	Bacteroides spp.
Fungi	*Candida* spp.
	Aspergillus spp.
	Fusarium spp.
	Alternaria spp.
	Rhizopus spp.
	Mucor spp.
Viruses	Herpes simplex virus
	Cytomegalovirus
	Varicella-zoster virus

CULTURE AND SURVEILLANCE

This section highlights the various diagnostic and microbiological approaches and laboratory techniques for diagnosis of burn wound infection and current recommendations for a best approach to burn wound infection surveillance. Clinical signs and symptoms cannot be solely relied upon for diagnosis of burn wound infection. This warrants a need for routine sampling of burn wound either by surface swab or tissue biopsy for culture to detect infection early. Although, laborious and costly, the technique of quantitative culture of tissue biopsies with histological examination to ascertain verification of microbial extension into viable unburned tissue is the "gold standard" for diagnosing invasive burn wound infection (importantly in unexcised areas of eschar).[6]

Since the advent of early excision, for infection surveillance, lot of burn centers are practicing of sending burn wound surface swabs for both qualitative and semi-quantitative culture. However, review of the studies has shown equivocal results for best approach for burn wound infection surveillance. This could be because of following reasons:

- Variations in burn injuries in terms of severity and extent of burns
- Different approaches in sampling techniques and laboratory methods
- Historic data before early excision therapy. If we compare excised wound with unexcised wound, we are still to find a single method which will be reliable and clinically relevant. As per general consensus and lack of clear evidence, quantitative cultures of burn wound tissue biopsy samples along with concomitant histological analysis (even from burn areas where the skin is too thin for a biopsy) are the preferred infection surveillance approach for burn areas that have not been or cannot be excised.

They carry the advantage of being most convenient and least invasive approach currently available logistically based on equivocal clinical evidence.[7] Swab cultures and biopsies should only be done when there is a change in wound appearance and signs of systemic infection (especially sepsis and MDR infections) and thus avoiding missing source of infection in a cost-effective manner. Measurement of serum procalcitonin can be diagnostic in burn patients as raised value will point toward sepsis mostly bacterial.

With equivocal clinical evidence testing a variety of different approaches, the optimal sampling technique continues to be debated. Infection surveillance requires taking samples on a regular basis, by either biopsying tissue or collecting surface swabs from with multiple samples from several areas (minimizing contamination during specimen transport) of the burn wound to increase sensitivity and accuracy of the types and amounts of microorganisms present. Initially samples should be collected daily or every 48 hours following injury, when microbial flora is growing, but later on once a week sample should be collected in the absence of systemic signs of infection, when wound has been excised. Burn wound samples should be after arrival in the clinical microbiology laboratory, primary analytical procedures should follow standard operating practice including: Gram stain, surface swab culture; qualitative tissue culture; histological analysis, and distinguishing between colonization and infection.

Finally, burn centers should serially track individual patient-oriented specific pattern of microbial colonization, time-related changes in the predominant microbial flora, the antimicrobial susceptibility profiles of microorganisms, and trends in the nosocomial spread of these pathogens. Antibiogram data and outcome analyses of a concerned hospital should be taken into account before development of empirical treatment algorithms by a team of doctors including infectious disease physicians, plastic surgeon, and clinical microbiologist.

BURN UNIT OUTBREAK

After initial management of burns which majorly focuses on resuscitation, these patients become vulnerable to infection because of multiple factors. Even after major advances in care of these patients, infectious complications remain the main cause of death. Patients with severe burns often receive courses of antibiotics. Invasive procedures and surgical interventions are often required. All this leads to high incidence of infection including infection with multidrug-resistant organisms (MDRO) and outbreaks related to it.

There have been several reported MDRO outbreaks in burn units with successful control.[8] One systematic review combined data from 21 studies to show that MDRO outbreaks in burn centers could be successfully managed by comprehensive infection control measures in 81% of the units. Different studies have undertaken different control measures such as microbial screening, continuous staff education, strict hand hygiene practices, strict contact isolation precautions, and enhanced cleaning and environmental disinfection.

To investigation the outbreaks, knowledge of the survival mechanisms of inanimate environments and the dispersion mechanisms of MDRO remains fundamental to stopping these outbreaks. It would be pertinent to investigate the taps designs and drains to decrease their contamination and to avoid dispersal, since one of the important mechanism of transmission is related to splash from the drain.[9]

Some of the widely used measures to avoid outbreaks includes: (1) Microorganism screening together with weekly prevalence screening can lead to early detection of colonized patients during outbreak period, (2) screening for healthcare workers for MRSA and decolonization, (3) using fresh and clean PPEs (personal protective equipment) in case of

physical contact with patients and their environment, and (4) proper environmental decontamination and adequate cleaning practices.

Closing down burn units during outbreaks remains controversial in view of scarcity of data with regard to the indication and efficacy of closure. Though this option has been found favorable by few researchers, especially when closing down was followed by intensive cleaning and disinfection of the whole facility. However, full consideration should be given to other mechanisms of spread. Above all comprehensive infection control measures remain critically important in MDRO outbreak management in burn units.

Infection Control

The core concepts of infection control in burns are well established for decades and have undergone many changes. Infection control measures include sterile gloves, aseptic technique, using separate room/cubicle, and wearing mask while changing dressing. Use of prophylactic antibiotics, use of infrequent dressing change, and use of sterile sheet after the burn wound has been exposed. In addition to obvious sources and areas of infection, there are other vulnerable tissues and organ systems in the burn patient that require special consideration. Indwelling catheters, intravenous lines, and intra-arterial lines should be taken care of as these are sources of infection.[10] Simple isolation techniques can control outbreak of resistant bacteria that has been effectively done by several burn centers.

Standard and transmission control: A protocol for proper hand hygiene and contact precautions needs to be followed stringently. Ongoing contextual education is a must to sensitize healthcare providers to infection control, prevention, and management in burns.[11] Antimicrobial stewardship protocol needs to be followed with unit-specific antibiograms which are regularly updated. Still there are no specific guidelines regarding the use of systemic prophylactic antibiotics in burn patients.

Strict upper airway management is the key to prevent pneumonia. In the prophylaxis of pneumonia, selective digestive decontamination may play an important role. Centers for Disease Control and Prevention (CDC) guidelines should be followed by burn units for prevention of healthcare-associated pneumonia.

The vascular access site should be in a nonburnt area or farthest away from the burn area. In burn patients, changing of central venous lines has not been extensively studied. Removal of all unnecessary devices constitutes an important strategy in infection prevention. The introduction of silver-impregnated devices (e.g., central lines and indwelling urinary catheters) may be used in the patients requiring these devices for a prolonged duration. Removal of the urinary catheter if clinically not indicated closed urinary drainage system and urinary catheter care.

Early excision for burn wounds is an important strategy to prevent infection. Every time burn wound has to be inspected to see the change in character or amount of wound drainage. While handling the open wound and dressing materials, strict aseptic technique should be used. Clinical assessment of wound determines frequency of dressings.

Isolation Protocols

Barrier protection including caps, masks, gowns, gloves, aprons, and shoe covers is a must while caring for burn patients. Burn wound infection and colonization are to be prevented by use of topical antimicrobials which include silver sulfadiazine, mafenide acetate, and nanocrystalline silver dressing along with nystatin or other antifungals. Cerium is used in combination with silver sulfadiazine.

Both patients and staffs should undergo nasal decolonization for *S. aureus*/MRSA carriers mupirocin ointment along with oral antibiotics at discretion and 4% chlorhexidine both for patients and staffs are to be used twice a week for nasal decolonization. Environmental measures: thorough cleaning; control of disinfection and sterilization procedures: should be done in a timely measure.

Candidemia: Topical nystatin is to be used to decrease fungal burn wound infection and also may be helpful in continuous systemic fungal infection. Early excision of burn wounds has been shown to decrease systemic *Candida* infections.

A multidisciplinary team should be treating burn patients which include infectious disease specialist, burn surgeon, and pharmacist.

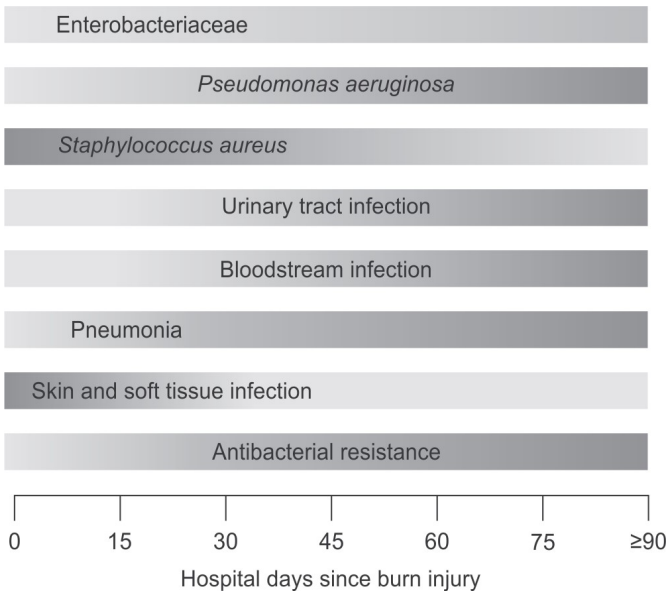


Fig. 1: Timeline of common infections and pathogens after burn injury.

REFERENCES

1. Greenhalgh DG, Saffle JR, Holmes JH 4th, Gamelli RL, Palmieri TL, Horton JW, et al. American Burn Association consensus conference to define sepsis and infection in burns. J Burn Care Res. 2007;28(6):776-90.
2. Church D, Elsayed S, Reid O, Winston B, Lindsay R. Burn wound infections. Clin Microbiol Rev. 2006;19(2):403-34.
3. Soedjana H, Nadia J, Sundoro A, Hasibuan L, Rubianti IW, Putri AC, et al. The profile of severe burn injury patients with sepsis in Hasan Sadikin Bandung General Hospital. Ann Burns Fire Disasters. 2020;33(4):312-6.
4. American Burn Association. National Burn Repository® 2016. [online] Available from:https://ameriburn.org/wp-content/uploads/2017/05/2016abanbr_final_42816.pdf. [Last accessed February 2022].
5. Lachiewicz AM, Hauck CG, Weber DJ, Cairns BA, van Duin D. Bacterial infections after burn injuries: Impact of multidrug resistance. Review Clinical Infectious Diseases; 2017;65(12):2130-6.
6. Steer JA, Papini RP, Wilson AP, McGrouther DA, Parkhouse N. Quantitative microbiology in the management of burn patients. I. Correlation between quantitative and qualitative burn wound biopsy culture and surface alginate swab culture. Burns. 1996;22(3):173-6.
7. Church D, Elsayed S, Reid O, Winston B, Lindsay R. Clin Microbiol Rev. 2006;19(2):403-34.
8. Aguilera-Sáez J, Andreu-Solà V, Larrosa Escartín N, Rodríguez Garrido V, Armadans Gil L, Sánchez García JM, et al. Extensively drug-resistant Pseudomonas Aeruginosa outbreak in a burn unit: management and solutions. Ann Burns Fire Disasters. 2019;32(1):47-55.
9. Wang C, Zhang F, Breland A, Lineaweaver WC. Efficacy of infection control measures in managing outbreaks of multidrug- resistant organisms in burn units. Ann Plast Surg. 2021;86(4S Suppl 4):S454-7.
10. Rafla K, Tredget EE. Infection control in the burn unit. Burns. 2011;37(1):5-15.
11. Hodle AE, Richter KP, Thompson RM. Infection Control practices in U.S. burn units. J Burn Care Res. 2006;27(2):142-51.

SECTION

10

Hemodynamic Monitoring

CHAPTER 59

Hypotension Prediction Using Artificial Intelligence

Avneep Agarwal, Kamal Maheshwari

INTRODUCTION

Intensive care units (ICUs) and operating rooms (ORs) are complex environment that require critical decision to be made by clinicians in timely fashion. Failure to act leads to poor patient outcomes. Increasing amount of continuous monitoring and electronic health records data, and sick patient population occasionally restricts appropriate clinical decision making. Making sense of the large amount of information is crucial for patient care and is an opportune setting to harness artificial intelligence (AI) technology in ICU and OR.[1] Artificial intelligence is broad field dedicated to theory and development of computer systems that can mimic human intelligence, such as visual perception, speech recognition, decision-making, and language skills.[2] Machine learning and natural language processing are techniques that enable AI **(Fig. 1)**. Artificial intelligence has the potential to improve both clinical decision-making and patient safety.[3] Not all problems can be solved with AI, but initial work in the area of hemodynamic management shows promise. Here we review development, validation, and the role of hypotension prediction algorithms in clinical care.

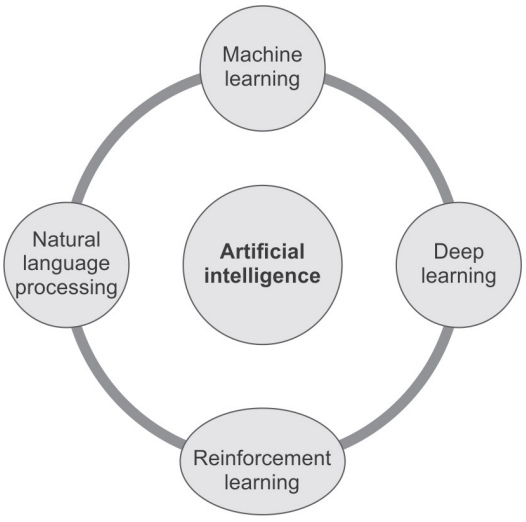


Fig. 1: Artificial intelligence and machine learning.

HYPOTENSION PREDICTION

Hypotension is associated with worse outcomes in ICU[4] and OR[5]. In general, hypotension management includes optimizing preload, afterload, and contractility and reversing or treating the primary cause.[6] However, hypotension is only treated once it has happened (*reactive management)*, and patients are always exposed to some amount of hypotension. In contrast, if we can predict hypotension in coming minutes or hours we can institute treatment early before patient gets exposed to hypotension (*proactive management)*. First we have to define what level of hypotension is significant, in other words what are we predicting. There is substantial evidence supporting that mean arterial pressure (MAP) should be kept above 60–70 mm Hg to reduce postoperative myocardial injury, renal injury, and cerebral injury.[4,5,7] Therefore, it is logical that lot of initial work on hypotension prediction is focused on predicting MAP <65 mm Hg. Next comes the question, what duration of the hypotensive episode is significant. In operating room, MAP <65 mm Hg for 1 minute[8] is commonly chosen as hypotension "alert" definition whereas in ICU few MAP reading <65 mm Hg for 30 minutes or 60 minutes below 65 is chosen as hypotension alert.

ALGORITHM DEVELOPMENT

An AI approach by which we can preemptively predict and possibly act to prevent these hypotensive episodes can have a meaningful impact on clinical outcomes. Hatib et al. have successfully developed a hypotension prediction algorithm by applying machine learning to large data sets of arterial pressure waveforms.[8] They used a retrospective cohort, consisting of 1,334 patients' records with 545,959 minutes of arterial waveform recording and 25,461 episodes of hypotension; and a prospective, local hospital cohort, consisting of 204 patients' records with 33,236 minutes of arterial waveform recording and 1,923 episodes of hypotension to develop their algorithm. The algorithm calculates a score [hypotension prediction index (HPI)] based

on analysis of arterial pressure waveform and assists in prediction of an upcoming hypotensive event defined as MAP < 65 mm Hg. They reported a sensitivity and specificity of 88 and 87% 15 minutes before a hypotensive event, 89 and 90% 10 minutes before, 92 and 92% 5 minutes before. Also, they found that HPI was significantly more accurate to predict arterial hypotension events 5, 10, and 15 minutes before they occurred; when compared to MAP trends. It is now commercially available as Acumen HPI software (Edwards Lifesciences, Irvine, USA). The HPI software analyzes the patient's arterial waveform and uses machine learning to compare it with a dataset of known waveforms to provide a numerical value. It is a value between 1 and 100; and higher the number, the more likely a hypotensive event is to occur. An alarm set at 85 can help in providing the clinician an early warning sign that hypotension is imminent.

Noninvasive arterial pressure waveform monitoring with, for example, finger cuff can also be used to predict hypotensive episode.[9] Moghadam et al. successfully used noninvasive blood pressure readings to predict hypotension in ICU.[10,11]

ALGORITHM EVALUATION

Hypotension prediction index has been shown to be superior to traditional parameters such as MAP, stroke volume variation, cardiac output, heart rate, and pulse pressure variation in predicting hypotension. Davies et al. showed that HPI could predict hypotension 5 minutes in advance with a sensitivity and specificity of 86% (0.93 area under the curve).[12] In another study, Ranucci et al. found that HPI had a poor level of calibration at the cut-off value of 85, as sensitivity was only 62% and specificity was 77%, with an associated negative predictive value of 98% and a positive predictive value of only 13%. When the cut-off value was increased to a HPI value of 98, positive predictive value (PPV) increased to 64% and negative predictive value (NPV) decreased to 95% in this study.[13]

Although AI algorithms have been shown to predict hypotension, but there is mixed evidence on whether this leads to less hypotension. Hypotension Prediction during Surgery (HYPE) trial published in JAMA last year showed that the use of HPI with therapeutic management decision algorithm reduces hypotension.[14] Wijnberge et al. randomized 68 patients who were undergoing elective noncardiac surgery to intraoperative management guided by an AI-based early warning system (intervention group) or standard care (control group). The primary objective was to test whether the use of machine learning-derived early warning system will reduce time-weighted average of hypotension during the surgery. In the intervention group, the software issued an alarm when the risk exceeded 85% and encouraged the anesthesiologist to take preemptive action. In the control group, patients were managed per standard care with invasive arterial monitoring, but arterial wave data still flowed to the AI algorithm in silent mode. Their preliminary study demonstrated that application of machine learning-derived early warning system for pending intraoperative hypotension significantly reduced the time-weighted average of hypotension during surgery. However, it was a single-center randomized control study with a small sample size and they assessed a physiological outcome instead of a clinical outcome.

In contrast, Maheshwari et al. evaluated if HPI algorithm made a difference when compared to usual care and found that it helped in predicting hypotension but did not actually reduce hypotension.[15] They randomized 214 patients who were undergoing elective noncardiac surgery to intraoperative management guided by an AI-based early warning system (index guidance group) or standard care (unguided group). The primary objective was to test whether the use of machine learning-derived early warning system will reduce the amount of hypotension defined as time-weighted average MAP <65 mm Hg. They found that index guidance did not reduce amount of hypotension <65 mm Hg, nor did it reduce hypotension <60 or 55 mm Hg. Authors noticed that half of the alerts were not followed by treatment, may be due to short warning time, complex treatment algorithm, or clinicians ignoring the alert. The disparate results from these two studies performed in different clinical setting highlight the need of critical evaluation of implementation of AI algorithms. A prediction alert should be followed by an appropriate intervention, to be successful.

CONCLUSION

Machine learning algorithms offer a promising approach for earlier detection of hypotension and to guide the precise clinical decisions under uncertain conditions. However, there are knowledge gaps to identify meaningful alerts and to identify appropriate clinical interventions. Personalized algorithmic treatment pathway in critical care setting requires further research before implementation in the clinical workflow. Appropriate evaluation in diverse patient population and clinical settings is needed to assess the impact of novel technology on postoperative outcomes.

REFERENCES

1. Maheshwari K, Ruetzler K, Saugel B. Perioperative intelligence: applications of artificial intelligence in perioperative medicine. J Clin Monit Comput. 2020;34:625-8.
2. Russell SJ, Norvig P. Artificial Intelligence: A Modern Approach Prentice Hall Series in Artificial Intelligence, 3rd edition. Upper Saddle River, NJ: Prentice Hall; 2010.
3. Mathur P, Burns ML. Artificial Intelligence in Critical Care. Int Anesthesiol Clin. 2019;57:89-102.

4. Maheshwari K, Nathanson BH, Munson SH, Khangulov V, Stevens M, Badani H, et al. The relationship between ICU hypotension and in-hospital mortality and morbidity in septic patients. Intensive Care Med. 2018;44:857-67.
5. Salmasi V, Maheshwari K, Yang D, Mascha EJ, Singh A, Sessler DI, et al. Relationship between Intraoperative Hypotension, Defined by Either Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury after Noncardiac Surgery: A Retrospective Cohort Analysis. Anesthesiology. 2017;126:47-65.
6. Rozental O, Thalappillil R, White RS, Tam CW. To Swan or Not to Swan: Indications, Alternatives, and Future Directions. J Cardiothorac Vasc Anesth. 2021;35:600-15.
7. Alhazzani W, Evans L, Alshamsi F, Moller MH, Ostermann M, Prescott HC, et al. Surviving Sepsis Campaign Guidelines on the Management of Adults with Coronavirus Disease 2019 (COVID-19) in the ICU: First Update. Crit Care Med. 2021;49:e219-e234.
8. Hatib F, Jian Z, Buddi S, Lee C, Settels J, Sibert K, et al. Machine-learning Algorithm to Predict Hypotension Based on High-fidelity Arterial Pressure Waveform Analysis. Anesthesiology. 2018;129:663-74.
9. Maheshwari K, Buddi S, Jian Z, Settels J, Shimada T, Cohen B, et al. Performance of the Hypotension Prediction Index with non-invasive arterial pressure waveforms in non-cardiac surgical patients. J Clin Monit Comput. 2021;35:71-8.
10. Moghadam MC, Masoumi E, Bagherzadeh N, Ramsingh D, Kain ZN. Supervised Machine-Learning Algorithms in Real-time Prediction of Hypotensive Events. Annu Int Conf IEEE Eng Med Biol Soc. 2020:5468-71.
11. Moghadam MC, Masoumi E, Kendale S, Bagherzadeh N. Predicting hypotension in the ICU using noninvasive physiological signals. Comput Biol Med. 2021;129:104120.
12. Davies SJ, Vistisen ST, Jian Z, Hatib F, Scheeren TWL. Ability of an Arterial Waveform Analysis-Derived Hypotension Prediction Index to Predict Future Hypotensive Events in Surgical Patients. Anesth Analg. 2020;130:352-9.
13. Ranucci M, Barile L, Ambrogi F, Pistuddi V, Surgical and Clinical Outcome Research (SCORE) Group. Discrimination and calibration properties of the hypotension probability indicator during cardiac and vascular surgery. Minerva Anestesiol. 2019;85:724-30.
14. Wijnberge M, Geerts BF, Hol L, Lemmers N, Mulder MP, Berge P, et al. Effect of a Machine Learning-Derived Early Warning System for Intraoperative Hypotension vs Standard Care on Depth and Duration of Intraoperative Hypotension During Elective Noncardiac Surgery: The HYPE Randomized Clinical Trial. JAMA. 2020;323:1052-60.
15. Maheshwari K, Shimada T, Yang D, Khanna S, Cywinski JB, Irefin SA, et al. Hypotension Prediction Index for Prevention of Hypotension during Moderate- to High-risk Noncardiac Surgery. Anesthesiology. 2020;133:1214-22.

CHAPTER 60

Artificial Intelligence and Management of Hypotension

Piyush Mathur, Ashish K Khanna, Tavpritesh Sethi

INTRODUCTION

Shock or hypotension amongst critically ill patients is common with a reported incidence as high as 50%.[1] Perioperative hypotension is associated with significant harm.[1,2] Specifically, mean arterial pressures in the range of 65–75 mm Hg or lower appear to be the inflection point for an increasing risk for myocardial injury, delirium, acute kidney injury, and mortality.[3-5] A similar situation is seen in critically patients, where even higher pressures than those are traditionally considered "normal" may not be entirely safe.[5] While several thousands of intensive care unit (ICU) patients have been tested using retrospective data and thresholds of harm anywhere between 75 and 90 mm Hg clearly established, the same cannot be said for the few randomized controlled trials of ICU hypotension. The only large randomized trial done by the SEPSISPAM group failed to establish a clear difference between a higher versus lower blood pressure target in septic shock.[6] While the authors did see higher incidence of renal injury in chronically hypertensive patients when exposed to lower pressures in posthoc analysis, this evidence has not changed guidelines as yet, which continue to recommend a mean pressure of 65 mm Hg in a patient with septic shock during resuscitation.[7] Traditionally, an approach to hypotension has been mostly reactive, i.e., responding with fluids, vasopressors, and inotropes and other combination therapy after the occurrence and documentation of hypotension has happened. However, exposure to even a few minutes of hypotension increases the risk for organ failure. Knowing this, it becomes necessary to proactively predict and modulate the risk of hypotension and where possible, prevent this from happening. Here the role of various machine learning models, most of which have been trained on the shape of the arterial line waveform, have come into play.[8] We describe the role of artificial intelligence (AI) in the realm of hypotension and resuscitation in the ICU, with a focus on new evidence and real world applications of the same.

ARTIFICIAL INTELLIGENCE

Artificial intelligence is a super-set of a spectrum of computational approaches which attempt to replicate human intelligence **(Fig. 1)**. These approaches include rule-based systems, machine learning, and deep neural networks. Heterogeneous data including structured tables, unstructured text, signals, and images are used to train such AI models. Although AI is almost synonymous with the deep learning in computational disciplines, there is tremendous scope for shallow learning yet more interpretable approaches in clinical models.

Machine learning refers to a subset of AI that focuses on learning with data, instead of starting from a hypothesis to derive classification or regression approaches with the goal of building models with high degree of prediction accuracy.[9] Deep learning utilizes neural networks with multiple layers and specialized architectures such as convolution, long short-term memory networks, and attention, in order to mimic the working of brain. The learning of such a network happens with multiple rounds of forward propagation and back propagation operations to find the optimum weights for the network.[9] Natural language processing (NLP) is the subset of AI that focuses on text and can be used to process words or

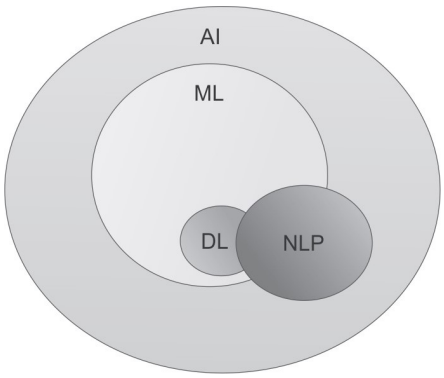


Fig. 1: Artificial intelligence (AI) and its subgroups.
(ML: machine learning; DL: deep learning; NLP: natural language processing)

sentences to develop models which can understand spoken or written content with a significant degree of accuracy. Another way to classify AI and its subsets is based on how AI learns to develop solutions such as supervised learning, unsupervised learning, and reinforcement learning. In supervised learning, the models are provided with labeled output data to learn from, whereas unsupervised learning is based primarily on pattern recognition. Reinforcement learning is based on an agent learning from positive or negative reinforcements based on interactions within its environment.[9] New algorithms and analytics techniques are introduced daily in this fast moving field to overcome many of these limitations and develop new solutions.

Patient monitoring generates an enormous amount of data, which if captured effectively can spur the development of AI-driven algorithms for critical care. The recent years have indeed seen an increasing number of such models researched and developed for the management of hypotension.[9] In critically ill patients, such algorithms are expected to lead to early detection to enable treatment planning and decision making for hypotensive patients.[10-13]

Artificial Intelligence and Prediction or Diagnosis of Hypotension

A key part of management of hypotension is accurate diagnosis and possibly predicting it ahead of time to prevent it from occurring. Over the last few years, many prediction models have been built using various different sources of data such as vital signs, arterial waveform, and noninvasive monitoring device data. Yoon et al. using time series data of vitals from MIMIC-3 dataset were able to build a random forest classifier model which predicts hypotension with an area under the receiver operating characteristic (AUROC) of 0.88 and an area under the precision-recall curve (AUPRC) of 0.77, up to 60 minutes before its onset.[12] They also linked this prediction to alerts for bedside implementation with high degree of sensitivity and reliability (0.79 alerts/subject/h with 92.4% sensitivity).

Hatib et al. developed hypotension prediction index (HPI), an index which predicts the risk of development of hypotension with high degree of accuracy (sensitivity of 88% and specificity of 87%), 15 minutes before its onset in an intraoperative setting. Instead of using vitals, this index is derived out of arterial waveform derived features.[14] While initial application of this index has been in the operating rooms, extension of the same can be considered for critical care settings.

Considering the challenges with invasive monitoring amongst ICU patients and since every patient does not have invasive hemodynamic monitors, Moghadam et al. investigated noninvasive mean arterial blood pressure-based machine learning prediction models and found high predictive value with them too [sensitivity of 84%, positive predictive value (PPV) of 73%, and F1-score of 78%].[13] This modeling was also performed using the MIMIC-3 dataset and showed that algorithm performance improved with increasing frequency of data (blood pressure) sampling. Considering the two studies, we could consider start of application of these AI model-based risk stratification approach using noninvasive blood pressure measurement and then based on predictions, consider advancing to either more frequent blood pressure monitoring or placement of invasive monitoring devices to capture blood pressure with higher accuracy and frequency. This approach would not be different from current standard practice of utilizing clinician's experience and intuition to advance to invasive hemodynamic monitoring in patients who they consider are at higher risk of deterioration.

There are other innovative methods consistent with our knowledge of pathophysiology of shock, which are being researched and developed for diagnosis and prediction of shock. Nagori et al. developed a machine learning model trained upon thermal images for continuous, noncontact detection and prediction of shock amongst the pediatric critical ill patients.[11] Using just thermal images of the pediatric patients, they were able to accurately classify shock (AUROC—0.75) and predict its likelihood up to 12 hours ahead of its onset (AUROC—0.77 at 3 hours, 0.69 at 12 hours).

With advances in automated interpretation of echocardiogram, the ability to continuously monitor patients and democratization of these key skill set is likely to change. A study done by Narang et al. showed deep learning model supported acquisition of echocardiography images can be successfully done by untrained bedside nurses at par with trained sonographers.[15] Thus, in the future, we can see expanded application of continuous echocardiographic assessments aiding clinicians in diagnosis, prediction, and management of hypotensive states.

Artificial Intelligence and Management of Hypotension

Management of hypotension beyond diagnosis and prediction involves understanding the cause and managing the key aspects of cardiac contractility, preload, and afterload. Early research has focused on development and validation of AI tools based on these key aspects.

Based on the HYPE trial, which focused on intraoperative hypotension management using HPI, there were decreased instances of hypotension when clinicians followed HPI guidance compared with standard of care.[16] Maheshwari et al. conducted a pilot study to assess utilization of guidance from HPI for management of intraoperative hypotension, where treatment suggestions included one of the following: Vasopressor administration, fluid administration, inotrope administration, or observation.[17] In this trial, index guidance did not reduce the amount of intraoperative hypotension,

possibly since half of the alerts were not followed by treatment, due to various factors including short warning time, complex treatment algorithm, or clinicians ignoring the alert.

Fluid and vasopressor management are a key part of the decision-making process in prevention and treatment of hypotension occurring from common disease states such as sepsis in ICU setting. Komorowski et al. developed a reinforcement learning agent, the AI clinician, built over two large datasets, MIMIC-3 and eICU Research Institute Database (eRI) and demonstrated that the patients who received treatment guided by the AI clinician had lower mortality compared to those actual treated by clinicians amongst the studied sepsis dataset patients.[10] They demonstrated that the policy set by the model provided for more use of vasopressor and possibly avoided excessive fluid administration. They concluded that their model provides individualized and clinically interpretable treatment decisions for sepsis that could improve patient outcomes. Similarly, Kwak et al., using serial physiological data, created a multivariate time series bidirectional long short-term memory (Bi-LSTM) model to predict the need for vasopressor therapy, using physiologic data collected 21 hours prior to prediction time with area under the curve (AUC) of 0.83 [95% confidence interval (CI) 0.82–0.83].[18] It is likely that in the near future, similar models will guide clinician decision-making, with precision guidance taking into context patient's pathophysiology. Better adherence to existing management guidelines supported by data-driven models, in a complex medical decision-making environment, might lead to better overall patient outcomes.

Despite significant advances in invasive and noninvasive fluid status monitoring tools such as noninvasive cardiac output monitors, echocardiography, determination of fluid status, and precision management of optimal fluid delivery at bedside still remains a significant challenge. AI provides us with an unparalleled opportunity to possibly leverage existing sources of data or integrate multimodal data and provide precision guidance. A recent multicenter, prospective study of an investigational fluid management software in patients undergoing surgery with an arterial catheter evaluated the impact of software-recommended fluid boluses on a target increase in the stroke volume (SV).[19] Fluid boluses recommended by the software, 66% (95% CI, 62–70%) resulted in desired SV increases more often, compared to 41% (95% CI, 38–44%) of the manual clinician-initiated boluses (p <0.0001). Also, the mean increase in SV after boluses recommended by the software was 14.2 ± 13.9% *versus* 8.3 ± 12.1% (p <0.0001) for those initiated independently by the clinicians. The authors concluded that automated assessment of fluid responsiveness, its related guidance, and based on a higher percentage of software-recommended boluses meeting the target increase, may help clinicians to optimize intraoperative fluid management during noncardiac surgery. AI systems such as these in combination with the work done by Komorowski et al. are likely to provide better guidance and continuation for dynamic fluid resuscitation, especially in the perioperative setting, to improve outcomes, especially amongst the critically ill patients.[10,19] Even challenge of vascular access amongst these critically ill patients, which is considered to be an important skill set of any critical care practitioner, is likely to be overcome with assistance of robotic and deep learning tools in the near future.[20]

Challenges

While there is significant excitement about adoption of AI tools in healthcare, it is not without its own set of challenges. One of the commonly cited barriers to adoption of AI-based clinical decision support tools is poor understanding of how the guidance is generated and therefore it is commonly labeled as a "black box."[21] While many aspects of AI such as deep learning and model development through its associated hidden layers may not be explainable, many other parts of AI are both explainable and interpretable. With increasing emphasis on development of explainable and interpretable guidance through AI systems, we are likely to see these concerns addressed and barriers going down.

Despite a steady increase in research and development of multiple models of application of AI in healthcare, generalizability, scalability, and utility in current clinical settings have been limited.[9] Bias and trust in the AI models are another set of common and valid concerns which are a challenge for their adoption in clinical practice. Reasons for bias are related to small datasets, missing or inaccurate data, biased datasets, inappropriate model development, or implementation amongst others. Clearly more work needs to be done to ensure we have tools and techniques to assess for bias, correct or adjust the models for bias, and then build trust amongst healthcare providers for adoption. Hence, certain frameworks for evaluation and implementation of AI in healthcare settings such as "Translational Evaluation of Healthcare AI" (TEHAI) proposed by Reddy et al. are likely to provide guidance in the future.[22]

There is a significant gap in understanding of AI amongst clinicians and of the complex nature of healthcare amongst data scientists. There have been many efforts to educate both these scientific groups and platforms being built to unify and synchronize efforts toward building a common strategy. Cosgriff et al. proposed building clinical AI departments within hospitals which can create and facilitate strategy for joint development of AI solutions.[23] In response, Mathur et al. proposed key metrics for evaluation of success of such a strategy.[24] At minimum, clinicians and data scientists need to develop a better understanding of the research, medical literature, and the AI tools being developed at an exponential pace, to be able to determine best utility and adoption for improved patient care.[9,25]

CONCLUSION

While we have seen early but limited success in research and development of focused AI solutions, it is evident that the AI presents us with an opportunity to leverage existing data in an unprecedented manner to manage our patients better. While key vital signs or their derivatives (e.g., SV variation) have been used traditionally in clinical settings for management of hypotension, the ability of AI to exploit unused features such as arterial waveform, combinational features across structured and unstructured data, thermal imaging, and echocardiography will likely change how we predict, diagnose, and manage hypotension. Explainable and interpretable decision support tools will guide precision management of fluids, vasopressors, and likely accurately predict response to therapy. Increased adoption of these AI tools is likely to be supported through validation of the AI systems, democratization of key skill sets, better education, comprehensive strategy for value-based implementation, and proven efficacy to impact patient care.

REFERENCES

1. Smischney NJ, Shaw AD, Stapelfeldt WH, Boero IJ, Chen Q, Stevens M, et al. Postoperative hypotension in patients discharged to the intensive care unit after non-cardiac surgery is associated with adverse clinical outcomes. Crit Care. 2020;24(1):682.
2. Khanna AK, Shaw AD, Stapelfeldt WH, Boero IJ, Chen Q, Stevens M, et al. Postoperative Hypotension and Adverse Clinical Outcomes in Patients Without Intraoperative Hypotension, After Noncardiac Surgery. Anesth Analg. 2021;132(5):1410-20.
3. Khanna AK, Maheshwari K, Mao G, Liu L, Perez-Protto SE, Chodavarapu P, et al. Association between mean arterial pressure and acute kidney injury and a composite of myocardial injury and mortality in postoperative critically ill patients: A retrospective cohort analysis. Crit Care Med. 2019;47(7):910-7.
4. Farag E, Liang C, Mascha EJ, Argalious MY, Ezell J, Maheshwari K, et al. Association between use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and postoperative delirium. Anesthesiology. 2020;133(1):119-32.
5. Maheshwari K, Ahuja S, Khanna AK, Mao G, Perez-Protto S, Farag E, et al. Association between perioperative hypotension and delirium in postoperative critically ill patients: A retrospective cohort analysis. Anesth Analg. 2020;130(3):636-43.
6. Asfar P, Meziani F, Hamel JF, Grelon F, Megarbane B, Anguel N, et al. High versus low blood-pressure target in patients with septic shock. N Engl J Med. 2014;370(17):1583-93.
7. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock 2021. Crit Care Med. 2021;49(11):e1063-43.
8. Geerts BF, Vlaar AP, Veelo DP. Reducing intraoperative hypotension using a machine learning-derived early warning system-reply. JAMA. 2020;324(8):807-8.
9. Mathur P, Burns ML. Artificial intelligence in critical care. Int Anesthesiol Clin. 2019;57(2):89-102.
10. Komorowski M, Celi LA, Badawi O, Gordon AC, Faisal AA. The artificial intelligence clinician learns optimal treatment strategies for sepsis in intensive care. Nat Med. 2018;24(11):1716-20.
11. Nagori A, Dhingra LS, Bhatnagar A, Lodha R, Sethi T. Predicting hemodynamic shock from thermal images using machine learning. Sci Rep. 2019;9(1):91.
12. Yoon JH, Jeanselme V, Dubrawski A, Hravnak M, Pinsky MR, Clermont G. Prediction of hypotension events with physiologic vital sign signatures in the intensive care unit. Crit Care. 2020;24(1):661.
13. Moghadam MC, Masoumi E, Kendale S, Bagherzadeh N. Predicting hypotension in the ICU using noninvasive physiological signals. Comput Biol Med. 2021;129:104120.
14. Hatib F, Jian Z, Buddi S, Lee C, Settels J, Sibert K, et al. Machine-learning algorithm to predict hypotension based on high-fidelity arterial pressure waveform analysis. Anesthesiology. 2018;129(4):663-74.
15. Narang A, Bae R, Hong H, Thomas Y, Surette S, Cadieu C, et al. Utility of a deep-learning algorithm to guide novices to acquire echocardiograms for limited diagnostic use. JAMA Cardiol. 2021;6(6):624-32.
16. Wijnberge M, Geerts BF, Hol L, Lemmers N, Mulder MP, Berge P, et al. Effect of a machine learning-derived early warning system for intraoperative hypotension vs standard care on depth and duration of intraoperative hypotension during elective noncardiac surgery: The HYPE randomized clinical trial. JAMA. 2020;323(11):1052-60.
17. Maheshwari K, Shimada T, Fang J, Ince I, Mascha EJ, Turan A, et al. Hypotension Prediction Index software for management of hypotension during moderate- to high-risk noncardiac surgery: protocol for a randomized trial. Trials. 2019;20(1):255.
18. Kwak GH, Ling L, Hui P. Predicting the need for vasopressors in the intensive care unit using an attention based deep learning model. Shock. 2021;56(1):73-9.
19. Maheshwari K, Malhotra G, Bao X, Lahsaei P, Hand WR, Fleming NW, et al. Assisted fluid management software guidance for intraoperative fluid administration. Anesthesiology. 2021;135(2):273-83.
20. Chen AI, Balter ML, Maguire TJ, Yarmush ML. Deep learning robotic guidance for autonomous vascular access. Nat Mach Intell. 2020;2(2):104-15.
21. Panch T, Mattie H, Celi LA. The "inconvenient truth" about AI in healthcare. NPJ Digit Med. 2019;2:77.
22. Reddy S, Rogers W, Makinen VP, Coiera E, Brown P, Wenzel M, et al. Evaluation framework to guide implementation of AI systems into healthcare settings. BMJ Health Care Inform. 2021;28(1):e100444.
23. Cosgriff CV, Stone DJ, Weissman G, Pirracchio R, Celi LA. The clinical artificial intelligence department: a prerequisite for success. BMJ Health Care Inform. 2020;27(1):e100183.
24. Mathur P, Maheshwari K, Papay F. In response to 'The clinical artificial intelligence department: a prerequisite for success'. BMJ Health Care Inform. 2020;27(3):e100221.
25. Liu Y, Chen PC, Krause J, Peng L. How to read articles that use machine learning: Users' guides to the medical literature. JAMA. 2019;322(18):1806-16.

CHAPTER 61

Artificial Intelligence and Algorithmic Approach to Circulatory Shock

Bharat Jagiasi, Tanmay Jain, Sheila Nainan Myatra

INTRODUCTION

Circulatory shock manifests when the organs and body tissues receive inadequate blood supply which causes deficiency of cellular oxygen and nutrients supply to such an extent that organs become damaged resulting in a life-threatening condition requiring immediate medical treatment. The most common signs seen are hypotension, tissue hypoperfusion, and hyperlactatemia.[1] Commonly four types of shock are described in literature: Hypovolemic shock (e.g., hemorrhagic shock), cardiogenic shock, distributive shock (e.g., septic shock), and obstructive shock. The mortality rate is high and depends on which type of shock is being described. Stringent hemodynamic monitoring for quick recognition of shock is thus an essential part of management of such intensive care unit (ICU) patients.

Artificial intelligence (AI) is a technical tool which helps us to understand and design existing computer systems to display intellectual processes, e.g., reasoning and decision-making, which are usual characteristics of human beings.[2,3] Machine learning (ML) which is a discipline of AI has emerged as a popular tool used for diagnosing conditions, assisting treatment, and predicting patient outcomes.[4] In this article, we will discuss the role and applications of AI in the diagnosis and management of circulatory failure.

CHALLENGES IN MANAGEMENT OF CIRCULATORY SHOCK

Blood pressure is considered one of the major determinants of organ perfusion. Hypotension during operative procedures or in the ICU setting has been previously defined as mean arterial pressure (MAP) of <65 mm Hg,[5] which is associated with higher rates of complications such as postoperative myocardial infarction and acute kidney injury, and these usually start to develop within only a few minutes of onset of hypotension.[6] Subtle clinical, hemodynamic, and biochemical signs often precede the fall in blood pressure and failure to recognize them leads to delay in therapeutic intervention.

Time is of the Essence

Intensivists largely rely on a combination of clinical, hemodynamic, and biochemical signs for detection of circulatory shock. In clinical practice, it is treated only once low blood pressure is indicated by the monitor or where obvious clinical signs are present such as change in mental status, very feeble pulse, cold clammy exteriors, and decreased urine output. Smith and Wood found that 51% of patients had one or more abnormal vital signs in the form of tachycardia, hypotension, hypothermia or hyperthermia, tachypnea, altered mental status, or decreased urine output in the 24-hour period prior to cardiac arrest.[7] Prompt identification of these warning signs and timely treatment of shock are absolutely necessary as it has been found that harmful effects of circulatory shock are initially reversible in majority of patients.

Monitor Alarms—Double-edged Sword

In clinical practice, intensivists intermittently monitor vital signs and primarily rely on monitor alarms for detecting abnormalities in physiological measurements, which in turn helps them to identify which patients are at risk of worsening. However, these repeatedly triggered alarm systems often become nonspecific and are ignored as they fail to utilize comprehensive patient information, leading to, what we commonly call as alarm fatigue. It was placed seventh on the list of issues by ECRI Institute for the top ten technology hazards related to health care.[8]

Large Amount of Data and Limited Human Resources

Critically ill patients with circulatory shock admitted in ICUs have continuous monitoring of their vital signs, other records such as multiple laboratory test results, routine progress notes along with daily medications, billing data all of which has to be stored. Hence, on a daily basis, intensivists have to deal with large quantities of data from several patients [nowadays stored in electronic patient-data management

systems (PDMS)]. Humans have a limited ability to process such large quantities of information which can lead to data overload, change blindness, and task fixation.[9] These large amounts of data make it difficult to identify, analyze, and act upon the most relevant information for making a clinical healthcare decision. The situation is further worsened due to low nurse-to-patient ratios and lack of continuous intensivist presence in certain ICUs.

Prediction of Shock and its Etiology

The most appropriate treatment for circulatory shock is based on a good understanding of the underlying physiological mechanisms. All types of shock have similar symptoms making the prompt identification of the etiology very difficult. Thus, it is most important to design fast, reliable tools to plan interventions for preventing irreversible consequences of shock or mortality.[10] With the use of current diagnostic and prognostic tools, intensivists find it very difficult to accurately predict which patients will develop shock, estimate prognostication and outcomes.

APPLICATIONS OF ARTIFICIAL INTELLIGENCE IN HEMODYNAMIC MONITORING

Complex and Multiple Large Data Handling

Artificial intelligence can be used to provide insights by analyzing multiple data sources and make predictions that can supplement the intensivist's decision-making abilities and thereby improve clinical outcomes of patients. Patient data monitoring and interpretation is a complex situation, where multiple and often poorly understood mechanisms interact. AI models could possibly be able to identify these unforeseen interactions at an early stage itself.[11]

Machine learning as mentioned before is becoming a popular discipline within computer science. ML techniques can handle large amounts of clinical data and thus allow for a more data-driven and comprehensive approach to diagnosis and prognostication as compared to traditional statistical methodology.[12]

Ability to Predict Changes in Patient Parameters

During surgeries or in the ICU, clinicians have to manage the onset of arterial hypotension and its effects with essentially no prior warning signs. Detection of imminent hypotension, even if recognized only 10–15 minutes prior to the event, could lead to implementation of diagnostic and therapeutic measures to tackle its clinical impact.[13] Multiple studies have concluded that hemodynamic instability in its prodromal stage is characterized by subtle, complex changes in different physiologic variables. These changes are a reflection of the various altered compensatory mechanisms resulting in unique dynamic signatures in arterial pressure waveforms which can predict likely occurrence of hypotension. ML and complex feature extraction techniques could very well make use of these subtle dynamic changes in arterial pressure waveforms which would in turn potentially provide ways to predict hypotension beforehand. With respect to sepsis and development of septic shock, AI models based on physiological variables, laboratory, and monitor values can predict which patients with sepsis have a high probability of developing septic shock in the near future.

PRINCIPLES USED BY ARTIFICIAL INTELLIGENCE AND SYSTEMS DEVELOPED

Machine learning applications have been extensively used for research in critical care targeting the pathophysiology of shock and its treatment.[10] The following are few examples of AI-based learning models:

- *Supervised learning*[14] models are trained on known input and output predictions based on evidence in the presence of uncertainty.
- *Reinforcement learning*[15] is the ability to find which action yields the best outcome through trial and error. As each action affects the next one, the user has to formulate ahead to select actions that will optimize the final outcome. This means that the machine not only considers the immediate effect of certain treatments, but also its long-term benefit to the individual patient.
- *Transfer learning*[16] allows for fine-tuning (the process of optimizing parameters in a neural network) of a previously trained model during external validation at new place. It has the ability to improve site-specific test characteristics from a general model.
- *Deep learning (DL) technique, namely deep reinforcement learning (DRL)* has been proposed recently by Raghu et al.[17] for defining continuous-space models for sepsis management.

It is important to note that no reliable methods currently exist to accurately predict hemodynamical instability, but several models do exist which monitor hemodynamic parameters and identify cardiovascular volatility and accordingly notify intensivists. As mentioned earlier, clinically imperceptible subtle dynamic linkages or interconnections exist among various different physiologic variables which can be identified by AI-based models.

RECENT STUDIES/MODELS BASED ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING

In 2009, an open challenge from PhysioNet and Computers in Cardiology led to the development of tools by participants which were to be used to forecast acute hypotensive episodes, and as a result, 10 different approaches were presented.[18] Majority of these techniques were based on the analysis of static or absolute measures obtained from arterial pressure waveforms.

Hypotension Prediction Index: Developed by Hatib et al.[13]

Patient Database

- *For development and internal validation*: Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC-II) database and from an Edwards Life Sciences Database.
- *For external validation*: University of California at Irvine Medical Center (Irvine, California).

Definitions Used

- *Hypotension*: Any period with MAP <65 mm Hg for at least 1 minute.
- *Nonhypotension*: MAP >75 mm Hg.
- *Early identification period for hypotension*: 15 minutes before an actual hypotensive event.
- *Event or positive data point*: Sample recorded 5, 10, or 15 minutes before the hypotensive event.

Arterial pressure waveform features were mapped into a prediction of machine hypotension. The prediction produced by the logistic regression model, ranging from 0 to 1, was then multiplied by 100 for scaling was named the resulting prediction the *Hypotension Prediction Index* (HPI).

Principle Used

The emphasis was on detecting the earliest appearance of dynamic changes in the arterial pressure waveform corresponding to physiologic interactions among left ventricular contractility, preload, and afterload and then predicts an upcoming hypotensive event.

Result

Sensitivity and specificity of HPI to predict hypotension at 5 minutes was found to be 86.8% and 88.5%, at 10 minutes; 84.2% and 84.3%, at 15 minutes; 83.6% and 83.3%, respectively which demonstrate that a trained ML model can analyze large data sets of high-fidelity arterial pressure waveforms, to predict arterial hypotension events in the data sets of surgical patients up to 15 minutes before they occur.[13]

CircEWS and circEWS-lite By Hyland et al.[19]

Hyland et al. constructed two early-warning systems, named circEWS and circEWS-lite, which are of differing complexity. These alert clinicians with regards to patients at risk of circulatory failure within the next 8 hours.

Patient Database

High time resolution ICU dataset (HiRID) from a large multidisciplinary ICU.

Definitions Used

Circulatory failure: Arterial lactate levels ≥2 mmol/L and either MAP ≤65 mm Hg or use of vasopressors or inotropes

Evaluation of Performance of circEWS and circEWS-lite Systems

It was based on an alarm/event-based evaluation measure which evaluated:

- The fraction of circulatory-failure events correctly predicted (that is, an alarm was raised for this event).
- The false-alarm rate (that is, there was an alarm but no event).

This system was applied and tested to the MIMIC-III database for external validation.

Results

A continuous prediction score, that too, every 5 minutes, regarding the risk of circulatory failure within the next 8 hours, could be generated by these models. It was observed that 81.8% of the events were identified >2 hours in advance which indicates that there was an increase in recall closer to the onset of circulatory failure.[19]

Artificial Intelligence Models Developed for Septic Shock and Postcardiac Surgery

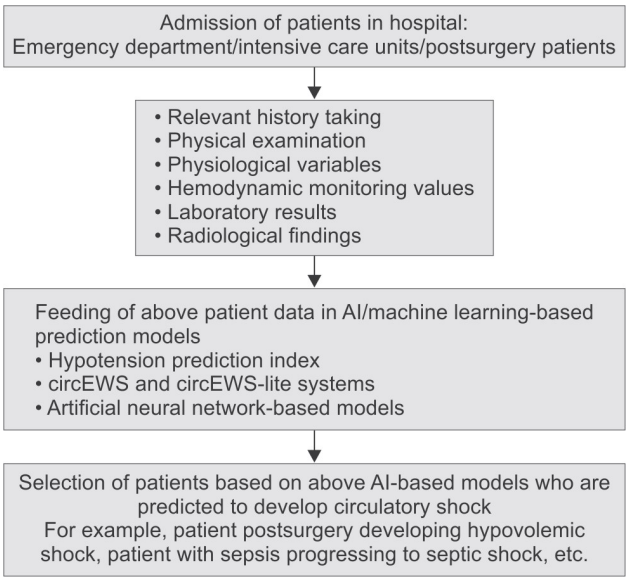
- Denai et al. described fuzzy decision support systems (DSSs) for the management of postsurgical cardiac intensive care patients.[20]
- Paetz et al. and Paetz et al. described the issue of rule generation for septic shock patients, the former together with an artificial neural network (ANN).[21,22]
- Brause et al. presented a diagnostic system for septic shock based on ANNs (radial basis functions—RBFs—and supervised growing neural gas) which addressed the more specific problem of the prediction of mortality caused by sepsis.[23]
- More specifically regarding hypotension per se in the critical care, *Ghosh et al.* have used sequential contrast patterns, mining the methodology of blood pressure monitoring to predict the onset of hypotension in the critical care unit.[24] However, this approach does not yet allow real-time prediction of hypotension.

A proposed method to use AI-based models in shock is given in **Flowchart 1**.

LIMITATIONS OF ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING

- ML methods and techniques use an algorithm which quantifies the complex processes of cardiac compensatory mechanisms mathematically, as they have powerful mathematical tools that allow accurate quantification of dynamic multivariate interconnections; but they do not capture statistical relationships which are important to the overall clinical status of the patient.[18] This assessment of the physiologic associations is very critical to the algorithm because it represents the effect

Flowchart 1: Algorithmic approach to circulatory shock management incorporating artificial intelligence (AI).



of the dynamic links among thousands of automatically derived hemodynamic features, majority of which are derived from the arterial pressure waveform.[13]

- Despite the fact that these AI models and tools have been designed to predict hypotension, it is uncertain as to how clinicians would respond to these alarms. The exact relationship between early warning systems and the clinician's responses or changes in their behaviors is not completely understood stemming from the uncertainty as to whether they would respond or not and even if they do respond it is unclear in what manner they would do so. Thus, it is imperative that a decision-support tool should be used in association with a hypotension prediction algorithm, which could suggest steps or treatment alternatives, which could prevent or at the least reduce the severity of hypotension.[13]
- The end goal of developing these AI models is initiating treatment before the onset of hypotension. AI models and tools using a predictive algorithm could decrease the duration and severity of hypotension during operative procedures and also in the ICU. But there are no robust clinical trials or studies which could clearly state the benefits of doing so. This is because even though the relationship between hypotension and complications is statistically significant, a direct causality has not been established yet. It is very difficult to state as to what degree patient outcomes would improve by decreasing the incidence and duration of hypotension.[13]

CONCLUSION

Artificial intelligence-based models described above could give intensivists an upper hand and pre-emptive warning before the occurrence of shock and this has huge potential for improving organ dysfunction and ultimately patient outcomes.

A stepwise approach may optimize treatment of circulatory shock. However, it is still unknown whether preventing hypotension altogether will reduce complications. Further research and newer AI algorithms will be needed for greater accuracy and with better predictability and consistency for it to make a practical entry in day-to-day practice.

REFERENCES

1. Vincent JL, De Backer D. Circulatory shock. N Engl J Med. 2013;369(18):1726-34.
2. Bali J, Garg R, Bali RT. Artificial intelligence (AI) in healthcare and biomedical research: Why a strong computational/AI bioethics framework is required? Indian J Ophthalmol. 2019;67(1):3-6.
3. Panch T, Szolovits P, Atun R. Artificial intelligence, machine learning and health systems. J Glob Health. 2018;8(2):020303.
4. Yu KH, Beam AL, Kohane IS. Artificial intelligence in healthcare. Nat Biomed Eng. 2018;2(10):719-31.
5. Salmasi V, Maheshwari K, Yang D, Mascha EJ, Singh A, Sessler DI, et al. Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery: A retrospective cohort analysis. Anesthesiology. 2017;126(1):47-65.
6. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. Anesthesiology. 2013;119(3):507-15.
7. Smith AF, Wood J. Can some in-hospital cardio-respiratory arrests be prevented? A prospective survey. Resuscitation. 1998;37(3):133-7.
8. ECRI Institute (2019). Top 10 health technology hazards for 2019. [online] Available from: https://www.ecri.org/top-ten-tech-hazards. [Last accessed February 2022].
9. Ehrenfeld JM, Cannesson M (Eds). Monitoring Technologies in Acute Care Environments: A Comprehensive Guide to Patient Monitoring Technology. Berlin: Springer Science and Business Media; 2013.
10. Aushev A, Ripoll VR, Vellido A, Aletti F, Pinto BB, Herpain A, et al. Feature selection for the accurate prediction of septic and cardiogenic shock ICU mortality in the acute phase. PLoS One. 2018;13(11):e0199089.
11. Clermont G. Artificial neural networks as prediction tools in the critically ill. Crit Care. 2005;9(2):153-4.
12. Wardi G, Carlile M, Holder A, Shashikumar S, Hayden SR, Nemati S. Predicting progression to septic shock in the emergency department using an externally generalizable machine-learning algorithm. Ann Emerg Med. 2021;77(4):395-406.
13. Hatib F, Jian Z, Buddi S, Lee C, Settels J, Sibert K, et al. Machine-learning algorithm to predict hypotension based on high-fidelity arterial pressure waveform analysis. Anesthesiology. 2018;129(4):663-74.

14. Mahapatra D, Schueffler P, Tielbeek JAW, Buhmann JM, Vos FM. A supervised learning based approach to detect Crohn's disease in abdominal MR volumes. Berlin, Heidelberg: Springer; 2012. pp. 97-106.
15. Gottesman O, Johansson F, Komorowski M, Faisal A, Sontag D, Doshi-Velez F, et al. Guidelines for reinforcement learning in healthcare. Nat Med. 2019;25(1):16-8.
16. Kermany DS, Goldbaum M, Cai W, Valentim CCS, Liang H, Baxter SL, et al. Identifying medical diagnoses and treatable diseases by image-based deep learning. Cell. 2018;172(5):1122-31.e9.
17. Raghu A, Komorowski M, Celi LA, Szolovits P, Ghassemi M. Continuous state-space models for optimal sepsis treatment-a deep reinforcement learning approach. arXiv preprint. 2017; arXiv:1705.08422.
18. PhysioNet and Computers in Cardiology Challenge: Predicting acute hypotensive episodes: The PhysioNet/Computing in Cardiology Challenge 2009. [online] Available from: https://physionet.org/challenge/2009/. [Last accessed February 2022].
19. Hyland SL, Faltys M, Hüser M, Lyu X, Gumbsch T, Esteban C, et al. Early prediction of circulatory failure in the intensive care unit using machine learning. Nat Med. 2020;26(3): 364-73.
20. Denai M, Mahfouf M, Ross J. A fuzzy decision support system for therapy administration in cardiovascular intensive care patients. In: Proceedings of the FUZZ-IEEE; 2007. pp. 1-6.
21. Paetz H. Metric rule generation with septic shock patient data. In: Proceedings of the ICDM; 2001. pp. 637-8.
22. Paetz J. Intersection based generalization rules for the analysis of symbolic septic shock patient data. In: Proceedings of the ICDM; 2002. pp. 673-6.
23. Brause R, Hamker F, Paetz J. Septic shock diagnosis by neural networks and rule based systems. Studies in Fuzziness and Soft Computing, Volume 96; 2002. pp. 323-56.
24. Ghosh S, Feng M, Nguyen H, Li J. Hypotension risk prediction via sequential contrast patterns of ICU blood pressure. IEEE J Biomed Health Inform. 2016;20(5):1416-26.

SECTION 11

Perioperative and Resuscitation

CHAPTER 62

Perioperative Risk Prediction

Gentle S Shrestha, Saurabh Pradhan, Tamanna Bajracharya

INTRODUCTION

Any surgery, even in a healthy individual, carries a risk of an adverse outcome, including death. With over 230 million surgeries performed worldwide annually,[1] and every procedure having inherent risks of morbidity and mortality, the significance of appropriate perioperative care cannot be undermined. A major aspect of such a service is preanesthetic evaluation, where patients, as well as surgeries, associated with higher risks of adverse outcomes, are identified and perioperative care planned to mitigate the anticipated risks. Although it has been suggested that perioperative morbidity and mortality may occur in 3–17% of cases,[2,3] 80% of deaths occur in a small subset of high-risk patients, which constitutes only 12% of the total surgical population.[4] Perioperative morbidity and mortality can have significant health issues, with an impact on both short- and long-term survival. Therefore, it is imperative that appropriate risk prediction be performed to identify these high-risk groups.

Though it is difficult to define what constitutes high-risk, efforts have been made to standardize the definition. A patient with an estimated perioperative mortality ≥5% has been considered as high risk.[5] Generally, the risk is determined by three factors: Patient-related factors, surgery-related factors, and anesthesia-related factors. Age, presence of comorbidities, and obesity are the common patient-related risk factors implicated. High-risk surgeries usually include cardiovascular and thoracic surgeries, laparotomies, neurosurgeries, and emergency surgeries. However, the risk of complications also depends on the experience of the surgical and the anesthetic team. A multitude of variables may, therefore, be responsible for an adverse outcome. Thus, it is difficult to determine which patient may be at a higher risk of complications. To standardize risk assessment, numerous risk prediction tools have been studied and validated. These tools ideally should be simple, easily reproducible, objective, applicable to all, and accurate. They may be risk scores, which assign a weighting to factors identified as predictors of an outcome and the sum of the weightings reflecting the overall risk; or they may be prediction models, where the individual probability of risk for a patient is estimated. These tools may be general, patient-specific, or procedure-specific. Apart from these clinical indices, the use of biomarkers and specialized testing has also been integrated into practice.

GENERAL RISK PREDICTION TOOLS

An example of a general risk prediction score is the American Society of Anesthesiology Physical Status (ASA-PS) score,[6] which categorizes patients into six subgroups using subjective preoperative measures of physical fitness. It has been shown to be a good predictor of mortality as well as morbidty[7,8] and now has become the most widely used predictive score. It was updated in 2014 to include, body mass index, smoking, and alcohol intake.[9] ASA-PS scoring may have significant interoperator variability due to its subjective criteria.[10] Furthermore general risk scores such as ASA have the disadvantage that it does not provide disease-specific or procedure-specific risk information.[11]

Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM) was developed in 1991 as a scoring system for surgical audit, which included a variety of emergency as well as elective procedures. POSSUM uses 12 physiological variables and 6 surgical variables to calculate 30-day mortality after surgery.[12] Using alternative risk equation, the Portsmouth Physiological and Operative Severity Score for enumeration of Mortality and Morbidity (P-POSSUM) was developed.[12] Unlike the ASA-PS, both of these systems are prediction models using multivariate logistic regression analysis and incorporate intraoperative information in addition to preoperative risks to calculate mortality risk. Being risk prediction models, they are more accurate in predicting an individual risk, but it has been shown to overestimate risk in some groups.[13]

A similar risk prediction model is the Surgical Outcome Risk Tool (SORT).[14] SORT uses six preoperative variables, which include ASA-PS, the urgency of surgery, surgical specialty, the severity of the surgery, cancer, and age; and is simpler to use.[14]

TABLE 1: Comparison of general risk prediction tools.

Risk prediction tool	*Description*	*Pros*	*Cons*
ASA-PS	General risk prediction score with 6 subgroups	Simple, reliable, most widely used risk score	• Interoperator variability • Not patient-specific • Less accurate than prediction models
POSSUM	12 physiological variables and 6 operative variables	Well validated, most commonly used prediction model	Intraoperative variables and the requirement of some blood test results preclude preoperative risk calculation
SORT	6 preoperative variables	Simple and rapid data entry, accurate	The newer tool requires external validation
ACS NSQIP	21 preoperative risk factors	Most accurate and comprehensive, studied in the largest database, calculates both mortality and morbidity	Not validated for emergency surgery Cumbersome to use

(ASA-PS: American Society of Anesthesiology Physical Status; ACS NSQIP: American College of Surgeons National Surgical Quality Improvement Project; POSSUM: Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity; SORT: Surgical Outcome Risk Tool)

Unlike other risk prediction models, the American College of Surgeons National Surgical Quality Improvement Project (ACS NSQIP) universal surgical risk calculator is an online-based calculator which predicts not just mortality but also 13 other outcomes. This was developed using data from one of the largest databases of 14 million people.[15] It is one of the most accurate, comprehensive, and patient-specific risk calculators. However, it is quite cumbersome, requiring data collection of many variables. Comparison of different risk prediction tools is depicted in **Table 1**.

Organ-specific Risk Prediction Tools

Cardiac Risk

The most common serious adverse events after surgery are cardiac. Starting with Lee Goldman in 1977, risk factors have been proposed to determine which patients undergoing noncardiac surgery are at higher risk of perioperative cardiac complications.[16] Various modifications of this scoring system have been developed. However, the more commonly used is the Revised Cardiac Risk Index (RCRI), which includes six independent factors, with risk classes classified according to the number of factors being present **(Table 2)**.[17] The RCRI is a simple, quick, and noninvasive tool, but the score was developed by analyzing data from only a single center in patients undergoing nonemergent surgeries.

Pulmonary Risk

The risk of postoperative pulmonary complications (PPCs) can be increased by the type of surgery (e.g., high abdominal, thoracic, and neurosurgery), general patient status (e.g., age and functional status), and pulmonary diseases [e.g., chronic obstructive pulmonary disease (COPD)]. Unlike cardiac risk prediction, there are currently few validated models of pulmonary risk stratification. Currently, Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) is the most widely used risk score for predicting PPC **(Table 3)**.[18]

TABLE 2: Revised cardiac risk index.

Risk factors		*Points*
High-risk surgery		1
Ischemic heart disease		1
History of congestive heart failure		1
History of cerebrovascular accident		1
Insulin therapy for diabetes		1
Preoperative serum creatinine > 2 mg/dL		1
Risk class	***Number of risk factors***	***Risk of major cardiac event***
I	0	0.4%
II	1	0.9%
III	2	6.6%
IV	3 or more	11%

TABLE 3: Assess respiratory risk in surgical patients in catalonia (ARISCAT) score.

1	*Age (in years)*	
	<50	0
	51–80	3
	>80	16
2	*Preoperative SpO_2 (in %)*	
	>96	0
	91–95	8
	<90	24
3	Respiratory infection in the last month	17
4	Preoperative anemia (<10 g/dL)	11
5	*Surgical incision*	
	Peripheral	0
	Upper abdominal	15
	Intrathoracic	24
6	*Duration of surgery (in hours)*	
	<2	0
	>2–3	16
	>3	23

However, the American College of Physicians has also adopted several scales for assessing the risk of perioperative pulmonary complications.

Renal Risk

Many perioperative factors have been shown to be predictors of acute kidney injury (AKI) after surgery. Combining estimated glomerular filtration rate using serum creatinine with albuminuria is one of the most valuable yet often underutilized clinical resources for clinicians. American College of Surgeons-National Surgical Quality Improvement Program has developed a scoring system called the general surgery acute kidney injury risk index **(Table 4)**.[19] However, a major concern regarding the assessment of AKI in the perioperative period is that serum creatinine or urine output may be unreliable markers of renal injury, with other factors that could contribute to the changes in the perioperative period.

Hepatic Risk

The Child–Turcotte–Pugh (CTP) score is the most commonly used score for assessing perioperative risk in patients with cirrhosis **(Table 5)**. It is based on the patient's levels of bilirubin, albumin, the international normalized ratio (INR), and the severity of encephalopathy and ascites.[20] Most of the studies have consistently reported the same perioperative outcomes. Model for end-stage liver disease (MELD) score was developed to risk stratify patients awaiting liver transplantation and more recently is also used to predict perioperative mortality.[21]

Procedure-specific Risks

Risk prediction tools have also been studied to predict outcomes after a specific type of surgery, especially in cardiovascular and thoracic surgeries. For example, the European System For Cardiac Operative Risk Evaluation (Euro-SCORE) is the most widely studied and utilized score for patients undergoing cardiac surgery, primarily coronary artery bypass grafting.[22] Recently, the newer and more accurate EuroSCORE II has replaced the older version.[23] The Society of Thoracic Surgeons mortality risk score (STS)[24] is the other risk stratification system that is currently used in cardiac surgery and is equally reliable as the EuroSCORE II in predicting postcardiac surgery mortality.[25] Although, both the EuroSCORE and STS score can be used to calculate the mortality for heart valve surgery as well, Ambler score is a specific risk stratification model developed for aortic and/or mitral valve surgeries with or without concomitant coronary artery bypass graft (CABG).[26] Vascular-POSSUM is commonly used to facilitate risk prediction of hospital mortality in patients undergoing major vascular surgery.[27] Several tools have also been developed to predict outcomes in patients undergoing thoracic surgery, but lack external validity, and most were developed prior to 2011 when the use of minimally invasive surgery was not prevalent.[28] Apart from cardiovascular and thoracic surgeries, a commonly used tool for emergency laparotomies is the National Emergency Laparotomy Audit (NELA) risk calculator, which estimates 30-day mortality.[29]

Biomarkers

The use of biomarkers in diagnostic and prognostic purposes has increased in medical practice. In perioperative care, particularly cardiac troponin and natriuretic peptides have been extensively examined for predicting perioperative risk.

TABLE 4: General surgery acute kidney injury risk index.

Risk factors	***Points***
Age >56 years	1
Male sex	1
Active congestive heart failure	1
Hypertension	1
Emergency surgery	1
Intraperitoneal surgery	1
Renal insufficiency—mild or moderate	1
Diabetes mellitus—oral or insulin therapy	1

Risk Class	***Number of risk factors***	***Risk of acute kidney injury***
I	0–2	0.2%
II	3	0.8%
III	4	2.0%
IV	5	3.6%
V	6+	9.5%

TABLE 5: Child–Turcotte–Pugh (CTP) score.

	Points		
Clinical and laboratory criteria	***1***	***2***	***3***
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate	Severe
Bilirubin (mg/dL)	<2	2–3	>3
Albumin	>3.5	2.8–3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4–6	>6
International normalized ratio	<1.7	1.7–2.3	>2.3

CTP class	***Points***	***Perioperative mortality risk***
CTP class A	5–6	10%
CTP class B	7–9	30%
CTP class C	10–15	76–82%

Natriuretic peptides are released from the myocardium in response to ischemia or stretching of the cardiac walls. Their roles in heart failure have already been established. Several studies have been conducted to evaluate their use in predicting postoperative cardiac complications. Systematic reviews of these studies indicate that preoperative natriuretic peptides are independent predictors of cardiac complications after noncardiac surgery.[30,31]

Similar to the natriuretic peptides, cardiac troponin is also released in response to myocardial injury. The development of assay of highly sensitive troponin allows detection of even minor increments in the circulation, which has shown to be associated with increased risks of postoperative myocardial infarction and mortality.[32,33]

Preoperative-specialized Testing

Additional specialized tests that might be performed before surgery to better inform perioperative risk include various organ-specific investigations. For example, for high-risk cardiac patients, preoperative resting echocardiography provides detailed information regarding cardiac structure and function, which may implicate elevated risk of perioperative death or cardiac complications.[34] Similarly reversible defects on cardiac stress imaging are indicative of increased perioperative cardiac risk.[35]

Cardiopulmonary exercise testing (CPET) is an increasingly popular preoperative test, which provides an objective measurement of cardiopulmonary fitness and predicts a range of perioperative complications aside from cardiac events, including pneumonia, respiratory failure, and infection. Several measurements such as anaerobic threshold and peak oxygen uptake can be derived.[36]

Pulmonary function tests particularly forced expiratory volume in 1 second (FEV1) have been extensively used as a preoperative test in thoracic as well as cardiac surgeries. These findings are also included as a component in many predictive models. However, recent studies have failed to demonstrate a strong like with postoperative outcome.[37,38] Nowadays, the importance of diffusion capacity of the lung for carbon monoxide (DLCO) as a component of risk stratification for lung resection has become increasingly well-established. [39]

CONCLUSION

There are many risks prediction tools that can be utilized in anticipating perioperative complications. It must be remembered that there are no ideal scoring systems or prediction models. There may be a lack of generalizability, with certain scores developed but yet not validated in other studies, or not applicable to all surgical populations. Some scores were developed decades ago, so their reliability in predicting outcomes in the current scenario, where major advances have been made, can be questioned. Also, not all factors that can increase the risk may have been considered in these tools. For example, the RCRI does not include arrhythmia and morbid obesity as risk factors. Therefore, these tools should be regarded as guides, and should not replace, but rather assist our clinical judgment. A newer version of the SORT tool, which also combines subjective clinical assessment with SORT, was found to be more accurate than other predictive tools.[40]

Accurate preoperative identification of high-risk patients can provide opportunities to better inform patients about expected risks, allow appropriate preoperative specialized testing, and optimization, make necessary intraoperative modifications, such as additional monitoring, and adjust postoperative care.

REFERENCES

1. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet. 2008;372(9633):139-44.
2. Kable AK, Gibberd RW, Spigelman AD. Adverse events in surgical patients in Australia. Int J Qual Health Care. 2002;14(4):269-76.
3. Gawande AA, Thomas EJ, Zinner MJ, Brennan TA. The incidence and nature of surgical adverse events in Colorado and Utah in 1992. Surgery. 1999;126(1):66-75.
4. Pearse RM, Harrison DA, James P, Watson D, Hinds C, Rhodes A, et al. Identification and characterization of the high-risk surgical population in the United Kingdom. Crit Care. 2006;10(3):R81.
5. Shah N, Hamilton M. Clinical review: Can we predict which patients are at risk of complications following surgery? Crit Care. 2013;17(3):226.
6. Saklad M. Grading of patients for surgical procedures. Anesthesiology. 1941;2:281-4.
7. Wolters U, Wolf T, Stutzer H, Schröder T. ASA classification and perioperative variables as predictors of postoperative out-come. Br J Anaesth. 1996;77(2):217-22.
8. Wolters U, Wolf T, Stutzer H, Schröder T, Pichlmaier H. Risk factors, complications, and outcome in surgery: a multivariate analysis. Eur J Surg. 1997;163(8):563-8.
9. American Society of Anesthesiologists. ASA Physical status classification system. [online] Available from: https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system [Last accessed February, 2022].
10. Sankar A, Johnson Sr, Beattie WS, Tait G, Wijeysundera DN. Reliability of the American Society of Anesthesiologists physical status scale in clinical practice. Br J Anaesth. 2014;113(3):424-32.
11. Koo Cy, Hyder JA, Wanderer JP, Eikermann M, Ramachandran SK. A meta-analysis of the predictive accuracy of postoperative mortality using the American Society of Anesthesioogists' physical status classification system. World J Surg. 2015;39(1):88-103.

12. Barnett S, Moonesinghe SR. Clinical risk scores to guide perioperative management. Postgrad Med J. 2011;87(1030): 535-41.
13. Stones J, Yates D. Clinical risk assessment tools in anaesthesia. Br J Anaesth Education. 2019;19(2):47-53.
14. Protopapa KL, Simpson JC, Smith NCE, Moonesinghe SR. Development and validation of the surgical outcome risk tool (SORT). Br J Surg. 2014;101(13):174-83.
15. American College of Surgeons National Surgical Quality Improvement Program. User guide for the 2016 ACS NSQIP participant data use file (PUF). October 2017. [online] Available from: https://erports.nsqip.facs.org/nsqippublicdocs/service?pubid=2017confpres&docid=99703. [Last accessed February, 2022].
16. Goldman L, Caldera DL, Nussbaum SR, Southwick FS, Krogstad D, Murray B, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med. 1977;297(16):845-50.
17. Lee Th, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation. 1999;100(10):1043-9.
18. Miskovic A, Lumb AB. Postoperative pulmonary complications. Br J Anaesth 2017;118(3):317-34.
19. Kheterpal S, Tremper KK, Heung M, Rosenberg AL, Englesbe M, Shanks AM, et al. Development and Validation of an Acute Kidney Injury Risk Index for Patients Undergoing General Surgery: Results from a National Data Set. Anesthesiology. 2009;110(3):505-15.
20. Friedman LS. Surgery in the patient with liver disease. Trans Am Clin Climatol Assoc. 2010;121:192-205.
21. O'Leary JG, Friedman LS. Predicting surgical risk in patients with cirrhosis: from art to science. Gastroenterology. 2007;132(4):1609-11.
22. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg. 1999;16(1): 9-13.
23. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. Eur J Cardiothorac Surg. 2012;41(4):734-45.
24. Anderson RP. First publications from the Society of Thoracic Surgeons National Database. Ann Thorac Surg. 1994;57(1):6-7.
25. Rabbani MS, Qadir I, Ahmed Y, Gul M, Sharif H. Heart Valve Surgery: EuroSCORE vs. EuroSCORE II vs. Society of Thoracic Surgeons Score. Heart International. 2014;9(2):53-8.
26. Ambler G, Omar RZ, Royston P, Kinsman R, Keogh BE, Taylor KM. Generic, simple risk stratification model for heart valve surgery. Circulation. 2005;112(2):224-31.
27. Mosquera D, Chiang N, Gibberd R. Evaluation of surgical performance using V-POSSUM risk-adjusted mortality rates. ANZ J Surg. 2008;78(7):535-9.
28. Taylor M, Hashmi SF, Martin GP, Shackcloth M, Shah R, Booton R, et al. A systematic review of risk prediction models for perioperative mortality after thoracic surgery. Interact Cardiovasc Thorac Surg. 2021;32(3):333-42.
29. Hare S, Moonesinghe R. NELA risk prediction tool. RCOA Bull. 2017;104:28-9.
30. Karthikeyan G, Moncur RA, Levine O, Heels-Ansdell D, Chan MTV, Alonso-Coello P, et al. Is a preoperative brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide measurement an independent predictor of adverse cardiovascular outcomes within 30 days of noncardiac surgery? A systematic review and meta-analysis of observational studies. J Am Coll Cardiol. 2009;54(17):1599-606.
31. Lurati Buse GA, Koller MT, Burkhart C, Seeberger MD, Filipovic M. The predictive value of peroperative natriuretic peptide concentrations in adults undergoing surgery: a systematic review and meta-analysis. Anesth Analg. 2011;112(5):1019-33.
32. Nagele P, Brown F, Gage BF, Thorlacius L, Buse GL, Botto, F, et al. High-sensitivity troponin T concentrations in patients undergoing noncardiac surgery: a prospective cohort study. Clin Biochem. 2011;44(12):1021-24.
33. Weber M, Luchner A, Seeberger M, Mueller C, Liebetrau C, Schlitt A, et al. Incremental value of high-sensitive troponin T in addition to the Revised Cardiac Index for perioperative risk stratification in noncardiac surgery. Eur Heart. 2013;34(11): 853-62.
34. Halm EA, Browner WS, Tubau JF, Tateo IM, Mangano DT. Echocardiography for assessing cardiac risk in patients having noncardiac surgery. Ann Intern Med. 1996;125(6):433-41.
35. Ethells E, Meade M, Tomlinson G, Cook D. Semiquantitative dipyridamole myocardial stress perfusion imaging for cardiac risk assessment before noncardiac vascular surgery: a meta-analysis. J Vasc Surg. 2002;36(3):534-40.
36. Huddart S, Young EL, Smith RL, Holt PJ, Prabhu PK. Preoperative cardiopulmonary exercise testing in England—a national survey. Perioper Med (Lond). 2013;2(1):4.
37. Brunelli A, Refai M, Salati M, Xiumé F, Sabbatini A. Predicted versus observed FEV1 and DLCO after major lung resection: a prospective evaluation at different postoperative periods. Ann Thorac Surg. 2007;83(3):1134-9.
38. Brunelli A, Sabbatini A, Xiume' F, Al Refai M, Borri A, Salati M, et al. A model to predict the decline of the forced expiratory volume in one second and the carbon monoxide lung diffusion capacity early after major lung resection. Interact Cardiovasc Thorac Surg. 2005;4(1):61-5.
39. Salati M, Brunelli A. Risk stratification in lung resection. Curr Surg Rep. 2016;4(11):1-9.
40. Wong DJN, Harris S, Sahni A, Bedford JR, Cortes L, Shawyer R, et al. Developing and validating subjective and objective risk assessment measures for predicting mortality after major surgery: An international prospective cohort study. PLoS Med. 2020;17(10):e1003253.

63

CHAPTER

Role of High-flow Nasal Cannula in Operating Room

Arjun Alva, Mohan Maharaj, Shailender Kumar

INTRODUCTION

High-flow nasal cannula (HFNC) is being used extensively in last 2 years during COVID pandemic, though it has been around for the past decade in the management of hypoxemic respiratory failure. Use of HFNC in operating room (OR) to prevent desaturation and prolong safe apnea time is being studied in few randomized controlled trials (RCTs). Maintaining oxygen saturation >90% and hemodynamic stability is the primary goal of an anesthesiologist in the perioperative period.

In the post-COVID scenario, many patients are on home oxygen who might have been on HFNC/noninvasive ventilation (NIV) or invasive mechanical ventilation in intensive care unit (ICU) for their COVID management. These patients pose higher risk of hypoxemia when they require surgery either elective or emergency.

The group of people at risk of desaturation or hypoxic respiratory failure (HRF) in perioperative period are the ones with preexisting respiratory failure due to various causes [chronic obstructive pulmonary disease (COPD), restrictive lung disease, and neuromuscular disorders] obesity [obstructive sleep apnea (OSA)], interstitial lung diseases, children, and pregnancy. After extubation of major thoracic or abdominal surgery, the patients are at risk of developing pulmonary complications.

High-flow nasal cannula is a device consists of an air/oxygen blender connected to a nasal cannula via an active heated humidifier through a single limb inspiratory circuit. It can deliver fraction of inspired oxygen (FiO_2) from 0.21 to 1.0 (21–100%) with a flow rate up to 60 L/min. FiO_2 adjustment is independent of flow rate and the flow can be above the patient's inspiratory flow demand.

In this chapter, we will discuss about benefits of using HFNC in OR during induction and postextubation.

PHYSIOLOGICAL ASPECTS DURING INDUCTION

When the patient is on operating table during induction, the functional residual capacity (FRC), end-expiratory lung volume (EELV), and lung compliance are reduced. Basal atelectasis and upward shift of diaphragm can complicate this further. This can cause desaturation even with transient periods of apnea, which is seen during induction and prior to placement of definitive airway and mechanical ventilation. Preoxygenation with 100% O_2 is given to the patient via conventional methods such as face mask with FiO_2 1.0 [conventional oxygen therapy (COT)] followed by bag mask ventilation. High flow nasal oxygen (HFNO/HFNC) maybe used in certain conditions where it could be more beneficial than conventional methods.

Preoxygenation

Preoxygenation denitrogenizes the lungs, increases alveolar oxygen reservoir.[1] Breathing 100% oxygen replaces nitrogen in FRC, increasing O_2 stores from 450 mL up to 3,000 mL. This O_2 reservoir can further be improved by reducing dependent atelectasis which is a common problem during general anesthesia. Compression of thoracic cavity by diaphragm and abdominal pressure further compromises the lung function. HFNC can be a more favorable tool for preoxygenation as it has the following benefits over other conventional methods of preoxygenation (COT):HFNC delivers humidified heated oxygen of set FiO_2 (1.0), reduces anatomical dead space, flow rate equal to or more than maximum inspiratory flow of patient, causes resistance to expiration with high flow developing small positive end-expiratory pressure (PEEP) (up to 5 cmH_2O) which can open up some alveoli thus reducing basal atelectasis and increases EELV up to 25%[24] and PaO_2/FiO_2 ratio.

Safe Apnea Time

Safe apnea time is defined as the time from cessation of breathing on induction until the SpO_2 drops to 90% after which it falls precipitously.[13] Preoxygenation prolongs the safe apnea time by increasing oxygen reserves and allows more time for intubation particularly in difficult intubation scenario or during rapid sequence intubation (RSI) where bag mask ventilation is avoided.

Few studies have been done to investigate the role of HFNC for preoxygenation in different types of surgeries.[3]

Preoxygenation in Obese Patients

Heinrich et al. compared HFNC with standard face mask and continuous positive airway pressure (CPAP) of 7 cmH_2O for preoxygenation in obesity patient with body mass index (BMI) >35 kg/m^2 undergoing bariatric surgery shown increase in PaO_2 levels in HFNO group than face mask and comparable to that of CPAP.[4]

PREOPTIPOP trial shown lower EtO_2 and SpO_2 with HFNO compared to NIV for preoxygenation in obese patients with BMI >35 kg/m^2.[5]

These discrepancies could be with the methodological issues. Nevertheless HFNO is an acceptable alternative to NIV in obese patients when NIV not available or contraindicated.

Preoxygenation in Pregnant Woman

Pregnant woman desaturates very rapidly during induction because of reduced FRC and decreased respiratory reserves. Shipman et al. compared standard face mask to HFNO in healthy full term pregnant women. Very few patients in HFNO group achieved EtO_2 value >90% target.[6] This could be because only part of HFNC patients kept their mouth closed (HFNO patient with closed mouth reduces air entrainment, gets set FiO_2 1.0 and have some PEEP effect with high flow rate).

Preoxygenation in ARF Patients

As in critically ill patient, in moderate-to-severe hypoxia—NIV has lower desaturation risk than HFNO.

OPTINIV Trial

Combination of HFNO with NIV in severely hypoxemic patients during intubation resulted in better SpO_2 than NIV alone and lower intubation-related complications (though statistically not significant) as it is underpowered.[7]

Preoxygenation in neurosurgical patients—face mask with bag mask ventilation compared with HFNO, PaO_2 was higher at the end of preoxygenation but reduced after apneic oxygenation, and also a rise in $EtCO_2$ in HFNC group, which could be dangerous in patients with raised intracranial pressure (ICP).[8]

Palliative Care

High-flow nasal cannula is an alternative modality in acute renal failure (ARF) in end-stage diseases, malignancy, or do not intubate order. HFNO can be used for prolonged period with better tolerance and few side effects. Peter and colleagues used HFNO before proceeding to NIV (if needed) in 50 patients (27–96 years of age) only 18% required NIV and 82% were managed with HFNO alone.[9]

Apneic Oxygenation

Preoxygenation by face mask or NIV or BM ventilation is interrupted during laryngoscopy and intubation may result in desaturation mainly in high-risk patients. Providing passive oxygenation via nasopharyngeal/nasal cannula is called apneic oxygenation.

High-flow nasal cannula has some advantages in prolonging safe apnea time as its high flow during inspiration prevents supraglottic collapse.[10] Nasopharyngeal dead space wash out reduces rate of increase in $EtCO_2$ and increases O_2 reservoir.[11]

Patel et al. used HFNO (THRIVE) in patients with decreased cardiorespiratory drive or anticipated difficult intubation observed median apnea time 14 minutes, CO_2 increase was much slower (0.15 kpal/min vs. 0.35 or 0.45 kpal/min).[12]

FELLOW trial—no benefit as HFNO compared to control in improving SpO_2 during apnea time in a RCT including 150 critically ill patients with 15 L/flow and 100% O_2. This could be because of low flow used in HFNO group.[13]

Postoperative Period

Hypoxemia in postoperative period could be because of residual effects of general anesthetic medication, opioids, pain, and upward shift/splinting of diaphragm causing reduction in FRC. This is further worsened in upper abdominal and laparoscopic surgeries. Conventionally O_2 by mask or nasal cannula is used for supplementing oxygen to maintain SpO_2.

Noninvasive ventilation is used in high-risk patients to reduce reintubation compared to COT.[14,15] Risk of gastric distension, pulmonary aspiration, and patient intolerance is present in NIV group. Also, NIV patients have to be monitored in ICU/high-dependency unit (HDU) and needs more resources.

High-flow nasal cannula increases PaO_2/FiO_2 ratio compared to low flow oxygen and recruits some atelectatic areas.[16,17] Its tolerance is much better compared to NIV and the patient gets heated, humidified oxygen which reduces catabolic effect,[18] and facilitates clearance of secretions.

Maggiore et al. studied the role of HFNC versus COT in patients after extubation in mixed population of surgical and medical patients[19] after being ventilated for 24 hours. HFNC improved oxygenation, reduced respiratory rate, $PaCO_2$, and need for reintubation.

A large RCT involving patients in mixed ICU with high risk for extubation failure[20] and low risk (HFNO vs. COT) for reintubation[21] shown that HFNO was not inferior to NIV in prevention of reintubation and postextubation respiratory failure, respiratory rate was higher in NIV group than HFNC, possibility due to intolerance of NIV.

In major abdominal surgery, direct extubation onto HFNC did not show clinically significant advantage in

oxygenation and respiratory function, pulmonary complications, and length of stay in hospital compared to COT.[22]

Studies on postoperative HFNC use in cardiothoracic surgeries are encouraging—Parke et al.[23] showed lower incidence of NIV requirement with use of HFNC compared to COT in postcardiac surgery patients.

Corley et al. used electrical impedance tomography showed increase in EELV by 25% in HFNC group particularly in BMI >30 kg/m patients.[2] But in their later study, it did not show any difference between "HFNC and COT" in terms of oxygen indices, dyspnea score, and atelectasis score warranting further studies to see the effect of increased EELV on patient outcomes.

Oxygenation during Procedure/Sedation

During procedures such as bronchoscopy and transesophageal echocardiography (TEE), gastrointestinal (GI) endoscopy patient is at risk of developing hypoxemia which may precipitate with administration of sedatives. Oxygen supplementation with COT by face mask, nasal cannula, or NIV is generally practiced during procedural sedation. But during bronchoscopy or upper gastrointestinal (UGI) endoscopy or TEE, it is not possible to continue with face mask or NIV and low flow oxygen by nasal cannula may not maintain SpO_2 or PaO_2 at safer levels. HFNC with high flow rate at 60 L/min could be a useful device in such situations in maintaining saturation and PaO_2/FiO_2 ratio.[24]

A prospective randomized trial shown NIV resulted in better oxygenation than HFNC during bronchoscopy. Heart rate, mean arterial pressure (MAP), respiratory rate, and need for intubation were similar in both groups.[25]

A Systematic Review and Meta-analysis on Effectiveness of HFNO during Intraoperative Period

In this systematic review and meta-analysis,[26] 2,474 studies were identified. After screening and meeting eligibility criteria, six studies included in meta-analysis. Obstetric and pediatric patient studies were excluded. These studies looked at one of four outcomes: (1) O_2 desaturation, (2) Minimum O_2 saturation, (3) safe apnea time, or (4) $EtCO_2$.

Meta-analysis

The meta-analysis shown that:

- Intraoperative desaturation (five RCTs—two induction and three procedure)[12-16] was lower in HFNO group compared to COT at induction ($p = 0.02$) and during procedural sedation $p < 0.001$.
- Minimum O_2 saturation was higher in HFNO than COT, at induction (MD 5.1%) procedures (MD 4%) which is statistically significant. The minimum O_2 saturation ranged from 96 to 99%.
- *Safe apnea time*: Four RCTs compared HFNC (flow 30–70 L/min). The meta-analysis shown longer safe apnea time in HFNC group, MD 33.4 seconds ($p < 0.001$).
- *$EtCO_2$*: Three RCTs[13,22] compared $EtCO_2$ between HFNO and COT groups. Meta-analysis shown that $EtCO_2$ was similar (38–44 mm Hg) in both groups with a mean difference of –1.0 (–2.4 to 0.4).

CONCLUSION

Compared with standard techniques, HFNO improves safety in patients with known or anticipated difficult airways undergoing elective intubation. It may reduce the incidence of hypoxemia during invasive procedures under sedation. HFNO is more effective than COT in improving oxygenation in mild-to-moderate ARF patients perioperatively. So far there are no definitive recommendations for use of HFNC in OR. Larger and well-designed RCTs are needed to establish its role in perioperative medicine.

REFERENCES

1. Weingart SD, Levitan RM. Preoxygenation and prevention of desaturation during emergency airway management. Ann Emerg Med. 2012;59(3):165-75.e.l
2. Corley A, Carunana LR, Barnett AG, Tronstad O, Fraser JF. Oxygen delivery through high-flow nasal cannulae increase end-expiratory lung volume and reduce respiratory rate in post-cardiac surgical patients. BRJ Anaesth. 2011;107(6): 998-1004.
3. Bhatia PK, Bhandari SC, Tulsiani KL, Kumar Y. End-tidal oxygraphy and safe duration of apnoea in young adults and elderly patients. Anaesthesia. 1997;52(2):175-8.
4. Heinrich S, Horbach T, Stubner B, Prottengeier J, Irouschek A, Schmidt J. Benefits of heated and humidified high flow nasal oxygen for preoxygenation in morbidly obese patients undergoing bariatric surgery: a randomized controlled study. J Obes Bariatrics. 2014;1(1):7.
5. Vourc'h M, Baud G, Feuillet F, Blanchard C, Mirallie E, Guitton C, et al. High flow nasal cannulae versus non-invasive ventilation for preoxygenation of obese patients: the PREOPTIPOP randomized trial. EClin Med. 2019;13:112-9.
6. Shippam W, Preston R, Douglas J, Taylor J, Albert A, Chau A. High-flow nasal oxygen vs. standard flow-rate facemask pre-oxygenation in pregnant patients: a randomized physiological study. Anaesthesia. 2019;74(4):450-6.
7. Jaber S, Monnin M, Girard M, Conseil M, Cisse M, Carr J, et al. Apnoeic oxygenation via high-flow nasal cannula oxygen combined with non-invasive ventilation preoxygenation for intubation in hypoxaemic patients in the intensive care unit: the single-centre, blinded, randomized controlled OPTINIV trial. Intensive Care Med. 2016;42(12):1877-87.
8. Ng I, Krieser R, Mezzavia P, Lee K, Tseng C, Douglas N, et al. The use of Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) for pre-oxygenation in neurosurgical patients: a randomized controlled trial. Anaesth Intensive Care. 2018;46(4):360-7.
9. Peters SG, Holets SR, Gay PC. High flow nasal cannula oxygen therapy in DO-Not intubate patients with hypoxaemic respiratory distress. Respir Care. 2013;58(4):597-600.

10. Parke RL, Mc Guinness SP. Pressures delivered by nasal high flow oxygen during all phases of the respiratory cycle. Respir Care. 2013;58(10):1621-4.
11. Moller W, Feng S, Domanski U, Franke KJ, Celik G, Bartenstein P, et al. Nasal high flow reduces dead space. J Appl Physiol (1985). 2017;122(1):191-7.
12. Patel A, Nouraei SA. Transnasal humidified rapid- insufflation ventilatory exchange (THRIVE): a physiological method of increasing apnoea time in patients with difficult airways. Anaesthesia. 2015;70(3):323-9.
13. Semler MW, Janz DR, Lentz RJ, Matthews DT, Norman BC, Assad TR, et al. Randomized trial of apneic oxygenation during endotracheal intubation of the critically ill. Am J Respir Crit Care Med 2016;193(3):273-80.
14. Jaber S, LescotT, Futier E, Paugam-Burtz C, Seguin P, Ferrandiere M, et al. Effect of noninvasive ventilation on tracheal reintubation among patients with hypoxemic respiratory failure following abdominal surgery: a randomized clinical trial. JAMA. 2016;315(13):1345-53.
15. Nava S, Gregoretti C, Fanfulla F, Squadrone E, Grassi M, Carlucci A, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit Care Med. 2005;33(11):2465-70.
16. Groves N, Tobin A. High flow nasal oxygen generates positive airway pressure in adult volunteers. Aust Crit Care. 2007;20(4):126-31.
17. Ritchie JE, Williams AB, Gerard C, Hockey H. Evaluation of a humidified nasal high-flow oxygen system, using oxygraphy, capnography and measurement of upper airway pressures. Anaesth Intensive Care. 2011;39(6):1103-10.
18. Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: mechanisms of action. Respir Med. 2009;103(10):1400-5.
19. Maggiore SM, Idone FA, Vaschetto R, Festa R, Cataldo A, Antonicelli F, et al. Nasal high flow versus Venturi mask oxygen therapy after extubation. Effects on oxygenation, comfort, and clinical outcome. Am J Respir Crit Care Med. 2014;190(3):282-8.
20. Hernandez G, Vaquero C, Colinas L, Cuena R, González P, Canabal A, et al. Effect of post extubation high-flow nasal cannula vs noninvasive ventilation on reintubation and postextubation respiratory failure in high-risk patients: a randomized clinical trial. JAMA. 2016;316(15):1565-74.
21. Hernandez G, Vaquero C, González P, Subira C, Frutos-Vivar F, Rialp G, et al. Effect of postextubation high-flow nasal cannula vs conventional oxygen therapy on reintubation in low-risk patients: a randomized clinical trial. JAMA. 2016;315(13):1354-61.
22. Futier E, Paugam-Burtz C, Godet T, Khoy-Ear L, Rozencwajg S, Delay JM, et al. Effect of early postextubation high-flow nasal cannula vs conventional oxygen therapy on hypoxaemia in patients after major abdominal surgery: a French multicentre randomized controlled trial (OPERA). Intensive Care Med. 2016;42(12):1888-98.
23. Parke RL, Mc Guinness SP, Eccleston ML. A preliminary randomized controlled trial to access effectiveness of nasal high-flow oxygen in intensive care patients. Respir Care. 2011;56(3):265-70.
24. Lucangelo U, Vassalo FG, Marras E, Ferluga M, Beziza E, Comuzzi L, et al. High-flow nasal interface improves oxygenation in patients undergoing bronchoscopy. Crit Care Res Pract. 2012;2012:506382.
25. Simon M, Braune S, Frings D, Wiontzek AK, Klose H, Kluge S. High-flow nasal cannula oxygen versus non-invasive ventilation in patients with acute hypoxaemic respiratory failure undergoing flexible bronchoscopy-a prospective randomized trial. Crit Care. 2014;18(6):712.
26. Spence EA, Rajaleelan W, Wong J, Chung F, Wong DT. The effectiveness of high-flow nasal oxygen during the intraoperative period: A systematic review and meta-analysis. Anesth Analg. 2020;131(4):1102-10.

CHAPTER 64

Postresuscitation Care: Temperature Management after Cardiopulmonary Resuscitation

Gavin D Perkins, Jerry P Nolan

INTRODUCTION

Each year hundreds of thousands of people sustain a cardiac arrest either within or outside a hospital.[1,2] Whilst between a quarter and a half of those who undergo resuscitation will achieve a return of spontaneous circulation (ROSC), on average only around 1 or 2 in 10 survive to go home from hospital.[1,2] Because of a significant, global ischemia reperfusion injury, the majority of patients who achieve ROSC will experience postcardiac arrest syndrome. Postcardiac arrest syndrome is characterized by postcardiac arrest brain injury, postcardiac arrest myocardial dysfunction, a systemic ischemia/reperfusion response and persistent precipitating pathology.[3]

Postcardiac arrest brain injury, to some degree, is present in the majority of those who achieve a ROSC. It is driven by impaired cerebrovascular autoregulation, cerebral edema, and postischemia neurodegeneration. The initial clinical manifestations include coma, seizures, and myoclonus. Later sequelae range from mild cognitive impairment through to persistent vegetative state and brain death.[3,4]

The search for effective treatments for postcardiac arrest brain injury has been on-going since the advent of modern-day cardiopulmonary resuscitation (CPR). Despite this no specific pharmacological therapy has been definitively shown to be effective.[4] Current resuscitation guidelines therefore recommend attention is focused on normalizing physiology (normoxia, normocarbia, and avoidance of hypotension) and controlling temperature.[5]

Case reports in the 1960s first described the use of hypothermia after cardiac arrest. Little progress was made until interest was renewed in the use of hypothermia to reduce postcardiac arrest brain injury in the early 1990s.[6] Animal models tested intra- and postcardiac arrest hypothermia following induction of ventricular fibrillation (VF) cardiac arrest. The studies characterized by very early (during cardiac arrest or within minutes of ROSC) induction of hypothermia showed consistently improved neurological outcomes. These studies provided the foundation for subsequent translational studies which sought to replicate these findings in humans.

EARLY CLINICAL STUDIES

One of the first clinical studies to test the role of induced hypothermia following cardiac arrest was led by Bernard et al. from Melbourne, Australia. In this single center study, investigators induced moderate hypothermia (33°C) using surface cooling in 22 adults who remained comatose following out of hospital cardiac arrest. Hypothermia was maintained for 12 hours followed by controlled rewarming to normothermia over 6 hours.[7] The study demonstrated that induced hypothermia was well tolerated. Survival with a favorable neurological outcome was superior (11/22) compared with a group of (3/22) historical controls. Subsequently, the Hypothermia After Cardiac Arrest (HACA) group presented the findings from a feasibility trial in which surface cooling was applied to adults admitted to the emergency department with ROSC following out of hospital cardiac arrest (OHCA) with an initial rhythm of VF. Hypothermia (target 32–34°C) was initiated within 62 minutes and achieved a core temperature of 33°C within 5 hours (range 42 minutes to 6.5 hours).[8] These seminal studies paved the way for large randomized controlled trials (RCTs) which have enhanced our understanding of the role of temperature control after cardiac arrest.

INTERNATIONAL LIAISON COMMITTEE ON RESUSCITATION

The International Liaison Committee on Resuscitation (ILCOR) is an international collaboration of clinicians and researchers with an interest in cardiac arrest who are united around the vision of saving more lives globally through resuscitation.[9] A key role undertaken by ILCOR is the evaluation of resuscitation literature to produce an international consensus on science and treatment recommendations. These recommendations are used by

regional resuscitation councils to produce clinical practice guidelines, suited to the specific healthcare setting where they will be implemented.

Following publication of two prospective controlled trials in 2002 (one randomized trial conducted in nine centers in Europe and a pseudorandomized trial within 4 hospitals in Melbourne), ILCOR produced a scientific advisory statement which recommended that "Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32–34°C for 12–24 hours when the initial rhythm was ventricular fibrillation (VF). Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest." These recommendations were updated in 2015 following publication of the Targeted Temperature Management (TTM)-1 trial, which showed no difference in mortality or functional outcome with a target temperature of 36°C compared with 33°C.[10] The recommendations supported the use of targeted temperature management (temperature range 32–36°C) for adults who remained comatose following in or out of hospital cardiac arrest with either shockable or nonshockable rhythms. Observational studies tracking the outcomes of patients following change to practice guidelines in light of these recommendations have suggested an increase in mortality, although there is some uncertainty in these findings because of likely confounding caused by the effect of temperature on the physiological values used for statistical adjustment.[11,12] It is timely therefore to consider the latest evidence and recommendations.

The most recent update (draft recommendations, October 2021) following publication of the TTM-2 trial makes the following recommendations:[13]

- We suggest actively preventing fever by targeting a temperature ≤37.5°C for those patients who remain comatose after ROSC from cardiac arrest (weak recommendation, low certainty evidence).
- Whether subpopulations of cardiac arrest patients may benefit from targeting hypothermia at 32–34°C remains uncertain.
- Comatose patients with mild hypothermia after ROSC should not be actively warmed to achieve normothermia (good practice statement).
- We recommend against the routine use of prehospital cooling with rapid infusion of large volumes of cold intravenous (IV) fluid immediately after ROSC (strong recommendation, moderate certainty evidence).
- We suggest surface or endovascular temperature control techniques when temperature control is used in comatose patients after ROSC (weak recommendation, low certainty of evidence).
- When a cooling device is used, we suggest using a temperature control device that includes a feedback system based on continuous temperature monitoring to maintain the target temperature (good practice statement).
- We suggest active prevention of fever for at least 72 hours in postcardiac arrest patients who remain comatose (good practice statement).

EVIDENCE INFORMING THE GUIDELINES

The current ILCOR recommendations are informed by a systematic review led by Granfeldt et al.[14] The review examined the use, target temperature, timing, duration, and method of targeted temperature management in adults with in- or out-of-hospital cardiac arrest improved clinical outcomes (specifically survival and survival with favorable neurological outcome). The review identified 32 trials which were published between 2001 and 2021. Across the studies the certainty of evidence was assessed as intermediate across all outcomes. **Figure 1** summarizes the findings from the meta-analyses of TTM trials, whilst **Table 1** presents the key study characteristics.

Targeted Temperature Management at 32–34°C Compared with Normothermia

The review identified nine trials which compared TTM with normothermia. Trials ranged in size from 22–1,861 participants, with only three enrolling >200 participants.[15-17] The studies were conducted between 1996 and 2020. Most of the trials enrolled participants following OHCA. Targeted temperature management was commenced following hospital arrival in most (n = 7) studies. The duration of TTM ranged from 4 to 72 hours. Six studies were assessed as being at intermediate risk of bias and three at high risk of bias.

Meta-analysis of the trial findings did not find evidence of benefit from TTM compared with normothermia for the outcomes of survival to hospital discharge {risk ratio 1.12 [95% confidence interval (CI) 0.92–1.35]}, favorable neurological outcome at discharge or 30 days [risk ratio, 1.3 (95% CI 0.83–2.03)] or longer term survival (90 or 180 days), risk ratio 1.08 (95% CI 0.89–1.30), or favorable neurological outcome [risk ratio 1.21 (95% CI 0.91–1.61)]. The meta-analyses were limited by significant clinical and statistical heterogeneity. Sensitivity analyzes, which excluded trials at high risk of bias, recent trials and when considering TTM at 36°C as normothermia moved the point estimates for the risk ratios closer to one. Predefined subgroup analyzes for shockable and nonshockable rhythms yielded similar findings.

Target Temperatures

The review identified three trials which compared different temperature targets. The TTM-1 trial compared target temperatures of 33 and 36°C in 939 adults with OHCA of presumed cardiac cause. The trial found no difference in all-cause mortality [50 vs. 48%, hazard ratio 1.06 (95% CI 0.88–1.16)] or unfavorable neurological outcome at

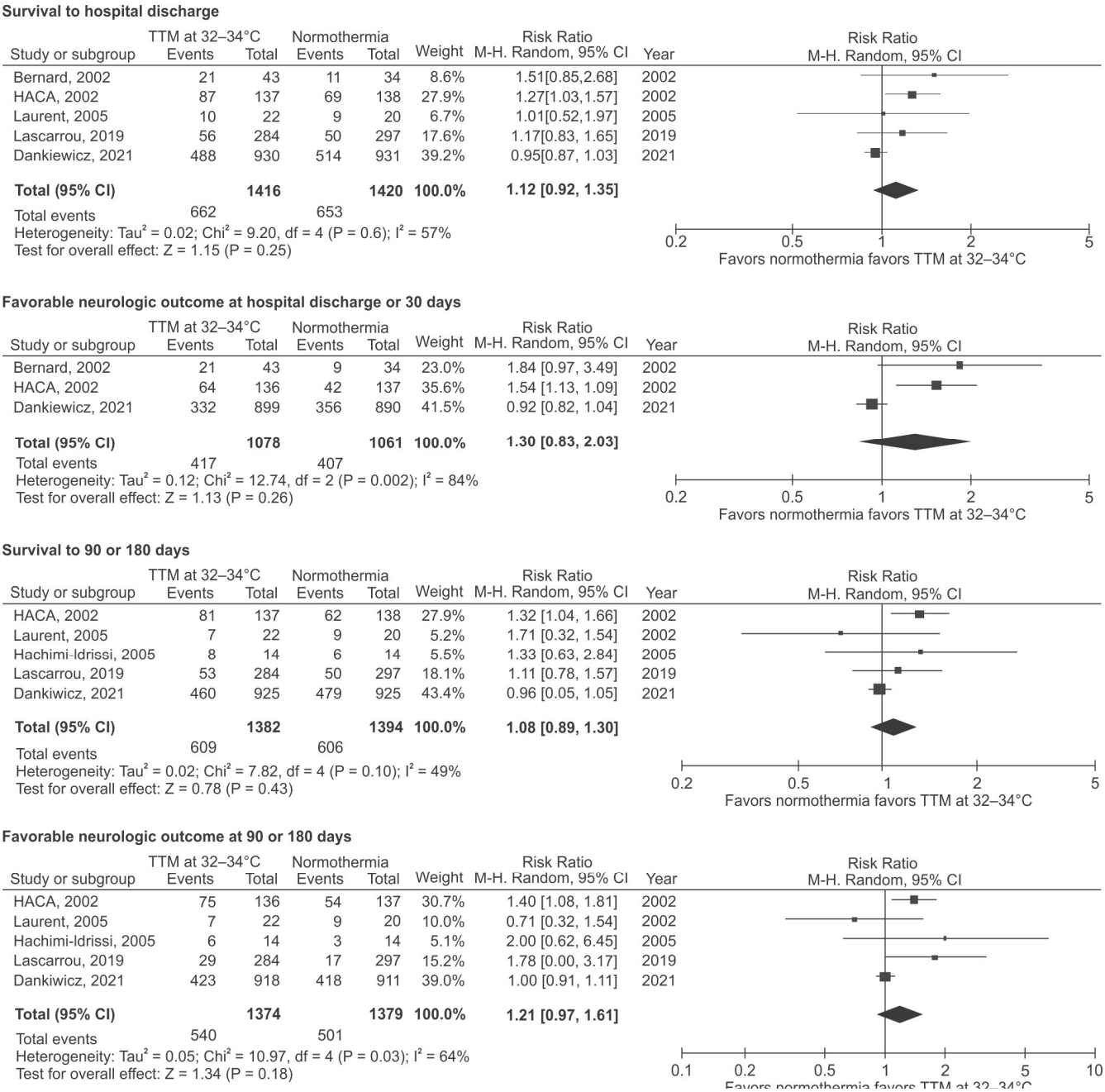


Fig. 1: Meta-analyses of targeted temperature management. Random-effects meta-analyses of TTM at 32–34°C compared to normothermia for outcomes at hospital discharge or 30 days and 90 or 180 days. Reproduced from Granfeldt et al.[14] in accordance with Creative Commons Attribution–NonCommercial–NoDerivs (CC BY-NC-ND 4.0).

6 months [54 vs. 52%, risk ratio 1.02 (95% CI 0.88–1.16)].[10] Most patients in the study had bystander witnessed cardiac arrest (90%), with bystander CPR (73%), and an initially shockable rhythm (80%). The median [interquartile ranges (IQR)] intervals between collapse and initiation of basic life support [1 minute (IQR 1–2)], advanced life support [10 minutes (IQR 5–13)], and ROSC [25 minutes (IQR 16–40)] were relatively short and the overall rates of survival with favorable functional outcomes are high. These data reflect a cohort of patients who have survived to reach intensive therapy unit (ITU) but it may affect the generalizability of findings outside of these parameters. Two smaller trials, which compared 32 or 33°C with 34°C, similarly found no difference in outcomes. The results of a large RCT, the CAPITAL CHILL trial, have been presented recently. This trial compared a target temperature of 31°C with 34°C among comatose all-rhythm OHCA survivors and found no difference in all-cause mortality or poor neurological outcome at 180 days. The data from the CAPITAL CHILL trial have been included in a network meta-analysis of

TABLE 1: Summary of larger trials comparing hypothermia with standard care (no hypothermia or fever avoidance).

Trial	*Number of participants*	*Intervention*	*Control*	*Setting*	*Rhythm*	*Participants*	*Neurological outcome and adverse events*
HACA 1996–2001	275	32–34 for 24 hours	Normothermia	IHCA/ OHCA	Shockable	• Witnessed 99% • Bystander CPR 46% • Low flow duration 21-22 min	• Favorable neurological outcome at 6 months • 75/136 (55%) intervention versus 54/137 (39%) control • Risk ration 1.4 (95% CI 1.08-1.81)
TTM-1 2010–2013	950	33 for 28 hours	36 for 28 hours	OHCA	• Shockable and non-shockable • Presumed cardiac	• Bystander witnessed 90% • Bystander CPR 73% • No flow duration 1 min • Low flow duration 25 min	• Death or unfavorable neurological outcome 6 months • 235/473 (50%) intervention versus 225/446 (48%) • Hazard ratio 1.06 (95% CI 0.89 to 1.28)
HYPERION 2014–2018	584	33 for 24 hours	36.5–37.5	IHCA/ OHCA	Non-shockable	• Bystander witnessed 94% • Bystander CPR 70% • No flow duration 1–2 min • Low flow duration 15–18 min	• Favorable neurological outcome at 90 days • 29/294 (10.2%) intervention versus 17/297 (5.7%) • Difference 4.5% (95% 0.1–8.9%). • No difference adverse events
TTM-2 2017–2020	1861	33 for 28 hours	37.5		• Shockable (72%) • Non-shockable (28%)	• Bystander witnessed (92%) • Bystander CPR (80%) • Low flow duration 25 min	• Death or unfavorable neurological outcome 6 months • 488/881 (55%) intervention versus 479/866 (55%) • Relative risk 1.00 (95% CI, 0.92 to 1.09) • Arryhthmia 24% intervention, 17% control
Cooling only initiated if. T >38.8 (approximately 50%)							

10 RCTs of comatose OHCA survivors that documented no improvement in survival or functional outcome when comparing 31–32°C, 33–34°C, and 35–36°C with normothermia (37–37.8°C).[18]

Timing for Inducing Hypothermia

The timing for induction of hypothermia has largely been evaluated in three scenarios:

1. Intra-arrest cooling—when cooling is commenced before ROSC being achieved
2. Prehospital post-ROSC cooling—started before hospital arrival
3. Late in-hospital cooling

Meta-analyses of trials which compared intra-arrest cooling with cold IV fluids (two trials) found no difference survival to hospital discharge [risk ratio 0.93 (95% CI 0.68–1.27)] or favorable functional outcome [risk ratio 0.98 (95% CI 0.71–1.35)]. The two studies which investigated intranasal cooling during cardiac arrest yielded similar findings with no evidence of the effect being modified by the mode of intra-arrest cooling.

Method of Temperature Management

Several different strategies have been tested for inducing hypothermia. Approaches include intranasal evaporative cooling, cold intravenous fluids, surface cooling with ice packs/blankets, controlled surface cooling, and intravascular cooling. Most studies comparing different approaches are small with six of eight studies identified in the ILCOR review recruiting <100 patients each.

Three trials comparing endovascular with surface cooling. However, the ILCOR meta-analysis did not find a significant difference in survival [risk ratio 1.14 (95% CI 0.93–1.38)] or favorable neurological outcome [risk ratio 1.22 (95% CI: 0.95–1.56)] between techniques.

Duration of Temperature Management

The review identified a single trial which compared 24 hours of temperature management (32–34°C) with 48 hours amongst 355 patients who achieved sustained ROSC following OHCA.

The study found no difference in survival or favorable functional outcome.[19]

STRENGTHS AND LIMITATIONS OF THE EVIDENCE BASE

The management of temperature following cardiac arrest is one of the most studied interventions in postresuscitation care with over 32 trials reported in the review. These studies have evaluated the optimal timing, dose (temperature), duration, and device. The randomized design of most studies will have protected against many of the biases seen in

observational studies. Most outcomes were objective (death and neurological outcome) and are unlikely to have been influenced by the open label nature of the studies. However, a limitation is that the open label design may have led to performance bias whereby knowledge of the randomized intervention may have influenced clinician behavior beyond solely the intervention (e.g., sedation use). There was variation in the postresuscitation care bundles provided in each of the index studies which may have influenced findings.

The ILCOR task force highlighted concerns about the generalizability of findings, particularly in relation to the time to achieve hypothermia target, patient selection may not be generalizable to all post-ROSC cardiac arrest patients and relatively few studies included patients with IHCA or nonprimary cardiac arrest. The group highlighted the need for further research, particularly whether certain subpopulations of cardiac arrest patients may benefit from lower (32–34°C) or higher (36°C) temperatures remains unknown, and further research may help elucidate this.

EVIDENCE INTO PRACTICE

The ILCOR ALS Task Force were unanimous in supporting the use of active temperature management in postcardiac arrest patients, although acknowledged that the evidence for this recommendation is limited.

Given the absence of benefit (and some evidence of harm), it is reasonable to avoid prehospital cooling with cold intravenous fluids.

As a minimum, clinicians should actively prevent fever in those who achieve ROSC after cardiac arrest. Whether subpopulations of cardiac arrest patients may benefit from targeting hypothermia at 32–34°C remains uncertain.

REFERENCES

1. Kiguchi T, Okubo M, Nishiyama C, Maconochie I, Ong MEH, Kern KB, et al. Out-of-hospital cardiac arrest across the World: First report from the International Liaison Committee on Resuscitation (ILCOR). Resuscitation. 2020;152:39-49.
2. Andersen LW, Holmberg MJ, Berg KM, Donnino MW, Granfeldt A. In-hospital cardiac arrest: A review. JAMA. 2019;321(12):1200-10.
3. Nolan JP, Neumar RW, Adrie C, Aibiki M, Berg RA, Böttiger BW, et al. Post-cardiac arrest syndrome: Epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. Resuscitation. 2008;79(3):350-79.
4. Perkins GD, Callaway CW, Haywood K, Neumar RW, Lilja G, Rowland MJ, et al. Brain injury after cardiac arrest. Lancet. 2021;398(10307):1269-78.
5. Nolan JP, Sandroni C, Bottiger BW, Cariou A, Cronberg T, Friberg H, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines 2021: Post-resuscitation care. Resuscitation. 2021;161:220-69.
6. Presciutti A, Perman SM. The evolution of hypothermia for neuroprotection after cardiac arrest: a history in the making. Ann N Y Acad Sci. 2021;1507(1):60-9.
7. Bernard SA, Jones BM, Horne MK. Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. Ann Emerg Med. 1997;30(2):146-53.
8. Zeiner A, Holzer M, Sterz F, Behringer W, Schörkhuber W, Müllner M, et al. Mild resuscitative hypothermia to improve neurological outcome after cardiac arrest: a clinical feasibility trial. Hypothermia After Cardiac Arrest (HACA) Study Group. Stroke. 2000;31(1):86-94.
9. Perkins GD, Neumar R, Monsieurs KG, Lim SH, Castren M, Nolan JP, et al. The International Liaison Committee on Resuscitation-Review of the last 25 years and vision for the future. Resuscitation. 2017;121:104-16.
10. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager, C, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. N Engl J Med. 2013;369(23):2197-206.
11. Nolan JP, Orzechowska I, Harrison DA, Soar J, Perkins GD, Shankar-Hari M. Changes in temperature management and outcome after out-of-hospital cardiac arrest in United Kingdom intensive care units following publication of the targeted temperature management trial. Resuscitation. 2021;162:304-11.
12. Salter R, Bailey M, Bellomo R, Eastwood G, Goodwin A, Nielsen N, et al. Changes in temperature management of cardiac arrest patients following publication of the target temperature management trial. Crit Care Med. 2018;46(11):1722-30.
13. International Liaison Committee on Resuscitation. Temperature management following cardiac arrest (draft consensus on science and treatment recommendations) 2021. [online] Available from: https://costr.ilcor.org/document/systematic-review-temperature-management-in-adult-cardiac-arrest-als. [Last accessed February 2022].
14. Granfeldt A, Holmberg MJ, Nolan JP, Soar J, Andersen LW; International Liaison Committee on Resuscitation (ILCOR) Advanced Life Support Task Force. Targeted temperature management in adult cardiac arrest: Systematic review and meta-analysis. Resuscitation. 2021;167:160-72.
15. Lascarrou JB, Merdji H, Le Gouge A, Colin G, Grillet G, Girardie P, et al. Targeted temperature management for cardiac arrest with nonshockable rhythm. N Engl J Med. 2019;381(24):2327-37.
16. Dankiewicz J, Cronberg T, Lilja G, Jakobsen JC, Levin H, Ullén S, et al. Hypothermia versus normothermia after out-of-hospital cardiac arrest. N Engl J Med. 2021;384(24):2283-94.
17. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med. 2002;346(8):549-56.
18. Fernando SM, Di Santo P, Sadeghirad B, Lascarrou JP, Rochwerg B, Mathew R, et al. Targeted temperature management following out-of-hospital cardiac arrest: a systematic review and network meta-analysis of temperature targets. Intensive Care Med. 2021;47(10):1078-88.
19. Kirkegaard H, Soreide E, de Haas I, Pettilä V, Taccone FS, Arus U, et al. Targeted temperature management for 48 vs 24 hours and neurologic outcome after out-of-hospital cardiac arrest: A randomized clinical trial. JAMA. 2017;318(4):341-50.

SECTION 12

Toxicology

CHAPTER 65

New Recreational Designer Drug Overdose Challenges

Sai Saran, Lalit Gupta, Haider Abbas

INTRODUCTION

The use of recreational drugs (psychoactive substances) causes significant health and social problems not only for the people who use them but also for their families and communities. As per, World Health Organization Report 2002, 8.9% of total burden of substance abuse and dependence globally is due to use of psychoactive substances.[1] Globally, cannabis is the most commonly used substance (129–190 million people), while in India, heroin and synthetic opioids (buprenorphine, pentazocine, and dextropropoxyphene) are the most commonly used.

Drug intoxication poses to a lot of clinical challenges as the diagnosis requires systematic and consistent approach along with necessity of advanced laboratories to confirm the diagnosis.[1] Sometimes such intoxication even requires advanced organ support, which may not be available at all centers, especially in developing countries such as India. As drug intoxication frequently presents with other pathologies such as infection and trauma, the diagnosis is often challenging and frequently missed.[2]

WHAT ARE NEW RECREATIONAL DESIGNER DRUGS?

New psychoactive substances (NPSs) of abuse include synthetic cannabinoids, aminoindanes, phencyclidine-type substances (ketamine and methoxyeticyclidine), phenylamines, few plant-based substances (khat, kratom, and *Salvia divinorum*), synthetic cathinones (mephedrone), tryptamines, and peiperazines.[3]

These drugs are branded and black-marketed as legal alternatives, designer drugs, legal highs, herbal highs, or bath salts.[4] The abuse of these is a direct threat to civilized society, clinicians, forensic toxicologists, and drug control policy making authorities.[2,4,5]

New psychoactive substance can be broadly classified into four classes **(Table 1)** which are as follows:

1. *Synthetic stimulants*: These are chemically engineered substances with stimulant properties that mimic with well-known substances such as amphetamine, methamphetamine, and cathinone. This group of drugs includes cathinones, aminoindanes, phenethylamines, piperazines, and tryptamines, of which "cathinones" are the most commonly used, reported as "bath salts."[4,6] Such drug intoxication leads to "sympathomimetic toxidrome." These drugs increase the levels of synaptic availability of neurotransmitters such as dopamine (DA) which lead to arousal and reward, and serotonin (5HT), which leads to entactogenic feelings (sense of emotional connectedness along with happiness). They are primarily used as "cognitive enhancers" or "nootropics" and these substances have high addiction potential. Since, the action on these two neurotransmitter systems is unpredictable, various complications such as cardiac, metabolic, neurological, and neuropsychiatric are reported, leading to morbidity and mortality. Although pill/tablet is the most common formulation available for ingestion, other formulations are also available for inhalation, insufflation, smoking, swallowing (often-wrapped in paper, known as "bombing"), injections, and suppositories.
2. *Synthetic cannabinoids*: They also mimic "sympathomimetic toxidrome," with significant effects on lungs and kidneys upon intoxication. They resemble cannabis intoxication with more potency (10–200 times) on cannabinoid receptor (CB_1) leading to addictive potential. "Spice" refers to mixture of recreational drugs, with cannabinoids forming the major category.[7] These compounds are abused as e-cigarette, vaping leading to associated lung injury (EVALI) presenting in different entities such as chemical pneumonitis, lipoid pneumonia, or organizing pneumonia (OP). These can get complicated and present to intensive care units as respiratory failure due to acute respiratory distress syndrome (ARDS) or diffuse alveolar hemorrhage.[8]
3. *Synthetic hallucinogens and dissociatives*: Synthetic hallucinogens include tryptamines [lysergic acid (LSD) with its derivatives], lysergamides, and phenethylamines. These agents primarily increase serotoninergic activity

TABLE 1: Challenges in management of new designer recreational drugs.

Name of the drug intoxication	***How to suspect: Toxidrome***	***Laboratory/imaging***	***Management***
Synthetic stimulants	*Sympathomimetic:* • Mydriasis, agitation, palpitations, tachycardia, hypertension (crisis), and hyperthermia • *Neurological*: Delirium and seizures (especially in pediatric age group)	*Quantitative-urine*: • Liquid chromatography/tandem *Mass spectrometry:* • *Cardiac enzymes*: If cardiac symptoms are present • *Brain imaging*: Abnormalities in cerebral perfusion, deficits in brain volume, and white-matter pathways	• Synthetic drug detox (symptomatic treatment of symptoms if drug is unknown) • Residential drug rehabilitation for synthetic drug addiction • Outpatient drug rehabilitation for synthetic drug addiction • Sober living for synthetic drug addiction (new place to live) • Aftercare for synthetic drug addiction
Synthetic cannabinoids	• *Neurologic*: Agitation, sleepiness, irritability, confusion, dizziness, incoordination, stroke, and seizures • *Psychiatric*: Poor concentration, hallucinations, delusions, psychosis, violent behavior, and suicidal thoughts • *Cardiorespiratory*: Tachypnea, tachycardia, and hypertension • *Gastrointestinal*: Severe nausea and vomiting, chest pain • *Renal*: Rhabdomyolysis, kidney failure, and death	• *Clinical diagnosis*: Most helpful in acute symptoms • Laboratory methods (takes time and hence not helpful in acute cases) • *Cardiac enzymes*: If cardiac symptoms are present • *Creatine phosphokinase*: If rhabdomyolysis is suspected (severe muscle spasms, swelling and pain in the extremities, or severe seizures)	• No specific antidote • Supportive (as needed) • Intravenous fluids, supplemental oxygen, and airway protection • Antiemetic medications • Intravenous benzodiazepines (for agitation, combativeness, and hyperactivity) • Drug rehabilitation as above
Synthetic hallucinogens and dissociatives	• Severe emotional swing • Intensified feelings and sensory experiences • Psychotic episodes • Respiratory depression, heart rate abnormalities, and withdrawal syndrome	• Urine or serum toxicology (limited scope if drug source is unknown) • Complete blood cell count and complete metabolic panel • *Cardiac enzymes*: If cardiac symptoms are present • *Additional diagnostic test*: On the basis of the initial presentation	• *Benzodiazepines*: In agitated patients and to blunt associated hypertension and tachycardia • *Antidotes*: Dextrose, thiamine, and naloxone as coma cocktail in an unconscious patient
Synthetic depressants	• *Neurological*: Slurred speech confusion, comatose, and dizziness • Problems with movement and memory, miotic pupils (in opioids) • *Cardiovascular*: Tachycardia, lowered blood pressure • *Respiratory*: Bradypnea and respiratory arrest	*Immunoassay*: Urine samples: Liquid chromatography, tandem mass spectrometry	• Specific antidotes such as naloxone/naltrexone and flumazenil (if source is known) • Intensive monitoring and symptomatic treatment with low threshold for ventilatory support

($5HT_2A$), along with some enhancement of glutaminergic (GA) activity. Dissociatives include arylcyclohexamines (ketamine, phencyclidine, and methoxetamine) and diarylethylamine which act on NMDA (N-methyl-D-aspartate) receptors predominantly. Their use leads to euphoria, depersonalization, spiritual, and mystical experiences. Such effects make these agents very popular amongst artists, leading to their abuse. The intoxication manifests as sympathomimetic and serotonergic toxicity with adverse effects including neurological, cardiac, and renal involvement.

4. *Synthetic depressants*: Synthetic benzodiazepines and opiates are included in this category of recreational designer drugs. Benzodiazepines are used for their anxiolytic and hypnotic effect [through gamma-aminobutyric acid type A ($GABA_A$) agonist effect]. These are used in order to combat the withdrawal symptoms, of addicted drugs, but when taken in high doses they too have addictive potential. The patients who take higher doses present with "sedative-hypnotic toxidrome," with clinical features such as ataxia, blurred vision, coma, confusion, delirium, diplopia, dysesthesias,

hallucinations, nystagmus, paresthesia, sedation, slurred speech, and stupor. Synthetic opioids act at mu, kappa, and delta receptors to produce effects such as euphoria, anxiolysis, and feelings of relaxation. These drugs are used as adulterants in cocaine and as a component of various cocktails. Most commonly used opioids include, fentanyl and its analogues such as acetylfentanyl, butyrylfentanyl, and 3-methylfentanyl. The drug intoxication manifests as an opioid toxidrome with features such as miotic pupils, constipation, decreased respiratory rate followed by clinical improvement upon opioid antagonist administration (naloxone, naltrexone). Intoxication may present as noncardiogenic pulmonary edema, acute lung injury, diffuse alveolar hemorrhage, and rhabdomyolysis.[9]

DIAGNOSIS

How can we Diagnose such New Psychoactive Substance Drug Overdose based on History?

Illicit drugs are often "rebranded" in the underground market with different names. Repeated and keen history taking from suspected patients and co-operation from the patient's family members, friends, and help from legal authorities is necessary to diagnose such drug abuse. Suspicion should be there when a young adult presents mysteriously to emergency with recent history of attending a rave party.[10]

CLINICAL EXAMINATION

How can we Suspect Intoxication based on Clinical Examination?

Toxidrome

Characteristic odor, pupillary findings (example, miosis in opioids and mydriasis in sympathomimetic agents such as cannabinoids and cathinones), neuromuscular abnormalities, mental status alterations, skin findings (dry versus wet), temperature alterations, blood pressure and heart rate alterations (excitation or depression), and respiratory disturbances should alert the clinician to suspect certain drug intoxication. Apart from this, thorough clinical examination for various puncture sites [intravenous (IV) drug abuse], and examination of nose and pharynx with nasal endoscope or nasopharyngoscopy to look for septal perforation can aid in the diagnosis of drug abuse. NPS toxidrome may be highly nonspecific, with a mixture of sympathomimetic, sedative-hypnotic, serotonin syndrome, and opioid toxidromes, making the clinician's job difficult. One has to depend on laboratory tests to make the specific diagnosis.[11] A myriad of atypical presentations to emergency includes arrhythmias (supraventricular), refractory status epilepticus, focal neurological deficits: intracerebral hemorrhage, ischemic stroke (synthetic cannabinoids) and rhabdomyolysis (cathinones, cannabinoids), and acute kidney injury. With the current limitations in laboratory diagnosis, the clinical toxidrome-based diagnosis is the only way available for the clinician to initiate management for such emergencies, which is a tough challenge.[4,5]

Investigations

Basic investigations such as serum electrolytes, blood urea nitrogen (BUN), creatinine, glucose, serum ketones, creatine kinase, liver function tests, amylase, lipase, ionized calcium, and magnesium should be performed. Viral serology [(human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV)] should be routinely performed in IV drug abusers.

Arterial blood gas to estimate the three gaps: Anion gap, osmolar gap, and saturation gap can guide the type of intoxication and its management. Electrocardiography features of ischemia especially type 2 myocardial infarction due to supply–demand imbalance (ST-T changes) may be evident, especially in a sympathomimetic toxidrome. Echocardiography may reveal features of catecholamine-induced myopathy (*Takatsubo or apical ballooning syndrome*) requiring supportive treatment.

Urine Toxicological Screen

Urological screening by immunoassay is single most important screening investigation, which can diagnose such drug intoxication. It can routinely detect various compounds such as opioids, benzodiazepines, cocaine metabolites, barbiturates, tricyclic antidepressants, tetrahydrocannabinol, and phencyclidine metabolites. Newer recreational drugs such as cathinones cross-react with immunoassays helping in their detection like CEDIA amphetamine/ecstasy drugs of abuse assays (ThermoFisher Scientific, Waltham, MA), but many drugs such as synthetic cathinones [Ethylone, 3-FMC (3-fluoromethcathinone), 4-FMC (4-fluoromethcathinone), methylenedioxyphenyl (MDP), methedrone, methylone, pyrovalerone, and α-pyrrolidinovalerophenone (α-PVP)] do not cross-react. Fast turnaround time, ability to detect multiple drug intoxication, even with in the same class are its advantages. Despite that, these immunoassays have limited specificity and sensitivity, in NPS intoxication as these immunoassays are based on antibody detection.[5]

Liquid (LC-MS) and Gas Chromatography (GC-MS) with Mass Spectrometry

Definitive identification of a specific drug and/or its metabolite(s) requires more sophisticated tests with mass spectrometry (MS), coupled with either gas or liquid

chromatography (GC and LC, respectively). LC with quadrupole time of flight mass spectrometry (LC-QTOF-MS) is helpful in detecting these compounds from serum.[3,5,12] These techniques can allow detection of NPS from samples obtained not only from blood, but also from urine, hair, saliva, urban wastewater, and from even dried blood samples. Setting up such diagnostic modalities in various hospitals is a real challenge.

Challenges Posed by New Psychoactive Substances

As these compounds have high turnaround time, and usually do not cross-react with immunoassays that target existing classes of drugs, it is extremely difficult to diagnose NPS intoxication. Current literature suggests that only 14% immunoassay kits show cross-reactivity.[3] As there is limited information about the chemical structure, lack of information about the metabolism, and pharmacokinetics of these compounds, techniques such as LC-MS/GC-MS are of limited utility.

Imaging

High-resolution computerized tomography (HRCT) may reveal features of interstitial lung disease, especially in young age, such as lipoid pneumonia, hypersensitivity pneumonitis (HP), OP, ARDS, and diffuse alveolar damage (DAD). In some cases, sympathomimetic drugs can produce "crack lung," manifesting as hemorrhagic alveolitis with signs of DAD. These findings in a suspected patient should alert the clinician the drug intoxication after excluding other possible etiologies.

Neuroimaging

Toxic leukoencephalopathy with white matter abnormalities, demyelinating injury, and leptomeningeal enhancement in a background of intoxication can lead to a clue in establishing diagnosis of drug-intoxication.[13] There is a definite role of functional magnetic resonance imaging (*f*MRI) in such scenarios to see which system (dopaminergic, serotonergic, GABA, cannabinoid, etc.) is suppressed or activated, although these are not available at all centers.[3]

CHALLENGES IN MANAGEMENT

The main challenge in the management of overdose of recreational drugs is that their diagnosis is often missed or confusing. Not only the diagnosis based on history is difficult but also its confirmation based on laboratory tests is equally difficult as explained above. Even if diagnosed, such cases pose challenge in management as majority of these substances lack antidotes. The treatment relies on symptomatic and meticulous supportive care. First aid and resuscitation with consideration of maintaining clear airway, establishing breathing, supporting circulation, and decontamination from the time of admission in the emergency ward is the basic management strategy in all such cases.

Activated charcoal may help only in cases with presenting within an hour of ingestion, and only in patients able to protect the airway. The sympathetic stimulation may present as accelerated hypertension with tachycardia, hyperthermia, and sometimes hyperreflexia, with or without seizures. The severely intoxicated patient may progress to become comatose with respiratory depression and acidosis leading to cardiac arrest. The agitated patient may be calmed by keeping them in calm rooms with minimal lighting, especially in patients with drug abuse with phencyclidine derivatives. Drugs such as midazolam or lorazepam, haloperidol can be used in controlling such combative and psychotic patients. Hyperthermia is an important complication to detect and treat promptly, with controlled external cooling in order to prevent dehydration and acute kidney injury.

Need for Intensive Care Unit Admission

Requirement of organ supports such as ventilation, hemodynamic, temperature control, renal replacement therapies should determine the ICU admission. Intoxicated patients should be placed on continuous cardiac monitoring with pulse oximetry and frequent neurological assessments should be done. Adequate hydration should be prescribed in patients with hyperthermia, and suspected history of rhabdomyolysis to prevent acute kidney injury. Urinary alkalinization has a role if the NPS compound is weakly acidic in nature, predominantly eliminated unchanged by the kidney, distributed primarily in the extracellular fluid compartment and minimally protein-bound. Urine alkalinization is done by administration of IV bolus of 1–2 mEq/kg of 8.4% sodium bicarbonate solution followed by continuous infusion of sodium bicarbonate, targeting urine pH of 7.5 or higher. This is contraindicated in patients with kidney failure, pulmonary edema, cerebral edema, and conditions that can precipitate heart failure.

Antidotes Available

No specific antidotes are available other than naloxone for opioids and flumazenil for benzodiazepines. Usually, these patients should be given a cocktail of glucose, thiamine, and naloxone if toxidrome matches. Naloxone may be administered through various routes, including intramuscular (IM), intranasal (IN), and IV. Dose in adults ranges from 100–400 μg IV, 2 mg IM or IN, respectively.[14] Few of the patients, who present with features of serotonin syndrome-like presentation, need to be managed with drugs such as cyproheptadine at initial dose of 12 mg, with the addition of 2 mg every 2 hours followed by maintenance dose of 8 mg every 6 hours. Benzodiazepines are used to blunt the hyperadrenergic symptoms in such patients.

Drugs such as chlorpromazine also can be used provided that the patient is not in shock.

Role of Molar Sodium Bicarbonate

Such therapy is used in the treatment of cocaine-induced ventricular tachycardia, and in cases with prolonged QRS >100 ms on ECG, arrhythmias, conduction blocks, etc. This therapy involves serum alkalinization with hyperosmolar boluses of sodium bicarbonate 1–2 mmol/kg IV, followed by infusion until the QRS interval narrows down, following which the infusion is stopped with decremental response (25 % per hour over 4 hours).[15]

Role of Intravenous Lipid Emulsion

20% intralipid emulsions are used for lipophilic compounds which work based on "lipid sink hypothesis," whereby the compounds are being diverted from organs of manifest toxicity such as myocardium into intravascular compartments, which enhances their elimination from systemic circulation. This was historically used in local anesthetic systemic toxicity (LAST). Such emulsions can be used in drug intoxications, which are lipophilic in nature, but the challenge remains whether they can be used in NPS overdose as many of the pharmacological characteristics for these compounds remain uncertain.[16]

Management of Aftereffects on Mental Health

In order to address any withdrawal symptoms, some people are placed in a medical detox program. An aftercare program in form of behavioral therapy by psychiatrist's sessions will help to avoid relapse.

PREVENTION

New synthetic drug products are rapidly proliferating and the formulas are unpredictable, making effective regulation difficult. Indian data regarding use of NPS is very limited despite its wide usage. There is an urgent requirement in strengthening the laboratory services to diagnose such intoxication apart from strict legal measures for licensing. Various government enforcement acts to ban synthetic drugs such as "*The Controlled Substance Analogue Enforcement Act of 1986*" and "*Synthetic Drug Abuse Prevention Act: Enacted in 2012 amended in 2016*" are in force to prevent such drug abuse.

REFERENCES

1. WHO. (2002) The World Health Report 2002. Geneva: World Health Organization. [online] Available from: http://efaidnbmnnnibpcajpcglclefindmkaj/viewer.html?pdfurl=https%3A%2F%2Fapp.who.nt%2Firis%2Fbitstream%2Fhandle%2F10665%2F42510%2FWHR_2002.pdf&clen=2057629&chunk=true. [Last accessed February 2022].
2. Montoya ID, McCann DJ. Drugs of abuse: management of intoxication and antidotes. EXS. 2010;100:519-41.
3. Mégarbane B, Oberlin M, Alvarez J-C, Balen F, Beaune S, Bédry R, et al. Management of pharmaceutical and recreational drug poisoning. Ann Intensive Care. 2020;10(1):157.
4. Shafi A, Berry AJ, Sumnall H, Wood DM, Tracy DK. New psychoactive substances: a review and updates. Ther Adv Psychopharmacol. 2020;10:204512532096719.
5. Liu L, Wheeler SE, Venkataramanan R, Rymer JA, Pizon AF, Lynch MJ, et al. Newly emerging drugs of abuse and their detection methods. Am J Clin Pathol. 2018;149(2):105-16.
6. Hall C, Heyd C, Butler C, Yarema M. "Bath salts" intoxication: a new recreational drug that presents with a familiar toxidrome. Can J Emerg Med. 2014;16(2):171-6.
7. Gershman JA, Fass AD. Synthetic cathinones ('Bath Salts'): Legal and health care challenges. PT. 2012;37(10):571-3.
8. Babi MA, Robinson CP, Maciel CB. A spicy status: Synthetic cannabinoid (spice) use and new-onset refractory status epilepticus—A case report and review of the literature. SAGE Open Med Case Reports. 2017;5:2050313X1774520.
9. Spaderna M, Addy PH, D'Souza DC. Spicing things up: Synthetic cannabinoids. Psychopharmacology (Berl). 2013;228(4):525-40.
10. Patil V, Tewari A, Rao R. New psychoactive substances: Issues and challenges. J Ment Heal Hum Behav. 2016;21(2):98.
11. Kronstrand R, Guerrieri D, Vikingsson S, Wohlfarth A, Gréen H. Fatal poisonings associated with new psychoactive substances. Handb Exp Pharmacol. 2018;252:495-541.
12. Parasuraman S. Toxicological screening. J Pharmacol Pharmacother. 2011;2(2):74.
13. Sacks J, Ray MJ, Williams S, Opatowsky MJ. Fatal toxic leukoencephalopathy secondary to overdose of a new psychoactive designer drug 2C-E ("Europa"). Baylor Univ Med Cent Proc. 2012;25(4):374-6.
14. Close B. Therapeutic Guidelines: Toxicology and Wilderness. Version 2. Aust Prescr 2013;36(1):8.
15. Bruccoleri RE, Burns MM. A Literature review of the use of sodium bicarbonate for the treatment of QRS widening. J Med Toxicol. 2016;12(1):121-9.
16. Rothschild L, Bern S, Oswald S, Weinberg G. Intravenous lipid emulsion in clinical toxicology. Scand J Trauma Resusc Emerg Med. 2010;18(1):51.

CHAPTER

66

Newer Trends in Organophosphorus/ Carbamates Revisits

Lalit Singh, Narendra Rungta, Diptimala Agarwal

INTRODUCTION

Organophosphates (OPs) are commonly used compounds as pesticides and insecticides all across the globe. These compounds also have some medicinal applications such as in the treatment of Alzheimer disease, myasthenia gravis, and glaucoma (donepezil and tacrine, pyridostigmine, and echothiophate), and the reversal of neuromuscular blockade (edrophonium, neostigmine, and pyridostigmine). Although there has been a slight diminution in their use over the last 10–20 years, partly due to the development of carbamate compounds, the toxicities of both are alike.[1] Yet, poisoning needing care is almost always because of OP products used as pesticides and insecticides.

Organophosphate compounds cause inhibition of cholinesterase leading to acetylcholine (ACh) accumulation resulting in increased stimulation of its receptors, present at the synaptic junctions of the central nervous system (CNS), the neuromuscular junction (NMJ), and autonomic nervous system; hence, they go by the name of anticholinesterase agents.[2]

EPIDEMIOLOGY

According to World Health Organization (WHO), the annual incidence of pesticide/insecticide poisoning is around 3 million cases worldwide.[3] Southeast Asia is the epicenter of most of these cases. OPs and carbamates are the predominantly responsible compounds. The incidence in our country is reported to be 12% of all intensive care unit (ICU) and about 70% of all poisoning cases.[4] In India, OP poisoning is the largest reported poisoning. Cases have been reported as accidental, suicidal, homicidal, and occupational. The poison is consumed mostly orally; however, a significant number of cases have also been reported secondary to inhalation and transdermal absorption. Therefore, it is very important to use appropriate personal protective equipment (mask and thick rubber gloves) during the handling of OP compounds.[2]

MECHANISM OF ACTION (FIG. 1)

Normally, the action of ACh on the postsynaptic receptors is regulated by the enzyme acetylcholinesterase (AChE) and excess of ACh is regularly metabolized by it. OP and carbamate compounds block these AChE molecules. This leads to the accumulation of ACh resulting in sustained and uncontrolled stimulation of postsynaptic receptors, present in the CNS, NMJ, and autonomic nervous system, resulting in cholinergic syndrome.[5,6]

Carbamates are derivatives of carbamic acid and are rapidly absorbed via all exposure routes. However, they are transient inhibitors of cholinesterase, and their spontaneous hydrolysis takes place from the enzymatic site within 48 hours. Therefore, toxicity due to carbamates tends to be of lesser duration in comparison to equivalent doses of OPs, although the associated mortality rates with both are comparable.[1]

After a while (dependent on the chemical structure of the organophosphorus agent), the AChE-organophosphorus compound undergoes a conformational change, known as "aging," which renders the enzyme irreversibly resistant to reactivation by an oxime.[7]

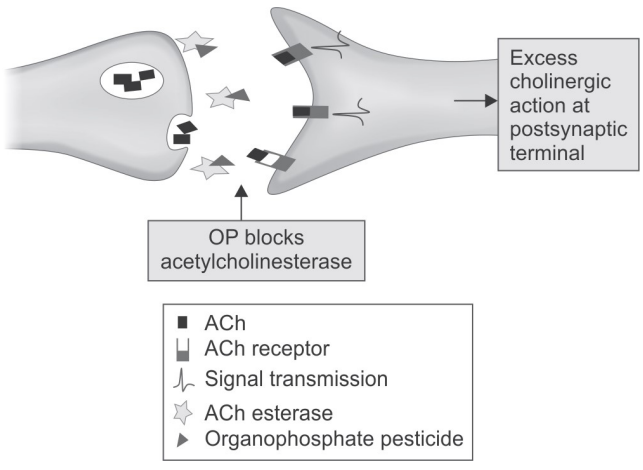


Fig. 1: Mechanism of action.
(ACh: acetylcholine; OP: organophosphate)

SIGNS AND SYMPTOMS

Muscarinic Symptoms

Muscarinic symptoms occur due to excessive stimulation of ACh receptors, leading to salivation lacrimation, nausea and vomiting, bronchoconstriction, wheezing, and bronchorrhea, urinary and bowel incontinence, dizziness, pain in abdomen, diarrhea, blurring of vision, miosis, diaphoresis, and bradycardia.[2,8]

Nicotinic Symptoms

As a result of nicotinic receptor stimulation patient can present with fatigue, weakness, muscular cramps, fasciculations and twitching of skeletal muscles, paralysis, tachycardia, increase in blood pressure, and convulsions.[8]

Central Nervous System Symptoms (Usually Seen in Moderate–Severe Cases)

Irritability, nervousness, anxiety, weakness, fatigability, and giddiness are common symptoms. Due to depression of the respiratory and circulatory centers, hypotension, cyanosis, and hypoventilation are also reported. Furthermore, confusion, memory impairment, psychosis, confusion, seizures, and coma may also occur.[2,8]

Cardiovascular Effects

Cardiovascular effects are seen in nearly two-third of patients. These include hypo/hypertension and pulmonary edema of noncardiac origin. Electrocardiogram (ECG) findings include nonspecific changes in ST-T segment (depression/elevation), abnormalities in T wave, and prolongation of QTc. Sinus bradycardia (vagal response), tachycardia-supraventricular or ventricular and arrhythmias, atrial fibrillation, ventricular premature complex, and complete heart block may also occur.[2,9]

Respiratory Symptoms

Respiratory symptoms generally result from respiratory failure due to a combination of depression of respiratory center, neuromuscular weakness, excessive respiratory secretions, and bronchoconstriction.[10]

Intermediate Syndrome

Intermediate syndrome is usually seen on days 1–4 after the exposure, following the acute cholinergic syndrome but prior to OP-induced delayed polyneuropathy. Electromyogram may be suggestive of a defect at the NMJ. Clinical features include weakness of proximal skeletal muscles, respiratory muscles, flexors of the neck, and cranial nerve palsy. Typical observations of the intermediate syndrome are usually seen after the patient who seems to have recovered completely from the cholinergic crisis suddenly reports increasing muscle weakness [lower motor neuron (LMN) quadriparesis and/or respiratory paralysis].[2,9]

Risk factors for the development of intermediate syndrome include exposure to a highly fat-soluble organophosphorus agent and inadequate doses of oximes.[11]

Nerve conduction studies on patients with intermediate syndrome reveal unique postsynaptic abnormalities that differentiate this disorder from delayed neurotoxicity.[12]

It needs to be differentiated from the acute cholinergic crisis, which may get precipitated due to rapid tapering/stopping of atropine.

Chronic-onset Symptoms

Chronic-onset symptoms are usually seen in agriculture workers, because of chronic OP exposure. OPIN (organophosphate-induced delayed neuropathy) occurs following 2–4 weeks of prolonged exposure and presents as distal weakness involving long axons more severely.[2,9]

Chronic Organophosphate-induced Toxicity

Chronic organophosphate-induced toxicity occurs after persistent exposures. There are usually no cholinergic symptoms. Can present as, cognitive impairment, mood changes, extrapyramidal symptoms, and/or peripheral neuropathy. Chronic fatigue and debilitating autonomic dysfunction may also be seen.

Motor Paralysis[9]

Type I paralysis	*Type II paralysis*	*Type III paralysis*
• Acute presentation + cholinergic symptoms • May present with – Weakness – Muscle cramps – Fasciculations – Twitching	• Occurs 24–96 hours after exposure to OP compound • Involves proximal muscle, neck muscle, muscles of respiration and cranial nerves • Recovery takes around 1–2 weeks	• Usually occurs 2–3 weeks after OP poisoning • Distal weakness—main symptom • May take weeks to months for recovery

Biochemical and Hematological Changes

Acid–base disturbances and dyselectrolytemia are commonly observed. Hyperglycemia, elevation in liver enzymes and serum amylase and proteinuria, leukocyturia, and hematuria on urine examination may also be seen.[2] These appear to be more of secondary events rather than the direct effect of OP poisoning. Direct measurement of red blood cell acetylcholinesterase (RBC AChE) activity provides a measure of the degree of toxicity. Sequential measurement of RBC AChE activity (if rapidly available) may also be used to determine the effectiveness of oxime therapy in the regeneration of the enzyme.[13]

DIAGNOSIS

- Diagnosis is mainly clinical, based on history and identification of cholinergic toxidrome **(Fig 2)**.
- A high degree of suspicion is needed especially in adolescents and the elderly.
- Garlic or petroleum-like smell may be present.
- There could be a marked variation in the toxicity due to the different nature of OP compounds. Clinicians should try their best to accurately recognize the agent. It is crucial to know whether the poison involved was a dimethyl or a diethyl compound. However, it may not be possible all the time.
- For both toxins, there is a considerable difference in duration of toxicity as well as therapeutic window during which the oxime therapy treatment can be beneficial. It is critical to start treatment with oximes early in dimethyl compounds as they go through rapid aging. Prolonged treatment may be required for diethyl compounds as they can demonstrate delayed toxicity.[14]
- If doubt exists as to whether an OP or carbamate has been ingested, a trial of 1 mg atropine in adults (or 0.01–0.02 mg/kg in children) may be used. The absence of signs or symptoms of anticholinergic effects after atropine challenge strongly supports the diagnosis of poisoning with an AChE inhibitor.
- *Laboratory tests*: Direct measurement of ACh activity in RBC is specific. Measurement in plasma is nonspecific because the enzyme is present in nervous tissue also. Sample should be drawn before administration of pralidoxime (PAM), however, one should not wait for the cholinesterase level report to initiate the therapy. Serial samples are more informative.[13]

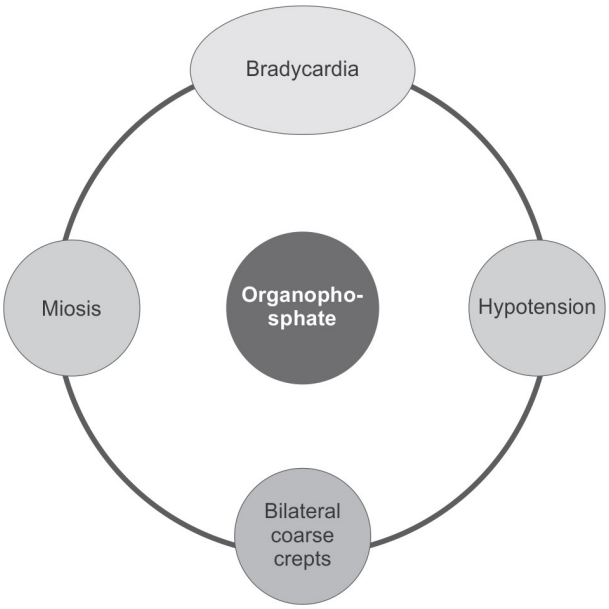


Fig. 2: The organophosphorus poison—toxidrome.

FATAL DOSE AND FATAL PERIOD

Fatal dose and fatal period both depend largely upon the compound consumed. However, parathion as low as 50 mg may be fatal and death may ensue in 6–72 hours if not treated appropriately.

MANAGEMENT

- Poisoning with organophosphorus compounds is considered an emergency and the utmost degree of patient care is required to prevent mortality, morbidities, and associated chronic complications.
- The basic approach of "ABC" (airway, breathing, and circulation) should be followed in all cases.
- No case should be discharged home from the emergency room without observation for 24 hours even if there are no symptoms and signs.
- Decontamination should be performed after securing the airway in these cases, to prevent further progress of poisoning.
- All clothing must be removed. The skin should be thoroughly washed (soap and water) by medical personnel wearing thick rubber gloves.[2,8,15,16]
- Left lateral position along with neck extension should be given to reduce the risk of aspiration.
- *Gastric lavage*: Plain water may be used, given in small 100–150 mL aliquots for gastric decontamination in case of oral consumption only if the patient presents within 1 hour of ingestion. The nasogastric tube should be put in only after ensuring a patient/secure airway. Repeat gastric lavage is not recommended.
- Activated charcoal (AC) is given to patients presenting within 1 hour of an organophosphorus agent or carbamate ingestion. The standard dose is 1 g/kg (maximum dose 50 g).[17]
- Ocular decontamination (irrigation with normal saline) should be carried out as early as possible in case of exposure of patients eyes to OP compounds.[8,16]

Antidotes

Atropine is the mainstay of treatment and a complete atropinization should be achieved and maintained.

Atropine acts by competitive antagonism of ACh at cholinergic muscarinic receptors. In case of moderate–severe cholinergic toxicity, administration of atropine is started at a dose of 2–5 mg IV (in adults) or 0.05 mg/kg IV (in children). If there's no response, the dose should be "doubled" every 3–5 minutes, till the time muscarinic signs and symptoms are resolved and the lungs are dry/clear.[18]

Atropinization

Atropinization is a target consisting of a sustained heart rate of above 80/min and dry airways. Dilatation of the

pupils is not the endpoint. Achievement and sustenance of the first two components are essential.

The dose has to be titrated till the cessation of bronchoconstriction and clearance of respiratory secretions.[19]

Failure of the patient to respond to atropine is strong evidence to exclude some other cause or associated poisoning.

Tachycardia and mydriasis are not appropriate markers for therapeutic improvement, as they may indicate continued hypoxia, hypovolemia, or sympathetic stimulation in patients with severe poisoning.

Glycopyrrolate

Glycopyrrolate is an antimuscarinic agent acting at the periphery without CNS penetration. It can be used as an alternative if atropine is not available.

Atropine can cause CNS anticholinergic toxicity as it passes the blood–brain barrier even before proper improvement in the peripheral cholinergic symptoms. Glycopyrrolate could be an effective, but expensive, alternative to atropine, with fewer CNS side effects and better control of secretions.[16]

Oxime

Early and high-dose oxime therapy may improve outcomes by enzyme reactivation (as it prevents OP aging). WHO recommends that all symptomatic patients should receive oxime therapy within the first hour. Nicotinic effect reversal is mainly due to oximes.[20]

In a retrospective study done by Ahmed et al., it was observed that fatality in OP poisoning had a direct correlation with poisoning severity, delay in initiation of oxime therapy, and mechanical ventilation duration.[21]

Oximes may help by reactivation of the Ach enzyme, but may not result in a mortality benefit. Oximes will, if at all, only activate the recently inactivated Ach enzyme and not the "Aged" inactivated Ach by OP compounds. Therefore, they should be given early. Delayed administration does not result in any mortality benefit.

Among oximes, the most common ones used are 2-PAM, obidoxime, and other new ones [HI-6, HLo-7, and trimedoxime (TMB4)].[8] Most commonly used oxime is PAM. A high-dose regimen of 2-PAM (30 mg/kg as a bolus, followed by 8 mg/kg/h infusion or 30 mg/kg 4 hourly) is suggested to be continued until the patient has fully recovered clinically (as recommended by the WHO). It has been observed that rather than repeated bolus administration, it is better to give a high dose of PAM as a continuous infusion.[2,16]

Obidoxime may be administered at a starting dose of 500 mg followed by 750 mg/day, as liver toxicity has been reported in higher initial doses. Since it crosses the blood–brain barrier, it is quicker in action.[8] However, it is not commercially available.

As carbamates undergo spontaneous hydrolysis from the site of AChE within a day, oximes are not helpful in carbamate poisoning.[22]

Bispyridinium Hagedorn-oxime (HI-6 and HLo-7) has been reported as better oxime compared to PAM and obidoxime in decreasing mortality. The recommended dose of HI-6 is 15–30 mg per four times daily.[8]

SUPPORTIVE TREATMENT

Mechanical Ventilation

It is needed in almost all patients with severe poisoning with respiratory failure[8,16] have to be treated as cases of pulmonary edema or early acute respiratory distress syndrome (ARDS). However, noninvasive ventilation (NIV) is not recommended in these cases even for a short duration trial because of increased airway secretions.

Drugs that are Still Under Study

- *Benzodiazepines*: Organophosphorus agent-induced seizures should be treated with a benzodiazepine. Prophylactic diazepam has been shown to decrease neurocognitive dysfunction after organophosphorus agent poisoning.
- Gacyclidine
- Sodium bicarbonate infusion[2,15]
- *Magnesium sulfate*: In one study, it was seen that intravenous administration of magnesium sulfate (4 g) given to the patient on the first day of admission was found to reduce the length of hospital stay and improve outcomes.[2,15]

New Treatments

Hemofiltration

In a nonrandomized controlled study done in China, it was seen that hemofiltration had valuable therapeutic effects after poisoning with dichlorvos.[23] However, it cannot be recommended as a standard of care.

Hemoperfusion

It was observed that early and repeated hemoperfusion was more effective in treating poisoning with organophosphorus compounds, in a study done in China.[24] However, the evidence to support its use is limited and it cannot be advocated outside research studies.

Bioscavengers (albumin) or FFP (fresh frozen plasma) are useful in the clearing of free organophosphorus compounds. In a nonrandomized controlled study that included 12 patients and 21 controls, it was seen that FFP therapy increased the levels of 2-BuChE in poisoning patients and may help to reduce intermediate syndrome and associated mortality.[2,15] However, there is no definitive evidence to support their routine use.

Antioxidants

Furosemide: It may be considered if pulmonary edema is unable to resolve even after full atropinization.[16]

Clonidine: Huperzine A (reversible selective AChE inhibitor) can be administered along with imidazenil (a nonsedative benzodiazepine) to prevent seizures postexposure.[25]

Antimuscarinic drugs that have antiglutamatergic properties, for example, caramiphen, aprophen, and benactyzine, may prevent nervous injury when given along with atropinization and oxime therapy. However, the evidence to support their use is lacking.[2]

PROGNOSIS

To date, there has been only one prospective study to look for factors affecting the prognosis of patients acutely poisoned with carbamate or organophosphorus compound (n = 1,365). It was observed that GCS (Glasgow Coma Score) of <13 augurs poor prognosis, and the GCS use was comparable to International Program on Chemical Safety Poison Severity Score.[26]

CONCLUSION

Organophosphorus poisoning is a matter of great concern especially in developing countries because of the associated morbidity and mortality and since it involves young people, mostly the earning member of the family. It is a medical emergency and can be fatal if not treated aggressively.

CONFLICTS OF INTEREST

None.

REFERENCES

1. Rotenberg M, Shefi M, Dany S, Dore I, Tirosh, M Almog S. Differentiation between organophosphate and carbamate poisoning. Clin Chim Acta. 1995;234(1-2):11
2. Balali-Mood M, Saber H. Recent advances in the treatment of organophosphorous poisonings. Iranian J Med Sci. 2012;37(2):74.
3. World Health Organization. The impact of pesticides on health. [online] Available from. http://www.who.int/mentalhealth/prevention/suicide/en/ PesticidesHealth2.pdf. [Last accessed February 2022].
4. Cherian AM, Jeyaseelan L, Peter JV, et al. Pralidoxime in the treatment of organophosphorus poisoning—a randomized double blind, placebo controlled trial. INCLEN Monograph Series on Critical International Health Issues No. 7, Dec 1977.
5. Tafuri J, Roberts J. Organophosphate poisoning. Ann Emerg Med. 1987;16(2):193-202.
6. Khurana D, Prabhakar S. Organophosphorus intoxication. Arch Neurol. 2000;57(4):600-2.
7. Eddleston M, Szinicz L, Eyer P, Buckley N. Oximes in acute organophosphorus pesticide poisoning: a systematic review of clinical trials. QJM. 2002;95(5):275-83.
8. Sinha PK, Sharma A. Organophosphate poisoning: a review. Med J Indonesia. 2003;12(2):120-6.
9. Peter JV, Sudarsan TI, Moran JL. Clinical features of organophosphate poisoning: a review of different classification systems and approaches. Indian J Crit Care Med. 2014;18(11):735-45.
10. Asari Y, Kamijyo Y, Soma K. Changes in the hemodynamic state of patients with acute lethal organophosphate poisoning. Vet Hum Toxicol. 2004;46(1):5-9.
11. Groszek B, Pach J, Kłys M. Intermediate syndrome in acute fenitrothion poisoning. 1995;52(5):271-4.
12. De Bleecker J, Van den Neucker K, Colardyn F. Intermediate syndrome in organophosphorus poisoning: a prospective study. Crit Care Med. 1993;21(11):1706-11.
13. Johnson, MK. Mechanisms of and biomarkers for acute and delayed neuropathic effects of organophosphorus esters. In: Amaral Mendes, J, Traviseds, CC (Eds). Use of Biomarkers in Assessing Health and Environmental I mpact of Chemical Pollutants. NATO Advanced Study Workshop. Luso, Portugal: Plenum Press; 1992. p. 169.
14. Eyer P. The role of oximes in the management of organophosphorus pesticide poisoning. Toxicol Rev. 2003;22(3):165-90.
15. Narang U, Narang P, Gupta O. Organophosphorus poisoning: a social calamity. J Mahatma Gandhi Institute Med Sci. 2015;20(1):46-51.
16. Sundaray NK, Ratheesh KJ. Organophosphorus poisoning: current management guidelines. Medicine. 2010;20:420-5.
17. Eddleston M, Juszczak E, Buckley NA, Senarathna L, Mohamed F, Dissanayake W, et al. Multiple-dose activated charcoal in acute self-poisoning: a randomised controlled trial. Lancet. 2008;371(9612):579-87.
18. Konickx LA, Bingham K, Eddleston M. Is oxygen required before atropine administration in organophosphorus or carbamate pesticide poisoning? A cohort study. Clin Toxicol (Phila). 2014;52(5):531-7.
19. Eddleston M, Roberts D, Buckley N. Management of severe organophosphorus pesticide poisoning. Crit Care. 2002;6:259.
20. Eddleston M, Buckley NA, Eyer P, Dawson AH. Management of acute organophosphorus pesticide poisoning. Lancet. 2008;371(9612):597-607.
21. Ahmed SM, Das B, Nadeem A, Samal RK. Survival pattern in patients with acute organophosphate poisoning on mechanical ventilation: a retrospective intensive care unit-based study in a tertiary care teaching hospital. Indian J Anaesth. 2014;58(1):11-7.
22. Eddleston M, Dawson A, Karalliedde L, Dissanayake W, Hittarage A, Azher S, et al. Early management after self-poisoning with an organophosphorus or carbamate pesticide–a treatment protocol for junior doctors. Crit Care. 2004;8(6):R391.
23. Peng A, Meng FQ, Sun LF, Ji Z-S, Li YH. Therapeutic efficacy of charcoal hemoperfusion in patients with acute severe dichlorvos poisoning. Acta Pharmacol Sin. 2004;25(1):15-21.
24. Bo L. Therapeutic efficacies of different hemoperfusion frequencies inpatients with organophosphate poisoning. Eur Rev Med Pharmacol Sci. 2014;18(22):3521-3.
25. Kumar SV, Fareedullah MD, Sudhakar Y, Venkateswarlu B, Kumar EA. Current review on organophosphorus poisoning. Arch Appl Sci Res. 2010;2(4):199-215.
26. Davies JO, Eddleston M, Buckley NA. Predicting outcome in acute organophosphorus poisoning with a poison severity score or the Glasgow coma scale. QJM. 2008;101(5):371-9.

CHAPTER 67

Extracorporeal Life Support in Poisoning

Vivek Gupta, Vinay Singhal, Gurpreet S Wander

INTRODUCTION

Acute poisoning with pharmacological or nonpharmacological products may present to emergency department with symptoms ranging from mild to life-threatening. The standard management practices such as supportive therapy and specific antidotes administration may usually be effective but patients with life-threatening overdoses and cardiovascular collapse may not respond. Children generally get accidental overdoses and symptoms are usually apparent immediately, while adult intoxication is usually deliberate and present late to emergency department. There is gradual rise in mortality due to acute intoxication secondary to accidental ingestion as well as for self-harm over the last few years. The poisoning victims are usually younger, however, the toxic substances varies in different part of the world.[1]

The use of extracorporeal membrane oxygenation (ECMO) has been increased significantly over the last decade. ECMO helps in sustaining cardiac and/or pulmonary functions in patient's refractory to conventional therapies targeting a specific end-point as per the underlying condition.[2]

Patients with acute severe poisoning usually die due to failure of various vital organs. Acute kidney injury following intoxication is successfully managed with various renal replacement therapies. Hepatic transplant following drug-induced fulminant hepatic failure has been reported. The severe intoxicated patients with cardiovascular collapse have successfully been treated with extracorporeal life support (ECLS). ECMO primarily maintains the cardiac output in these severely intoxicated patients with hemodynamic instability. The improved organ perfusion allows natural elimination of drug or toxic substance. Moreover renal replacement therapy (RRT) may be used during ECMO for dialyzable toxin.

Various extracorporeal therapies such as RRT, hemadsorption, and ECMO have been used for severely intoxicated patients. The increased use of ECMO is credited to advancement in technology including miniaturization of the circuit, percutaneous cannulation, and better outcomes. This chapter focus on the current practices and outcomes in severe intoxication, use of various ECLS modalities, and current evidences on use of ECLS.

CLINICAL EPIDEMIOLOGY

The toxic substances can be divided in three categories: Agricultural and industrial chemicals, medicines, and poisons associated with plants and animals. The toxicity of these substances may produce mild symptoms to severe and life-threatening organ dysfunction. Nearly 85% patients present with minor symptoms and usually aggressive management is not required. Intentional exposures have more severe effects and are associated with poorer outcomes.[3]

Approximately 3 million cases of pesticide poisoning are reported and around 8–10% of victims die every year. Pesticide ingestion and accidental exposure among agricultural communities have been recognized as a major concern in low- and middle-income countries, such as China, India, Sri Lanka, and Vietnam.[4] The substances leading to intoxication vary in different parts of the world. Cardiovascular medications and analgesics are common in the western world, while pesticides intoxication is common in the developing world.[5]

TOXIN-INDUCED CARDIOGENIC SHOCK AND DEATH

Severe intoxication may produce hemodynamic instability or cardiovascular collapse, along with respiratory depression or arrest, altered gas exchange in the lungs, convulsions, and acid–base abnormalities. The worsening metabolic factors aggravate the cardiac dysfunction and further deteriorate the clinical condition. The basic principles for managing a severely poisoned patient include a prompt airway assessment and maintenance of compromised airway, supporting the breathing as required, and hemodynamic

optimization. Mechanical ventilatory support may be required in patients with poor ventilator drive. Hemodynamic optimization requires adequate intravenous (IV) fluids administration, antidote administration, and vasopressor and inotropic support in those cases who are unresponsive to fluid resuscitation.[6] The proarrhythmic potential of inotropic agents may further deteriorate cardiac toxicity. The use of antiarrhythmic drugs produces not only a negative inotropic effect but have proarrhythmic potential as well. Nonpharmacological factors such as acidosis, hypokalemia, hypomagnesemia, and hypoxia also have potential to precipitate arrhythmia.[6] The advancements in toxin-induced cardiovascular shock management has improved survival. These include invasive hemodynamic monitoring, interpretation of shock mechanism, and guided supportive therapy for hemodynamic stabilization.[7] The cardiovascular effects may be observed shortly after intoxication and depend on various factors such as quantity, the severity of toxin, and type of toxin. Despite aggressive initial management, the incidence of cardiovascular collapse is high in intoxicated patients. Sudden cardiac arrest in a young and healthy population is most likely due to poisoning.[8]

POTENTIAL CARDIOTOXIC SUBSTANCES

- *Drugs*: The drug-induced myocardial toxicity and hypotension occur due to hypovolemia, depressed myocardial function, arrhythmias, and systemic vasodilatation. Acute toxic heart failure is mainly due to systolic dysfunction secondary to reduced myocardial contractility. Cardiotoxic potential is not restricted to cardiovascular drugs only, the mortality remains higher in compounds having membrane stabilizing activity.
  - With membrane stabilizing activity:
    - Antiarrhythmics (Vaughan Williams class I)
    - Beta-blockers (propranolol, pindolol, etc.)
    - Dopamine and norepinephrine uptake inhibitors (bupropion)
    - Antiepileptics (phenytoin)
    - Antimalarial agents (quinine and chloroquine)
    - Polycyclic antidepressants (desipramine, amitriptyline, doxepin, etc.)
    - Recreational agent (cocaine)
    - Amphetamine-like substances
  - Other drugs:
    - Calcium channel blockers (nifedipine, nicardipine, etc.)
    - Colchicine
    - Beta-blockers (without membrane stabilizing activity)
    - Digoxin
- Pesticides:
  - Insecticides:
    - Organophosphate and carbamates
  - Herbicides:
    - Paraquet
  - Rodenticides:
    - Aluminum phosphide
    - Zinc phosphide
    - Yellow phosphorus
- *Herbal toxins*: Plant toxins may produce conduction defect, bradyarrhythmia, tachyarrhythmia, or ventricular arrhythmia.
  - Aconite
  - *Taxus*
- Others:
  - Cyanide
  - Carbon monoxide

ROLE OF EXTRACORPOREAL MEMBRANE OXYGENATION IN POISONING

The use of ECMO is recommended in acute severe cardiac, pulmonary, or cardiopulmonary dysfunction unresponsive to initial optimal conventional management having a high mortality risk. ECMO should be considered in patients with a mortality risk of 50%, whereas ECMO initiation should not be delayed when the mortality risk is around 80%.[9] The outcomes in these severely intoxicated patients may be better due to relatively younger age and usually absence of comorbidities. ECMO initiation supports the cardiac output and maintains tissue oxygenation and perfusion, promotes redistribution of toxins, and enhances their metabolism and excretion. Venoarterial (VA) ECMO supports both cardiac and respiratory functions while venovenous (VV) ECMO supports respiratory function alone. The ECMO support is required in those patients who have severe cardiovascular dysfunction or ventilation and/or oxygenation failure after intoxication and are unlikely to survive in spite of adequate conventional hemodynamic support and mechanical ventilation.[10] Organic hydrocarbons such as paint remover and thinner on aspiration produce lung damage, and may lead to acute respiratory distress syndrome (ARDS) without hemodynamic instability **(Box 1)**. Currently there is no recommendation regarding the appropriate timing

BOX 1: Suggested indications for extracorporeal membrane oxygenation (ECMO) support in poisoning.

VA ECMO:
- Persistent/progressive hemodynamic instability despite high inotropic support
- Refractory arrhythmias
- Persistent severe metabolic and/or lactic acidosis
- Cardiorespiratory arrest

VV ECMO:
- Acute reversible lung injury with inhalational toxins
- Severe hypoxemia (PaO_2/FiO_2 <60)
- Uncompensated hypercapnia (pH <7.2)

(VA: venoarterial; VV: venovenous)

for ECMO initiation in severely poisoned patients and the decision primarily depends on the clinical judgment by attending clinician. It is prudent that ECMO is initiated early to avoid irreversible organ injury. The use of existing scoring system has several limitations including absence of objective criteria which limits the use of the scoring system for initiation of ECMO.[11]

Bridge-to-recovery

Cardiotoxic substances have the potential for cardiovascular collapse and death in cases where the antidote is not available or even before administration of antidote even with conventional management protocols. VA ECMO can support the cardiac output in these patients with severe left, right, or biventricular dysfunction, refractory life-threatening arrhythmias, or even cardiac arrest. The ECMO support is usually provided till the cardiac function starts recovering. The recovery is expected following the metabolism and/or excretion of the toxic substance from the body. The various factors which determine the duration of ECMO support include the severity of toxicity, half-life of toxin, and organ dysfunction at the time of initiation, etc. VA ECMO provides support to both heart and lung, thereby reducing myocardial oxygen utilization. Patients who have suffered with toxin-induced severe ARDS and hemodynamically stable may be supported with VV ECMO if unresponsive to high positive end expiratory pressure (PEEP) and ventilatory support. The duration of VV ECMO will depend upon recovery of the gas exchange function.[12]

Bridge-to-antidote

Extracorporeal membrane oxygenation can be life-saving during arrhythmia, cardiovascular collapse, or cardiac arrest even for those toxins having antidote but immediate antidote availability is an issue or patient collapsed prior to antidote administration. Digoxin toxicity may produce life-threatening arrhythmia and administration of digoxin-specific antibodies fragments (Fab) rapidly improves these arrhythmias and cardiac toxicity. But due to limited shelf-life and high costs, it this is not readily available. Moreover, poisoning with digoxin is uncommon. These patients are thus supported with ECMO till Fab is available and administered.[13]

Bridge-to-toxin Elimination with Renal Replacement Therapy

Acute salicylate intoxication can be managed successfully by removing salicylate using RRT.[14] The properties of poison such as molecular weight, protein binding, and volume of distribution should be taken in consideration while deciding about removal via dialysis. Substances with large molecular weight medications are poorly dialyzed. The removal of highly protein-bound toxins is minimal with dialysis. Toxins having a large volume of distribution will be removed only from plasma so prolonged RRT will be required for adequate elimination. In patient with hemodynamic instability, life-threatening arrhythmias VA ECMO may be initiated along with RRT to enhance the toxin elimination.[15] The various modalities which help for poison elimination include hemodialysis, hemoperfusion, hemofiltration, and plasmapheresis with plasma exchange. Dialysis basically involves diffusion through a semipermeable membrane, while convection is used during hemofiltration. The toxin is adsorbed on the surface of dialyzer during hemoperfusion. These therapies may be applied alone or in combination with other therapies. The plasmapheresis is used for highly protein bound toxins. Continuous renal replacement therapy (CRRT) and slow low-efficiency dialysis (SLED) are preferred therapies in unstable patients or during ECMO.

Bridge-to-transplant

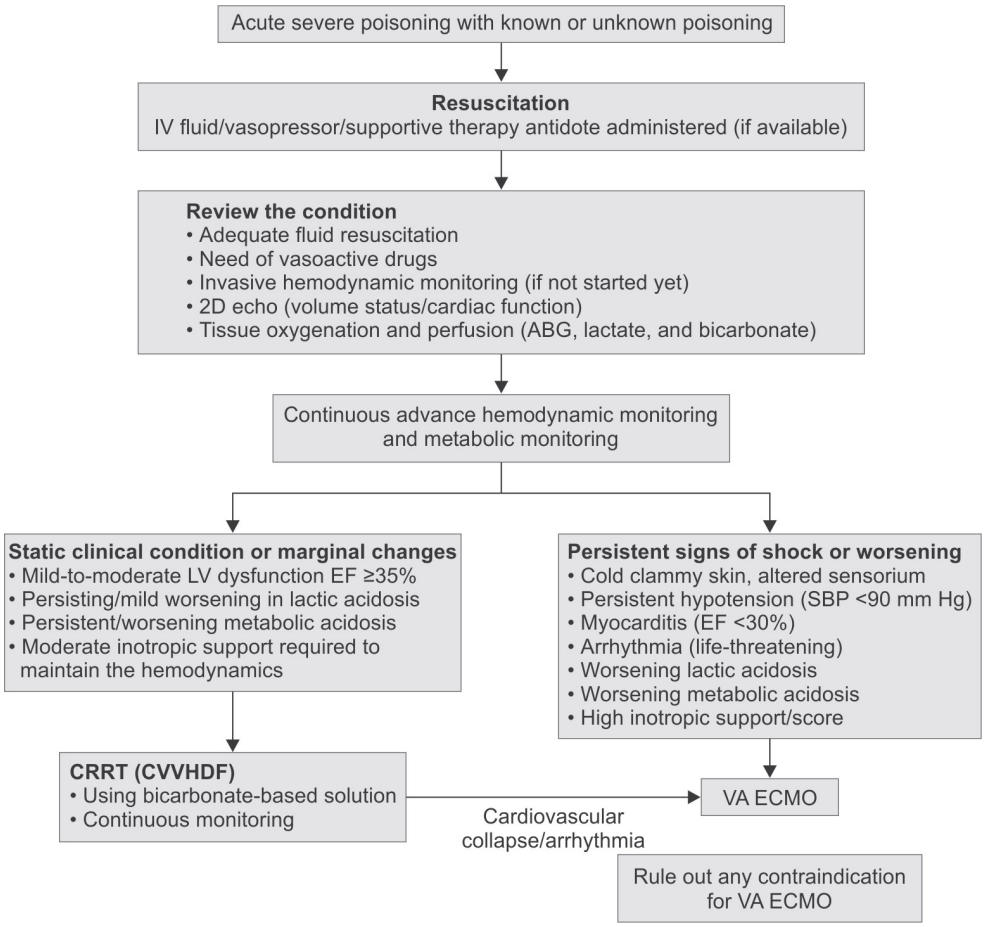
Toxins which produce irreversible damage to lungs leading to pulmonary fibrosis may be temporarily supported with VV ECMO and can be planned for lung transplant in due course.[16] Similarly support with VA ECMO can be useful temporarily as bridge to permanent assist device in patients with refractory cardiac failure.

ROLE OF OTHER EXTRACORPOREAL THERAPIES IN POISONING

Both continuous and intermittent renal replacement therapies may be useful in acute severe poisoning. Removal of dialyzable toxins will provide recovery from toxic effects, while hemodynamic optimization is achieved by correction of metabolic acidosis. The improved hemodynamics help in redistribution, metabolism, and elimination of the poison. The removal of toxin depends on surface area and pore size of the artificial kidney, type, and quantity of administered dialysate and blood flow rate. Nonprotein bound substance with <500 dalton, small volume of distribution, and substance with low lipid solubility are easily dialyzable. This include salicylates, methanol, lithium, ethylene glycol, and theophylline, etc. Convective therapies may be helpful in the removal of higher molecular weight substances depending on protein binding and sieving coefficient. These include vancomycin, methanol, procainamide, thallium, lithium methotrexate, and hirudin.

Continuous renal replacement therapy may be helpful in improving hemodynamics in an acutely intoxicated patient for even nondialyzable toxins. In intensive care unit (ICU), a pH <7.2 is usually associated with hemodynamic instability and usually responds to metabolic correction **(Flowchart 1)**. The metabolic acidosis may further worsen the myocardial dysfunction. Patients with severe metabolic acidosis are

Flowchart 1: Proposed approach for extracorporeal life support (ECLS) initiation in poisoning.



(ABG: arterial blood gas; CRRT: continuous renal replacement therapy; CVVHDF: continuous venovenous hemodiafiltration; ECMO: extracorporeal membrane oxygenation; EF: ejection fraction; IV: intravenous; LV: left ventricular; SBP: systolic blood pressure; 2D; two-dimensional)

relatively resistant to the vasopressors and require higher doses.[17] Continuous therapies are preferred for correction of pH, lactate clearance, and prevention of rebound. Though lactate clearance with CRRT may be very less as compared to normal kidney, however improvement in hemodynamics may enhance the lactate clearance.[18]

LITERATURE REVIEW

The available evidence is restricted to a few animal studies, case reports, case series, and cohort studies. The literature related with the use of ECMO in intoxication is mostly from the developed countries. The experimental evidence using different drugs such as lidocaine,[19] desipramine, and amitriptyline for intoxication and cardiovascular collapse in animal has shown better outcome with the use of ECLS. The human experiences include an observational cohort demonstrating better outcome in use of VA ECMO in intoxication as compared to the use of ECMO for other indications.[20] A retrospective cohort study in two French hospitals also concluded a favorable outcome with VA ECMO (86 vs. 48%) in severely intoxicated patients as compared to conventional supportive management.[21] However, careful interpretation is warranted due to smaller number of patients in the study.

Besides this, there are several case reports both for adult and pediatric patients of successful management of severe intoxication with drug with refractory shock using ECMO. The drugs include flecainide, antiarrhythmic agent, β-blocker, calcium channel blockers, digoxin, tricyclic antidepressant, bupropion, methamphetamine, and mepivacaine. In another case series of 17 patients with various cardiotoxic drug intoxication, nearly 90% patients were successfully weaned from ECLS and 76% were discharged without significant neurological dysfunction. Few patients required RRT during ECLS to manage acute kidney injury.[15]

There is limited literature on the use of ECMO in nonpharmacological toxic substances such as pesticides, carbon monoxide, cyanide, and plant toxins. These are commonly used for poisoning in the developing world with high mortality. However, the use of ECMO is limited. Carbon monoxide (CO) produces tissue hypoxia, multiple-organ failure, and cardiovascular collapse. The choice of modality (VV or VA ECMO) which depends on hemodynamics help in managing tissue hypoxia. The successful management of

severe aluminum phosphide intoxication with VA ECMO has been demonstrated at various centers in those patients where death was imminent due to severe myocardial dysfunction, arrhythmias, or severe metabolic derangements.[22,23] The cardiogenic shock with ventricular arrhythmia produced by *Taxus*, a plant toxin, has been successfully managed with VA ECMO. Organophosphorus poisoning leading to ARDS has also been successfully managed with VV ECMO.[12] Even patients with toxin-induced lung fibrosis may be supported with VV ECMO to maintain gas exchange while awaiting the lung transplant.[16] The use of other therapies such as CRRT and hemoperfusion has been reported but their use is limited to the case reports only.

CONCLUSION

Extracorporeal life support is useful though underutilized in the management of severely poisoned patients with refractory cardiogenic shock or refractory hypoxemia to conventional management strategy. The available evidence is limited to case reports and case series; however, there is growing evidence regarding its use. Poisoning is a challenging subject, because of a long list of toxic substances, different toxic profile, and kinetics. Our understanding regarding the use of ECLS in poisoning is still limited and several issues are unanswered. These include selection of modality, timing of initiation, and combining other therapies to facilitate metabolic optimization. Future research may address these issues.

REFERENCES

1. Report of National Crime Records Bureau. Accidental Deaths & Suicides in India – 2019. [online] Available from: http://ncrb.gov.in. [Last accessed February 2022].
2. Allen S, Holena D, McCunn M, Kohl B, Sarani B. A review of the fundamental principles and evidence base in the use of extracorporeal membrane oxygenation (ECMO) in critically ill adult patients. J Intensive Care Med. 2011 ;26(1):13-26.
3. Nadeem UK, Ricardo PN, Nudrat S, Khan U, Naseer N, Feroze A, et al. Intentional and unintentional poisoning in Pakistan: a pilot study using the emergency departments surveillance project. BMC Emerg Med. 2015;15(Suppl 2):S2.
4. Kishi M, Ladou J. International pesticide use. Int J Occup Environ Health. 2001;7(4):259-65.
5. Eddleston M. Pattern and problems of deliberate self-poisoning in the developing world. Q J Med. 2000;93(11):715-31.
6. Jones AL, Dargan PI. Churchill's Pocket Book of Toxicology. London: Churchill Livingstone; 2001.
7. Clemessy JL, Taboulet P, Hoffman JR, Hantson P, Barriot P, Bismuth C, et al. Treatment of acute chloroquine poisoning: a 5-year experience. Crit Care Med. 1996;24(7):1189-95.
8. Hörburger D, Kurkciyan I, Sterz F, Schober A, Stöckl M, Stratil P, et al. Cardiac arrest caused by acute intoxication-insight from a registry. Am J Emerg Med. 2013;31(10):1443-7.
9. ELSO Guidelines for Cardiopulmonary Extracorporeal Life Support. Extracorporeal Life Support Organization, Version 1.4 August 2017 Ann Arbor, MI, USA.
10. Mielck F, Quintel M. Extracorporeal membrane oxygenation. Curr Opin Crit Care. 2005;11:87-93.
11. Schwarz ES, Kopec KT, Wiegand TJ, Wax PM, Brent J. Should we be using the poisoning severity score? J Med Toxicol. 2017;13(2):135-45.
12. Mohamed YA, Akram AA, Mohamed MK. Venovenous extracorporeal membrane oxygenation in a case of organophosphorus poisoning. Egypt J Crit Care Med. 2016;4:43-6.
13. Idialisoa R, Jouffroy R , Lamhaut L, Baud FJ, Carli P. Extracorporeal life support in life-threatening digoxin overdose: A bridge to antidote. Austin Emerg Med. 2016;2(5):1029.
14. Mirrakhimov AE, Barbaryan A, Gray A, Ayach T. The role of renal replacement therapy in the management of pharmacologic poisonings. Int J Nephrol. 2016;2016:3047329.
15. Daubin C, Lehoux P, Ivascau C, Tasle M, Bousta M, Lepage O, et al. Extracorporeal life support in severe drug intoxication: a retrospective cohort study of seventeen cases. Crit Care. 2009;13(4):187-93.
16. Tang X, Sun B, He H, Li H, Hu B, Qiu Z, et al. Successful extracorporeal membrane oxygenation therapy as a bridge to sequential bilateral lung transplantation for a patient after severe paraquat poisoning Clin Toxicol. 2015;53(9):908-13.
17. Levy B, Collin S, Sennoun N, Ducrocq N, Kimmoun A, Asfar P, et al. Vascular hyporesponsiveness to vasopressors in septic shock: from bench to bedside. Intensive Care Med. 2010;36(12):2019-29.
18. Levraut J, Ciebiera J-P, Jambou P, Ichai C, Labib Y, Grimaud D. Effect of continuous venovenous hemofiltration with dialysis on lactate clearance in critically ill patients. Crit Care Med. 1997;25(1):58-62.
19. Freedman MD, Gal J, Freed CR. Extracorporeal pump assistance - novel treatment for acute lidocaine poisoning. Eur J Clin Pharmacol. 1982;22(2):129-35.
20. Vanzetto G, Akret C, Bach V, Barone G, Durand M, Chavanon O, et al. Percutaneous extracorporeal life support in acute severe hemodynamic collapses: single centre experience in 100 consecutive patients. Can J Cardiol. 2009;25(6):e179-86.
21. Masson R, Colas V, Parienti JJ, Lehoux P, Massetti M, Charbonneau P, et al. A comparison of survival with and without extracorporeal life support treatment for severe poisoning due to drug intoxication. Resuscitation. 2012;83(11):1413-7.
22. Mohan B, Gupta V, Ralhan S, Gupta D, Puri S, Wander GS, et al. Role of extracorporeal membrane oxygenation in aluminum phosphide poisoning–induced reversible myocardial dysfunction: A novel therapeutic modality. The J of Emerg Med. 2015;49(5):651-6.
23. Mohan B, Singh B, Gupta V, Ralhan S, Gupta D, Puri S, et al. Outcome of patients supported by extracorporeal membrane oxygenation for aluminum phosphide poisoning: An observational study. Indian Heart J. 2016;68(3):295-301.

CHAPTER 68

What's New about Antivenom and its Dosing

Dilipbhai Patel, Nagarajan Ganapathy, Sanjay Dhanuka

INTRODUCTION

There are so many breeds of snakes, each one will shoot up with a different quantity of venom during the bite. Toxicity produced by the venom of each breed is a great challenge while treating the cases. Most venomous snakes routinely dangerous for humans belong to one of two families, *Elapidae* and *Viperidae*. However, the "classic" literature suggesting that elapids cause neurotoxic effects and vipers cause local and hemorrhagic effects is misleading and inaccurate.[1] Many elapid snakes cause predominantly local effects, rather than systemic effects (typically the "spitting" cobras), while others cause predominantly coagulopathic rather than neurotoxic systemic effects (e.g., Australian brown snakes). Similarly, some *Viperidae* snakes cause minimal local effects and predominantly systemic effects, including paralysis, coagulopathy, and/or rhabdomyolysis (e.g., South American rattlesnakes). Early care of snakebite victims should focus on supporting patients with life-threatening respiratory depression, cardiac failure, or shock. This may include cardiopulmonary resuscitation (CPR) if there is cardiac arrest, followed by the administration of antisnake venom **(Table 1)**.

Regions with the highest incidence of venomous snakebites and snakebite deaths include Southeast and South Asia (e.g., India, Pakistan, Sri Lanka, and Bangladesh), sub-Saharan Africa, and Latin America.[3]

Commercially available antisnake venoms neutralize specific venom in milligrams.

The whole blood clotting time (WBCT) has also been considered a useful bedside screening test when more formal coagulation testing is not available; failure of the blood to clot in a clean glass tube after 20 minutes has been considered evidence of severe hypofibrinogenemia. The WBCT has low sensitivity but high specificity. Thus, a positive test is a reasonable indication for antivenom administration.[4] However, a negative test does not mean that antivenom should be withheld, especially if there are clinical features of coagulopathy (e.g., blood oozing at puncture sites, bleeding gums, or epistaxis).

Antivenom may attenuate rhabdomyolysis but will not reverse it for selected snakes.

COMPONENTS OF ANTISNAKE VENOM

Antivenoms consist of animal immunoglobulins developed against the whole venom.[5] The process involves immunizing animals (commonly horses, sheep, goats, or rabbits) with the venom and extracting the antivenom from the animal serum.[6]

AVAILABLE FORMS OF ANTISNAKE VENOM

Antivenoms are classified with respect to the number of venoms against which they are raised as mentioned below.[5]

Monovalent

Most monovalent antivenoms are raised against a single genus or species of snake and are only effective for bites by that snake or group of snakes.[5] A few "monovalent" antivenoms (e.g., all the Australian "monovalent" snake antivenoms) are actually made from polyvalently immunized animals and may contain activity against nonlisted species of snakes.[7] Monovalent antisnake venom is not available in India.

Polyvalent

Polyvalent antivenoms are developed against venoms from multiple different snakes that typically share a geographical region and can be used to treat envenomations by any of the included species.[5] Substance in the polyvalent venom is effective against four habitual breeds, Russell's viper (*Daboia russelii*), common cobra (*Naja naja*), common krait (*Bungarus caeruleus*), and saw scaled viper (*Echis carinatus*).

There is no clear "rule" that monovalent is better than polyvalent, but when the snake identity is established and because of lower risks and cost, monovalent antivenom is preferable to polyvalent antivenom.[8]

TABLE 1: Site of action of venom, clinical features, tests, and management.[2]

Site of action	*Clinical features*	*Ancillary testing*	*Management*
Local tissue	• Pain • Fang marks • Swelling • Blistering • Ecchymoses • Tissue Necrosis • Lymph node swelling and tenderness		• Antivenom • Manage signs of compartment syndrome (Rare)
Neuromuscular junction	• Ptosis • Diplopia • Dysphagia • Bulbar palsy: "Drooling" pooling of secretions in pharynx • Dyspnea • Limb weakness	• Positive neostigmine trial indicates postsynaptic paralysis responsive to antivenom and anticholinesterase • Low maximal inspiratory and expiratory forces	• Antivenom • Anticholinesterase (e.g., neostigmine) • Maintain and support airway and breathing, as needed
Coagulopathy	• Epistaxis • Gingival oozing • Bleeding from venipuncture site • Ecchymoses and bruising • Clinically evident bleeding (hemoptysis, hematemesis, hematuria, and intracranial hemorrhage)	• Thrombocytopenia (complete blood count) • Anemia • Prolonged INR or aPPT • Decreased fibrinogen level • Increased fibrin degradation products or D-Dimer • 20-minute whole blood clotting test (resource-limited settings)	• Antivenom primary treatment • Blood products (e.g., whole blood, fresh frozen plasma, or platelets) only if life-threatening bleeding and, when available, after antivenom administration • Heparin, aminocaproic acid not helpful
Shock	• Hypotension • Tachycardia • Signs of poor perfusion (prolonged capillary refill, decreased urine output, and altered mental status)	Central pressure monitoring	• Antivenom • Intravenous isotonic fluids (e.g., normal saline) and vasoactive infusions to maintain perfusion pressure depending upon whether shock is hypovolemic, cardiogenic, or both
Rhabdomyolysis	Red or brown urine oliguria	• Rapid urine dipstick positive for blood with microscopic urinalysis showing no red blood cells • Positive urine for myoglobin • Increased serum creatinine, kinase, potassium, creatinine, and/or blood urea nitrogen • EKG changes indicating hyperkalemia	• Intravenous normal saline in volumes sufficient to re-establish urinary output • Hemodialysis, as needed, for acute kidney injury

(aPPT: activated partial thromboplastin time; EKG: electrocardiogram; INR: international normalized ratio)

In India, it is available in two forms that is, lyophilized and liquid form.

Lyophilized antisnake venom is in the powdered form. It does not require refrigeration to preserve its efficacy. Hence, this form of antisnake venom can be used in remote areas. It has a long shelf-life of 3–5 years. But it should be administered within 30–60 minutes of reconstitution. Liquid antisnake venom is ready to use but requires refrigeration to preserve its efficacy. It has a shorter shelf-life of 2 years.[9]

Composition of Polyvalent Antisnake Venom

Efficacy of Indian polyvalent antivenom is such that each milliliter of its substance will neutralize 0.6 mg of venom of Indian common cobra and Russell's viper, 0.45 mg of Common Krait and Saw Scaled Viper venom. The quantity of venom that is lethal to humans can vary from species to species. The fatal doses of each species are: 120 mg for Indian cobra (*Naja naja*), 150 mg for Russell's viper (*Daboia russelli*),

60 mg of common krait (*Bungarus caeruleus*) venom, and 80 mg of saw scaled viper (*Echis carinatus*) venom.[2]

Reviews report that lethal dose in case of Indian common cobra is 120 mg, 150 mg for Russell's viper, 60 mg for common krait, and 80 mg for saw scaled viper.

Route for Administration

It should be administered only intravenously as a slow infusion. The intramuscular (IM) route of administration has poor bioavailability and should never be given. Local administration at the bite site does not have any therapeutic benefit. It causes extreme pain and increases the chances of intracompartmental pressure.

DOSAGE OF ANTISNAKE VENOM

Dosage varies according to the type of envenomation.

Dosing is determined by the snake species and individual patient characteristics. It does not differ between adults and children; there is no "pediatric dose" for antivenom.

Antisnake venom can be given as infusion at low doses or intermittent bolus at high doses. The intravenous (IV) route of administration is preferred to IM injection whenever possible to ensure the most effective and rapid neutralization of snake venom. In small children, if IV access is not possible, the intraosseous infusion is appropriate if life-threatening envenomation is likely.[10] The clinician may administer IV antivenom in one of two ways:

1. Antivenom diluted in a compatible solution and infused over 30–60 minutes.
2. Reconstituted (if required; e.g., lyophilized antivenoms; not required for liquid antivenoms) and given by slow IV injection over 10–20 minutes.

Preliminary evidence suggests that the IV injection does not increase the risk of allergic reaction over IV infusion. In general, IV infusion of diluted antivenom is still preferred because it permits slower administration with the ability to hold the infusion if an adverse reaction occurs and to restart the infusion at a slower rate after the reaction is treated.

Resuscitation equipment and medications to treat anaphylaxis, most importantly, epinephrine (drawn up in a syringe or prepared for continuous IV infusion), should be immediately available.[11]

Dosage for Neuroparalytic Snakebites

10 vials of antisnake venom should be administered over 30 minutes and signs of improvement are noted. The second dose of 10 vials should be administered if no improvement occurs after an hour. If relapse of signs of neurotoxicity is noted after 2–3 hours (which may be due to delayed absorption), a second dose may be repeated. For neurotoxic snakebites, a maximum dose of 20 vials is recommended.[2]

Dosage for Hematotoxic Snakebites

For low dose infusions, 10 vials for Russell's viper six vials, for saw scaled viper is taken. Administer for 30 minutes followed by two vials after 6 hours in 100 mL normal saline (NS), until clotting time is normalized. It is administered until the clotting time is normalized.

For administering intermittent boluses at high doses, infuse 10 vials of antisnake venom for 30 minutes and then 6 vials for 6 hours until clotting time is normalized or the inflammation is reduced. Low-dose infusion therapy is highly responding one than high-dose intermittent bolus therapy. For hematotoxic snakebites, a maximum dose of 30 vials is recommended. If the abnormality in coagulation continues after administration of more doses, fresh frozen plasma or cryoprecipitate should be administered. Fresh whole blood transfusion is transfused if fresh frozen plasma or cryoprecipitate is not available. Antisnake venoms do not contain antibodies against sea snake, hump-nosed pit snake viper, green pit snake, and king cobra (Naja Hannah) envenomation.[12]

Dose of Antisnake Venom in Pregnancy

Pregnant women should be given the same dose of antisnake venom and under the same criteria as standard victims. To assess any abnormalities in the fetus, a gynecologist's consultation is required.

Dose of Antisnake Venom in Pediatric Victims

The quantity of venom injected by snakes does not differentiate in children and adults. So the dosage of antisnake venom does not vary for children as well as adults.[13]

RESPONSE TO TREATMENT

The effect of the antivenom should be monitored carefully. Lack of response is usually caused by the administration of inadequate amounts of antivenom or the use of the wrong antivenom.[14] Lack of response may also occur because it is too late for the antivenom to be effective, such as a patient with advanced paralysis due to presynaptic neurotoxins in the venom.

The typical timing to reversal of toxic effects after adequate amounts of antivenom has been given, varies by the type of envenomation.[15]

Coagulopathy

Spontaneous bleeding ceases by about 20 minutes. Coagulation tests often normalize or whole blood clotting is restored by about 6–8 hours. However, for some snakes (e.g., Australian snakes), the coagulopathy may take longer than 6 hours. If formal coagulation tests are used to assess antivenom response to toxicity from these species, then a response is generally defined as an improvement in

coagulation parameters, and not a return to normal values; it may take >24 hours to return to normal values in some cases. Inadequate antivenom dosing is the first consideration in patients with persistent bleeding.[16]

Hypotension and Cardiotoxicity

Marked improvement should occur within 20–30 minutes.

Neurotoxicity

Detectable improvement within 30 minutes with a complete reversal in several hours is seen in responsive patients (where the snake has injected only postsynaptic neurotoxins).[15]

Failure to Respond

Failure of response to antivenom may be due to the following reasons:

- Insufficient antivenom
- Wrong antivenom
- Inactive or poor quality antivenom
- Excessive delay in administration after envenomation
- A venom effect not reversible by antivenom (e.g., presynaptic neurotoxic paralysis).

Premedication

We suggest that patients treated in the following settings receive premedication with subcutaneous epinephrine:[17]

- Use of antivenom is associated with high rates of allergic reactions.
- There is a significant risk of allergic reaction associated with antivenom use and the management of acute allergic reactions is problematic because of limited staffing or facilities.[18]
- By contrast, the evidence does not support routine pretreatment with either antihistamines or corticosteroids.

Contraindications

There are no absolute contraindications to antivenom administration. However, antivenom should be used with greater restraint and special caution in the following situations:[5,15]

- *Prior allergic reaction to antivenom or one of its components*: Prior reaction to antivenom with the same animal component (e.g., equine, ovine, or rabbit serum). However, if the likely effect of envenomation is life-threatening, then withholding antivenom because of a past adverse reaction to antivenom is rarely appropriate. Particular care should be taken while administering antivenom to ensure any adverse reaction can be promptly managed. This may involve, in selected cases, having an IV epinephrine infusion prepared and available before giving the antivenom.
- *Patients with asthma*: These patients may be at higher risk for immediate allergic reactions with severe respiratory distress. However, such patients with major envenomation (e.g., serious systemic signs) should still receive antivenom with precautions in place to immediately treat an allergic reaction.
- *Patients receiving beta-adrenergic blockers or angiotensin-converting enzyme inhibitors*: The effectiveness of antivenom depends upon the site of action of the snake venom as follows:
  - *Presynaptic toxicity*: In patients with paralysis caused by presynaptic neuromuscular junction (NMJ) toxicity (e.g., kraits, most Australian elapid snakes, mambas, South American rattlesnakes, some Russell's vipers, and some European adders), the response depends upon timely administration of antivenom. Antivenom cannot reverse established presynaptic neurotoxic paralysis.[19,20]
  - *Postsynaptic toxicity*: In patients with paralysis caused by postsynaptic NMJ toxicity, Philippine cobra (*Naja philippinensis)*, and some other Asian and African cobras (*Naja* species), anticholinesterase, such as edrophonium, if available, or neostigmine may be of benefit, especially if antivenom is not available or is associated with high rates of adverse reactions.[21]

When antivenom is not available or not effective for weakness or paralysis secondary to envenomation by a snake capable of causing postsynaptic neurotoxicity, patients should undergo a neostigmine trial to determine if anticholinesterase therapy may be beneficial. In patients with neurotoxic snakebite for whom antivenom is not available or is ineffective and who have a positive neostigmine trial, we recommend treatment with an anticholinesterase. Neostigmine is the anticholinesterase that has primarily been used in snakebite victims.[22]

PROPERTIES OF ANTISNAKE VENOM

Antisnake venom binds with the unbound venom molecule circulating in the lymph or blood and neutralizes it. Hence, it inhibits the binding of the venom molecule to the target cells so that it prevents the patient's condition from being worsened. It will not prevent local necrosis and inflammation because the venom fastly destroys the tissues and is not freely available for antivenom to bind. Krait snake venom affects the presynaptic junction. Administration of large amounts of antisnake venom is not effective since the damage of nerve tissues is structural and synaptic vesicles should be regenerated by the body. Antisnake venom will not revert respiratory failure or coagulopathy.[9]

CONCLUSION

Antisnake venom is administered only if it is indicated. There is no absolute contraindication to antisnake venom.

We should be always ready with adequate medications to treat anaphylaxis. Test dose does not prevent or determine anaphylaxis or late serum sickness. Hence, test dose is not necessary. Its administration should not be delayed or postponed due to fear of anaphylactic reactions for a deserving case. Adrenaline IM/SC is the drug of choice for an anaphylactic reaction.[23]

REFERENCES

1. Tshewang S, Letro L. The herpetofauna of Jigme Singye Wangchuck National Park in central Bhutan: status, distribution and new records. J Threat Taxa. 2018;10:12489-98.
2. A Module on the "Management of Snakebite Cases" For Medical Officers. Developed By PUBLIC Health Branch Of The Directorate of Health Services & Institute Of Health & Family Welfare Kolkata. Department of Health & Family Welfare. Government of West Bengal.
3. Chippaux J-P. WHO Guidelines for the production, control and regulation of snake antivenom immunoglobulins. Biologie aujourdhui. 2016; 204(1):87-91.
4. Srimannanarayana J, Dutta TK, Sahai A, Badrinath S. Rational use of antisnake venom (ASV): Trial of various regimens in hemotoxic snake envenomation. J Assoc Phys India 2004;52:788-93.
5. White J. Overview of venomous snakes of the world. In: Dart RC (Ed.). Medical Toxicology, 3rd edition. Philadelphia: Lippincott, Williams & Wilkins; 2004. p.1543.
6. Sapkota S. Knowledge of health workers, health seeking behaviour of snakebite victims and retrospective study of snakebites in Bhutan. Royal University of Bhutan. PLoS Negl Trop Dis. 2020;14(11):e0008793.
7. O'Leary MA, Isbister GK. Commercial monovalent antivenoms in Australia are polyvalent. Toxicon. 2009;54(2):192-5.
8. Koirala BK, Koirala J, Sapkota S. Retrospective study on epidemiology of snakebite in Sarpang District, Southern Bhutan. J Threat Taxa. 2018;10:12749-54.
9. Department of Forest and Park Services. Bhutan National Forest Inventory Report. Stocktaking Nation's Forest Resource. 2016. [online] Available from: http://www.dofps.gov.bt/wp-content/uploads/2017/07/National-Forest-Inventory-Report-Vol1.pdf. [Last accessed February 2022].
10. Deshmukh VS, Motghare VM, Gajbhiye D, Birajdar SV, Deshpande R, Pise H, et al. Study on acute adverse drug reactions of Anti Snake venom in a rural tertiary care hospital. Asian J Pharm Clin Res. 2014;7(5).
11. Deshpande PR, Motghare VM, Padwal SL, Pore RR, Bhamare CG, Deshmukh VS, et al. Adverse drug reaction profile of anti-snake venom in a rural tertiary care teaching hospital. J Young Pharma. 2013;5(2):41-5.
12. Varadarajan P, Shankaerlingam T, Sangareddy S, Jeyachandran P. Peripheral Locked in syndrome following snake envenomation. Paediatric. 2013;10(3):89-90.
13. Mohapatra B, Warrell DA, Suraweera W, Bhatia P, Dhingra N, Jotkar RM et al. Snakebite Mortality in India: A Nationally Representative Mortality Survey. PLOS Tropical Neglected Diseases. 2011; 5(4):e1018.
14. Pawade BS, Salvi NC, Shaikh IK, Waghmare AB, Jadhav ND, Wagh VB, et al. Rapid and selective detection of experimental snake envenomation - Use of gold nanoparticle based lateral flow assay. Toxicon. 2016;119:299-306.
15. Warrell DA. Envenoming and injuries by venomous and nonvenomous reptiles worldwide. In: Auerbach PS (Ed). Wilderness Medicine, 6th edition. Philadelphia: Elsevier Mosby; 2012. p. 1040.
16. Rahmani AH, Jalali A, Alemzadeh-Ansari MH, Tafazoli M, Rahim F. Dosage comparison of snake anti-venomon coagulopathy. Iran J Pharm Res. 2014;13(1):283-9.
17. Cheng AC, Winkel KD. Antivenom efficacy, safety and availability: measuring smoke. Med J Aust. 2004;180(1):5-6.
18. Menon JC, Joseph JK. Complications of hematotoxic snake bite in India. Indian J Public Health. 2014;58:17-21.
19. Johnston CI, O'Leary MA, Brown SG, Currie BJ, Halkidis L, Whitaker R, et al. Death adder envenoming causes neurotoxicity not reversed by antivenom—Australian Snakebite Project (ASP-16). PLoS Negl Trop Dis. 2012;6(9):e1841.
20. Anil A, Singh S, Bhalla A, Sharma N, Agarwal R, Simpson ID. Role of neostigmine and polyvalent antivenom in Indian common krait (Bungarus caeruleus) bite. J Infect Public Health. 2010;3(2):83-7.
21. Hudson BJ. Positive response to edrophonium in death adder (Acanthophis antarcticus) envenomation. Aust N Z J Med. 1988;18(6):792-4.
22. Watt G, Theakston RD, Hayes CG, Yambao ML, Sangalang R, Ranoa CP, et al. Positive response to edrophonium in patients with neurotoxic envenoming by cobras (Naja philippinensis). A placebo-controlled study. N Engl J Med. 1986;315(23):1444-8.
23. de Silva HA, Pathmeswaran A, Ranasinha CD, Jayamanne S, Samarakoon SB, Hittharage A, et al. Low-dose adrenaline, promethazine, and hydrocortisone in the prevention of acute adverse reactions to antivenom following snakebite: A randomised, double-blind, placebo-controlled trial. PLoS Med. 2011;8(5):e1000435.

SECTION

13

Hematology Oncology

CHAPTER 69

Managing Acute Hemolysis in Intensive Care Unit

Subhal Dixit, Khalid Khatib

INTRODUCTION

Hemolysis as a cause of anemia is seen in a fraction of critically ill patients. Studies in critically ill patients have found anemia (hemoglobin <13 mg/dL in men and <12 mg/dL in women) to be very common in intensive care units (ICUs). Approximately 66% of patients had anemia on the day of admission to ICU and at the end of the first week, almost all patients developed anemia.[1,2] The cause of hemolysis in patients may be intravascular or extravascular and may be congenital or acquired. Management of hemolysis includes correction of the cause and correction of anemia. There is still some controversy regarding hemoglobin targets for blood transfusion in critically ill patients, with restrictive transfusion strategies being favored currently.[3-5]

CAUSES OF ACUTE HEMOLYSIS IN ICU

The various causes of acute hemolysis in critically care set up may be broadly categorized as:

- *Extravascular*: Spleen and reticuloendothelial system-mediated hemolysis
  - *Immune-mediated*:
    - Warm autoimmune hemolytic anemia (AIHA)
    - Cold AIHA
    - Alloimmune delayed hemolytic transfusion reaction (HTR)
    - Drug-induced AIHA
  - *Abnormal hemoglobin and hemoglobin defects*:
    - Thalassemia
    - Sickle cell anemia
    - Unstable hemoglobin
  - *Membrane defects*:
    - Hereditary spherocytosis
    - Hereditary elliptocytosis
  - *RBC enzyme defects*:
    - Glucose-6-phosphate dehydrogenase (G6PD) deficiency
    - Phosphatase kinase deficiency
- *Intravascular*: Hemolysis within the circulation
  - *Infections*:
    - Malaria
    - Babesiosis
    - *Clostridium perfringens*
  - *Complement-mediated*:
    - Cold AIHA
    - Paroxysmal cold hemoglobinuria (PCH)
    - Paroxysmal nocturnal hemoglobinuria (PNH)
    - Drug-induced immune-complex hemolytic anemia
    - Acute HTR
  - *Mechanical shearing*:
    - Microangiopathic hemolytic anemia (MAHA) (thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, hemolytic uremic syndrome)
    - Prosthetic heart valves
    - Arteriovenous malformations

CLINICAL PRESENTATION

Acute hemolysis may be asymptomatic (found during testing) or may present clinically as anemia accompanied with icterus. Patients may develop weakness, dyspnea, angina, tachypnea, tachycardia, pallor, icterus, and dark urine (due to hemoglobinuria). Splenomegaly may be present in some patients. Some patients with long-term hemolysis may develop cholelithiasis as well.

WORKUP OF THE PATIENT WITH HEMOLYSIS

Hemoglobin

The presence of anemia may be mild (Hb > 10 g/dL) or moderate (Hb 8–10 g/dL) in patients with features of hemolysis. Rarely, anemia due to hemolysis may be moderately severe (Hb 6–8 g/dL) or very severe (Hb 6 g/dL).

Reticulocyte Count

The reticulocye count is normally 1%, but it is increased in hemolytic anemia. The absence of elevated reticulocyte count in patients with hemolysis may be seen in concomitant bone marrow involvement (hematologic malignancy, dyserythropoiesis), associated iron, and vitamin B_{12} deficiency, infections, or autoimmune reaction against bone marrow-precursor cells.

Schistocytes

These are fragmented red blood cells and are seen in MAHA.

Unconjugated Bilirubin

It is elevated due to the metabolism of hemoglobin and usually does not increase to >3 mg/dL in hemolysis. An increase of bilirubin more than this level is suggestive of associated liver cell destruction or obstruction to bile outflow.

Serum Lactate Dehydrogenase

It is increased in hemolysis. It is also increased in other conditions such as malignancies and liver diseases. The serum lactate dehydrogenase (LDH) isoenzyme 1 and 2 is more specific for RBC lysis but may also be increased in myocardial infarction.

Serum Haptoglobin

It is reduced in hemolysis, but may be normal or increased in infections. The haptoglobin is reduced as it binds to free hemoglobin.

Direct Antiglobulin Test or Direct Coombs Test

It is positive in AIHA.

Others: Other tests which may be required includes plasma and urine free hemoglobin, urine hemosiderin test, red blood cell survival test, cold agglutinin titer, G6PD screen, sickle cell screen, and flow cytometry for PNH.

TREATMENT

General Considerations

Folic acid supplementation should be given as there is increased consumption which may lead to megaloblastosis.

Transfusion Therapy

Packed RBC transfusion may be necessary for cardiac unstable patients. Problems during transfusion may pertain to grouping and cross-matching, volume overload, and destruction of transfused RBCs (prevented by transfusing slowly).

Treatment of the Cause of Hemolysis

Warm autoimmune hemolytic anemia: Corticosteroids are given in AIHA. Intravenous methylprednisolone 500 mg/day for 3 days may be given in some cases. Rituximab may be given in steroid nonresponsive AIHA and may even be tried as a first-line agent in AIHA.[6]

Drugs: Offending drugs (penicillin, cephalothin, ampicillin, methicillin, quinine, quinidine in immune hemolysis and furazolidone, isobutyl nitrite, nalidixic acid, and sulfa drugs in G6PD deficiency) should be stopped.

Malaria: Treat it with artemisinin-based combination therapy in areas with high chloroquine resistance.

Hemolytic uremic syndrome (HUS): It is thrombotic microangiopathy characterized by thrombocytopenia, hemolysis, and acute kidney injury. It is classified as typical [following infection with enterohemorrhagic *Escherichia coli* (shiga toxin-producing *E. coli* or STEC), or shigella infection] and atypical or noninfection related (inherited disorders, malignancy, autoimmune disease, pregnancy, severe hypertension, and in response to some drugs). Initial clinical features include abdominal pain, dysentery (in 60% of patients), and vomiting. Renal involvement occurs in most cases and renal replacement therapy (RRT) is required in 1 out of 2 patients. Renal function usually recovers within 15–20 days but some patients may develop hypertension and chronic renal affection.[7] Extrarenal manifestations may be seen in a few patients and include neurological involvement (seizures and altered consciousness level) intestinal tract and pancreas, eyes, and heart.[8,9] HUS is associated with a mortality rate of approximately 2–5% in the acute phase.[7] The management of patients with typical HUS is supportive. Renal replacement therapy and mechanical ventilation (if required for acute respiratory failure) should be provided as for other patients. Patients may require blood transfusions. Some patients may respond to therapeutic plasma exchange. Eculizumab, a monoclonal antibody that is a complement inhibitor has been used in patients with atypical HUS and found to be beneficial.

Thrombotic thrombocytopenic purpura (TTP):[10,11] It is thrombotic microangiopathy characterized by thrombocytopenia, hemolysis, and neurological symptoms. It is caused by deficiency (congenital or acquired) of ADAMTS13 which is responsible for the degradation of polymers of the von Willebrand factor. These polymers accumulate on the surface of vascular endothelial cells causing platelet-rich thrombi to form. In patients who are suspected to have thrombotic microangiopathy, an ADAMTS13 activity of <10% is considered to be suggestive of TTP. If the level is normal or >10%, a diagnosis of HUS is suggested. Clinically, TTP presents with any of the features of the "classic pentad"

of fever, thrombocytopenia, MAHA, renal dysfunction, and neurological symptoms.[12] Treatment of TTP involves the following steps:

- Resuscitation
- Stabilization of any critical organ dysfunction
- Plasma exchange, started as early as possible. Some patients may need to be stabilized with plasma infusion if plasma exchange is going to be delayed for any reason.
- Steroids (intravenous methylprednisolone 1 g OD for 3 days)
- Rituximab

CONCLUSION

Hemolysis seen in ICU patients may turn fatal if not picked up and treated in time. Diagnosis is quite easy if all the investigations are ordered quickly, but suspecting the diagnosis is tricky. Management of hemolysis is the treatment of the cause. TTP and HUS are serious causes of hemolysis and may turn deadly. Judicious use of available modalities of treatment is important to save lives.

REFERENCES

1. Thomas J, Jensen L, Nahirniak S, Gibney RT. Anemia and blood transfusion practices in the critically ill: a prospective cohort review. Heart Lung. 2010;39:217-25.
2. Hajjar LA, Auler Junior JO, Santos L, Galas F. Blood transfusion in critically ill patients: state of the art. Clinics (Sao Paulo). 2007;62:507-24.
3. Walsh TS, Boyd JA, Watson D, Hope D, Lewis S, Krishan A, et al. Restrictive versus liberal transfusion strategies for older mechanically ventilated critically ill patients: a randomized pilot trial. Crit Care Med. 2013;41(10):2354-63.
4. Hirano Y, Miyoshi Y, Kondo Y, Okamoto K, Tanaka H. Liberal versus restrictive red blood cell transfusion strategy in sepsis or septic shock: a systematic review and meta-analysis of randomized trials. Crit Care. 2019;23(1):262.
5. World Health Organization. (1989). Preventing and Controlling Anaemia through Primary Health Care: A Guide for Health Administrators and Programme Managers. [online]. Available from: http://www.who.int/nutrition/publications/micronutrients/anaemia/iron deficiency/9241542497.pdf [Last accessed December, 2021].
6. Barcellini W, Fattizzo B. How I treat warm autoimmune hemolytic anemia. Blood. 2021;137(10):1283-94.
7. Garg AX, Suri RS, Barrowman N, Rehman F, Matsell D, Rosas-Arellano MP, et al. Long-term renal prognosis of diarrhea-associated hemolytic uremic syndrome: a systematic review, meta-analysis, and meta-regression. JAMA. 2003;290(10):1360-70.
8. Hahn JS, Havens PL, Higgins JJ, O'Rourke PP, Estroff JA, Strand R. Neurological complications of hemolytic-uremic syndrome. J Child Neurol. 1989;4(2):108-13.
9. Sheth KJ, Swick HM, Haworth N. Neurological involvement in hemolytic-uremic syndrome. Ann Neurol. 1986;19(1):90-3.
10. Sarode R, Bandarenko N, Brecher ME, Kiss JE, Marques MB, Szczepiorkowski ZM, et al. Thrombotic thrombocytopenic purpura: 2012 American Society for Apheresis (ASFA) consensus conference on classification, diagnosis, management, and future research. J Clin Apher. 2014;29:148-67.
11. Tsai HM. Thrombotic thrombocytopenic purpura and the atypical hemolytic uremic syndrome: an update. Hematol Oncol Clin North Am. 2013;27:565-84.
12. Moschcowitz E. An Acute Febrile Pleiochromic Anemia with Hyaline Thrombosis of the Terminal Arterioles and Capillaries—an undescribed disease. Arch Int Med. 1925;36:89-93.

CHAPTER 70

Airway Management Issues in Oncology

Rekha Das, Amol Kulkarni, Syed Moied Ahmed

INTRODUCTION

Airway management issues in oncology are faced by anesthesiologists and intensivists as unique, diverse, and unrelated. The access to the airway required during anesthesia for elective surgeries or managing cardiorespiratory co-morbidities in emergency department (ED) or intensive care unit (ICU) can present as anatomical abnormalities, physiological variations, or both.

National Audit Project 4 (NAP4) in 2011 revealed that the incidence of airway-related events was 50–60 times more in ICU and EDs and the mortality was 61% as compared to 14% in anesthesia. Further, out of 38 deaths, 18 deaths were in ICU and all were preventable.[1] This was attributed to poor airway assessment, planning, and outcome; approach to airway management should include physiological assessment, optimization, plan of airway management, backup plan, and a safe extubation.

HOW TO ASSESS THE AIRWAY OF THESE PATIENTS?

In elective surgery, preoperative assessment helps us to prepare ourselves for a difficult airway. Patients in ICU are likely to need ventilation or patients on NIV should be evaluated or documented for difficult airway when they are conscious and cooperative so as to prepare themselves and their subsequent team.[2,3] The various types of difficult airway encountered in oncology are distorted interface, compromised airway, securing an emergency airway access due to obstruction to airflow within the upper aerodigestive tract, trachea, or bronchus, and external compression of neck.[4]

Clinical History

Previous difficult airway management is considered to be one of the most important predictors of subsequent airway management difficulties.[5]

Common presenting symptoms of airway obstruction include dyspnea at rest or on exertion, dysphagia, cough, voice changes—muffled voice in supraglottic lesion, coarse scratchy/hoarseness in glottic lesions. Other physical findings are agitation, intercostal, suprasternal, and supraclavicular retraction. Stridor and acute respiratory distress indicate severe narrowing of airway needing immediate management. Stridor character suggests the location of airway narrowing.[6,7] History of previous irradiation, surgery of oral cavity and neck, and any obvious neck masses may result in loss of contour or reduced neck mobility, causing difficult mask ventilation and difficult intubation.[8]

Anatomical Difficult Airway

The anatomical factors could be primary anatomical abnormalities or pathological due to cancer in the head, neck, and upper airway.

There are four steps/approach of airway assessment:

1. Assessment for difficult bag-mask ventilation.[9]
2. Assessment of difficult laryngoscopy and intubation.[9,10]
3. Assessment of difficult supraglottic airway device (SAD) insertion.
4. Assessment of difficult surgical airway.
5. A fifth dimension is *psychological assessment/preparation*, where the patient is informed and counselled and consent is taken **(Fig. 1)**.

Critically Ill Patients

Assessment of difficult airway in ICU involves patients critically ill for whom the MACOCHA scoring system has been developed. Assessment parameters are based on patient-related, pathology-related, and operator-related factors.[11] Score of >3 is taken as a predictor of difficult intubation **(Table 1)**.

Evaluation of potentially difficult airway should be undertaken under awake condition or with use of judicious intravenous sedation and topical anesthetic.[12] This preserves spontaneous respiration and oxygenation. Infiltration or instillation of lignocaine may result in airway collapse making partial obstruction complete and intubation more difficult under fiberoptic or awake conditions. A similar picture is observed in an awake patients after use of sedation and relaxant.

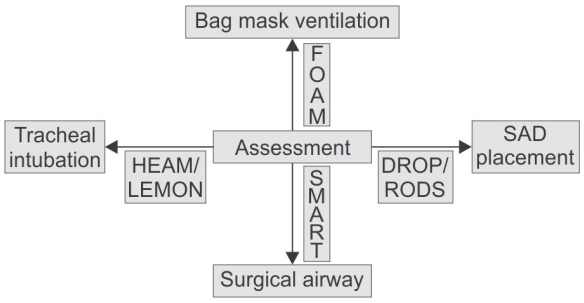


Fig. 1: Methods of airway assessment.
(MOANS: M–Mask seal, Beards, O–Obstruction, Obesity, A–Age, Elderly, N–No teeth, S–Snoring/Stiffness of chest; LEMON: L–Look externally, E–Evaluation –3– 3–2, M–Mallampati grade 3 and 4, O–Obstruction, Obesity, N–Neck mobility; RODS/DROP: R–Restricted mouth opening, O–Obstruction, obesity, D–Distorted anatomy, S–Stiffness of chest; SMART/BANG: S–Surgery undergone/ undergo, M–Mass, A–Access anatomy, R–Radiation therapy undergone previously, T–Tumor, FOAM: F-Facial abnormality, O-Obesity/Obstructed breathing, A-Age >60, Absence of teeth, M-Movement restriction of head and neck. HAEM: H-History of difficult laryngoscopy and intubation, snoring, diabetes mellitus, A-Appearance of short neck, poor dental status, obesity, small /large chin, facial trauma, swelling, E-3-6-12-24 3-, <3 cm inter-incisor space <6 cm mentothyroid distance, <12 cm sternomental distance with neck fully extended, >24 cm ratio of patients height to thyromental distance. M-Mobility of head restricted, Mallampati - 2 or more)

TABLE 1: MACOCHA Score for airway assessment.

	Factors	***Points***
Patient-related		
	*M*allampati score III or IV	5
	*A*pnea syndrome (obstructive)	2
	*C*ervical spine limitation	1
	*O*pening mouth <3 cm	1
Pathology related		
	*C*oma	1
	*H*ypoxemia	1
Operator-related		
	Non-*A*nesthesiologist	1

Physiological Difficult Airway

Patients with decreased cardiorespiratory reserve are vulnerable to life-threatening situation during intubation and mechanical ventilation[13] and may succumb during intubation if prior optimization has not been done. Awake intubation in these physiologically deranged patients can cause precipitous rise in intracranial pressure or cardiac ischemia. Hypoxemia and hypotension are sensitive predictor and along with shock index of ≥0.9 increase the risk of cardiac arrest by fourfold **(Table 2)**.

Special Investigation for Airway Assessment

In stable patients, flexible laryngoscopy or indirect laryngoscopy performed in ICU may help with anticipation and planning for a difficult airway.

Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI): CT and MRI may help in determining the size, location, and nature of the obstruction; especially with multiplanar CT scans and spiral CT virtual bronchoscopy, exact status of airway anatomy can be identified with subsequent planning.[14]

Ultrasonography (USG): USG may be used to identify compromised airway like subglottic narrowing, postextubation stridor which can be undertaken bedside with a good device and experience.[15]

X-ray: Lateral view of neck can tell us the degree of airway compression but as a necessary tool to evaluate difficult airway has limited sensitivity and specificity.[16]

HOW TO APPROACH TO SECURE AIRWAY? (FIG. 2)

Securing an airway in hospital settings varies for planned surgery from ED or in ICU based on etiology.

Anesthesia for Elective Surgical Procedures

Techniques

Majority of these patients are anticipated to have difficult airway because of the reasons mentioned above. The choice and techniques for airway access are as follows:

- Awake fiberoptic intubation—nasal or oral.
- Awake video laryngoscopy guided intubation—nasal or oral.
- Lighted stylet-guided intubation.
- Retrograde intubation (RI) —in trismus/failed intubation.
- SAD—as a sole device, as an aid to intubation, or as a rescue device, if not contraindicated.
- Tracheostomy—percutaneous tracheostomy (PCT) is performed on intubated patients or as a definitive airway following emergency cricothyroidotomy.

The Difficult Airway Society (DAS) in 2019 published guideline for awake tracheal intubation (ATI) and coined a pnemonic, *sTOP* for ATI where *s* stands for low dose sedate, *T* for topicalize, *O* for oxygenate, and *P* for perform; for most of these patients, the choice for airway access is awake technique: Patients are psychological prepared with explanation of procedure; vasoconstrictors are used to decongest nasal passage, glycopyrrolate to dry secretions prior to the procedure.

Perioxygenation

All India Difficult Airway Association (AIDAA) and DAS recommend preoxygenation and peri-intubation oxygenation. The methods of oxygenation are as follows:[17,18]

- 10 L/min of O_2.
- Continuous positive airway pressure (CPAP) and pressure support ventilation (PSV).
- Apnoeic oxygenation through 15 L/min nasal O_2.

TABLE 2: Components of physiologically difficult airway.

Physiological derangement	*Mechanism*	*Management*
Hypoxemia	Limited oxygen reserve leading to rapid desaturation during apnea	• *Preoxygenation*: SpO_2 >95%: NRB/BVM + HFNC, SpO_2 <95%: NIPPV/BVM + PEEP plus HFNC • Apneic oxygenation and ventilation • Supraglottic • Delayed sequence intubation (DSI) • Head-elevated positioning
Hypotension	• Decreased venous return with PPV • Attenuation of catecholamine surge with the resolution of hypoxia/hypercarbia • Vasodilation and myocardial depression.	• *Resuscitate before intubation:* Two peripheral IV lines, volume loading ± blood in responders • Norepinephrine infusion in non-responders while epinephrine boluses (10–50 µg) can be given in urgent situations • Phenylephrine bolus for transient vasodilation • Use hemodynamically stable induction agents
Right ventricular (RV) failure	RV afterload is further increased due to PPV, PEEP, and HPV	• Bedside echo is quite useful to differentiate dysfunction and failure • Avoid factors causing HPV • Adequate preoxygenation and apneic oxygenation • Ventilation with low mean airway pressures • Pulmonary vasodilator, e.g., inhaled nitric oxide (iNO) and epoprostenol • Avoid any fluid, resuscitate with norepinephrine
Severe metabolic acidosis	Compensatory hyperventilation interruption by any brief period of apnea leads to a profound drop in pH and consequent cardiovascular collapse	• Try to avoid intubation and put on NIPPV till correction • Ventilator-assisted preoxygenation • Maintain spontaneous respiration—awake intubation • Try to avoid RSI or use low dose sedatives and short-acting NMB • Maintain pre-intubation $EtCO_2$ and RR • Consider pressure mode ventilation • No role of bicarbonate therapy
Neurological	Sudden increase of ICP during RSII in TBI and stroke can cause secondary injury to brain	• Invasive BP monitoring • Blunt stress response • Induce with propofol, thiopentone, ketamine, and midazolam • Avoid succinylcholine
Hepatic	Hepatic failure patients have raised ICP due to hepatic encephalopathy	• Follow neuroprotective strategy • Consider coagulopathy and bleeding
Renal	Severe metabolic acidosis leads to exhaustive hyperventilation. Any interruption during intubation leads to acidemia and dangerous hyperkalemia	• Avoid succinylcholine • Vasopressor should be used • Soda bicarbonate infusion can be considered
Gut	Risk of regurgitation and aspiration	Use RSII and fluid resuscitation
Sepsis	Distributive shock, lactic acidosis and coagulopathy	• Use fluid resuscitation, vasopressors • Induction with ketamine

(BP: blood pressure; BVM: bag valve mask; $EtCO_2$: end-tidal carbon dioxide; HPV: hypoxic pulmonary vasoconstriction; HFNC: high frequency nasal cannula; NIPPV: noninvasive positive pressure ventilation; NMB: neuromuscular blocker; NRB: nonrebreather mask; RR: respiratory rate; RSII: rapid sequence induction intubation; SpO_2: oxygen saturation)

- Transnasal humidified rapid—insufflation ventilatory exchange (THRIVE)/high-flow nasal oxygen (HFNO).
- HFNO @ 30–60% O_2 and flow >30 L/min will maintain adequate while flow <30 L/min can result in desaturation (SpO_2 < 90%).

Topicalization

Awake tracheal intubation can be achieved with adequate topicalization alone. Local anesthesia (LA) of the airway passage is done with lignocaine in form of spray, gargle, nebulization, infiltration of nerves (glossopharyngeal, internal laryngeal, superior laryngeal, and transtracheal infiltration), and spray-as-you-go.

Sedation

Low level of sedation with midazolam and remifentanil helps to reduce anxiety and discomfort while preserving respiration and patient's cooperation.

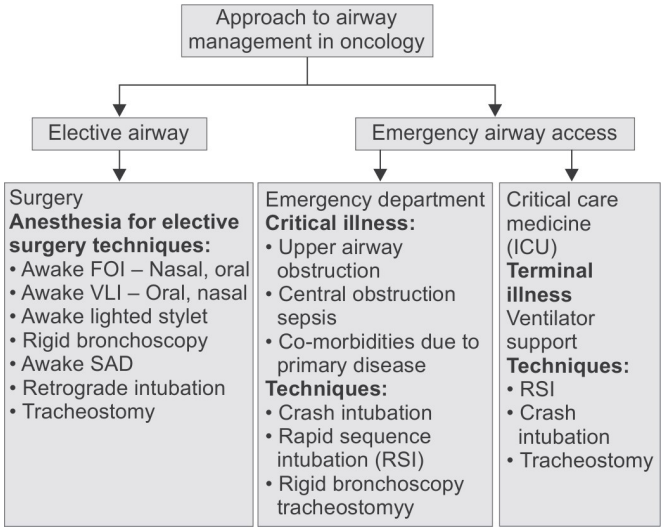


Fig. 2: Approach to airway management.
(FOI: fiberoptic intubation; SAD: supraglottic airway device; VLI: video-laryngoscope-guided intubation)

Perform and Confirm

Choose an operator right, right tube, and right size fiber-optic bronchoscope (FOB). The incidence of esophageal intubation is 2.3% with fiberoptic bronchoscope and 4.9% with video laryngoscope (VL). A two-point check confirms the position of the tracheal tube:

1. Passage of endotracheal (ET) tube under visualization of tracheal lumen/vocal cords with FOB
2. *Capnography*: 100% sensitive and specific in identifying correct tube placement.

Induction of anesthesia should be done once the two-point check has been confirmed.

Extubation

Patients who had difficult mask ventilation, difficult intubation/reintubation, delayed recovery, or pre-existing disease (cardiorespiratory) should be always extubated over an airway exchange catheter (AEC) or FOB. Patients who are likely to have airway edema or airway collapse should undergo cuff leak test and if negative should be extubated under deep sedation over AEC or FOB so that they can be re-intubated and tracheostomized if required. Limb 2 and 3 of AIDAA extubation guidelines describes this.[19]

Emergency Airway Management

Preoxygenation and Apneic Oxygenation

Standard preoxygenation is done for 3–5 minutes with a good fit face mask. Apneic oxygenation is continuous flow of oxygen during apnea till the beginning of positive pressure ventilation. Apneic oxygenation can maintain good PaO_2 with continuous high flow oxygen and patent airway at the cost of severe hypercapnia and acidosis. Transnasal humidified rapid insufflation ventilatory exchange (THRIVE) creates a CPAP of around 7 cmH_2O and consequent CO_2 clearance **(Table 3)**.

TABLE 3: Techniques of apneic oxygenation (ApOx).

Technique	*Oxygen flow rate*	*Approx. apnea time (in standardized conditions)*
NODESAT (nasal cannula)	5–15 L/min	2–5 minutes
THRIVE	70 lit/min (adult); 8–12 lit/min flow in infants, 20–30 L/min in children <12 years	15 minutes
Buccal oxygen delivery	10 L/min (does not provide CPAP)	12 minutes
Nasopharyngeal catheter	5–15 L/min	45 minutes
Tracheal catheter	0.5–1 L/min	30 minutes
Endobronchial catheter bilateral	0.6–0.7 L/min	30 minutes
Oxygenating laryngoscopes (manikin study)		Over 20 minutes

Rapid Sequence Intubation and Delayed Sequence Intubation

Rapid sequence intubation (RSI) is undertaken in emergency situation with appropriate induction agent (etomidate or propofol or ketofol), short-acting muscle relaxant suxamethonium, application of cricoid pressure, and avoiding PPV. Hypotension is prevented by a right balance of fluid and vasopressor administration. In modified RSI, positive pressure ventilation is given through BMV with variable application of cricoid pressure. Delayed sequence intubation (DSI) is indicated in agitated patients with low-dose ketamine which helps to preoxygenate the patients adequately and prevent hypotension. Ketamine sequence intubation (KSI)/graded sequence intubation (GSI) is similar to DSI, except that neuromuscular blockade is not used.[20]

Crash Intubation

Crash intubation is undertaken without administration of drugs—when patients are rapidly deteriorating, hypoxic, or in impending or after cardiac arrest.

Rigid Bronchoscopy

Rigid bronchoscopy is a useful device in oncology emergencies—massive airway hemoptysis, large tumors of aerodigestive regions compromising airway, and placement of airway stents. It reduces airway-related adverse outcomes;[21] useful where flexible bronchoscope if fraught with problems of complete obstruction.

Surgical Tracheostomy

Surgical tracheostomy is undertaken in acute respiratory distress due to upper airway obstruction and failure to intubate. Percutaneous tracheostomy (PCT) done by Ciaglia[22] or Griggs technique are elective procedures and not to be undertaken in emergency situations.

TROUBLE SHOOTING DURING INTUBATION

Troubleshooting during RSI Intubation

Both during ATI and RSI, it may not be possible to revert back the patient and make him conscious or continue with rescue device such as SAD for long. A definitive airway is mandatory in critically ill patients.

- During modified RSI, face mask ventilation (FMV) could be unsuccessful. As per ADIAA guidelines immediately call for a help. Maintaining the SpO_2 >95%, single attempt for tracheal intubation may be taken.
- If succeeded in FMV, attempt intubating the patient. If unsuccessful, maximum of two more attempts can be taken. In between attempts, FMV should be continued to maintain SpO_2 >95%. Can change the operator, device, reposition patients head, in subsequent attempts.
- If intubation is unsuccessful, then attempt second-generation SAD insertion and endotracheal intubation (ETI) through the SAD under FOB guidance and confirmation by capnography.
- If SAD insertion is unsuccessful, rescue FMV is attempted ensuring full neuromuscular blockade, optimal position, and both hand techniques. If successful in FMV, get a PCT done. If failed, declare as complete ventilation failure (CVF), continue FMV, call for an additional help and perform emergency cricothyroidotomy.
- Emergency cricothyroidotomy should be performed by scalpel bougie technique over the cricothyroid membrane.

Troubleshoot during Awake Tracheal Intubation (As Per DAS Guidelines)

- In situation where the first attempt of ATI is unsuccessful, immediately call for help, reassess, optimize sedation, topicalization, and oxygenation (sTOP).
- If fails change the device, the technique to VL with a more experienced operator.
- If unsuccessful, immediately call for help, administer 100% oxygen, and stop sedation.
- Stop the procedure and think whether immediate airway management is essential.
- If it is not essential, then abandon the procedure.
- If it is essential, then assess whether surgical access is appropriate. If it is not appropriate, then deliver general anesthesia under high risk consent.

SPECIFIC DISEASES

Upper Airway Obstruction

Upper airway obstruction due to malignant neoplasm is a medical emergency that may present as acute or chronic or slow progressive. Superadded edema and hemorrhage can lead to an acute obstruction.

- Primary head and neck tumor of pharynx, pyriform fossa, supraglottic, and glottic and subglottic area.
- Extrinsic compression due to multiple neck nodes, thyroid cancers, superior vena cava syndrome.
- Invasion of airway from thyroid and esophageal cancers
- Tracheomalacia, anxiety, and panting can precipitate airway compromise.
- Rarely metastatic lesions from other sites of cancer.[23]

Patients with cancer of the pyriform fossa, epiglottis, vocal cords, and larynx who are not comfortable in supine position due to near complete obstruction will usually require a surgical airway such as tracheotomy or cricothyrotomy. If airway is amenable to intubation, small sized endotracheal tube should be inserted. Caution should be taken to prevent trauma and soiling of the confined airway or precipitate patients anxiety.

In oral cavity cancers, base of the tongue, nasopharynx trial of awake intubation should be given followed by insertion of ET tube preferably flexometallic. Sedation administration will depend on feasibility of achieving airway control. Long-acting sedatives and muscle relaxants should be avoided as they predispose airway obstructions to airway collapse and respiratory failure. Patients who have received neoadjuvant chemo- or radiotherapy are especially vulnerable.

Consideration should also be given to awake, flexible fiberoptic laryngoscopy to assess the airway and the possibility of awake, nasotracheal, flexible fiberoptic intubation.

Central Airway Obstruction

A central airway obstruction (CAO) is an airflow obstruction either at the trachea, carina, or main stem bronchi.

Causes

- Lung cancers—mostly squamous cell carcinoma followed by adenocarcinoma.
- Metastasis from breast, kidney, and colon.
- Lymphoma, malignancy of adjacent structures—esophagus, thyroid, and mediastinal growth. CAO occurs through three basic mechanisms; the airway is obstructed either by direct invasion, compression, or endoluminal disease. Signs and symptoms include cough, localized wheezing, respiratory failure, stridor, and postobstructive pneumonia. Oxygenation and ventilation should be prioritized and patients must be assessed for the necessity of ventilator support. If

airway obstruction is in the upper part, tracheostomy or retrograde intubation may relieve obstruction. Lower down endoluminal lesions will require bronchoscopic ablative therapy/debulking followed by stenting. Extraluminal obstructions are managed with dilation and stenting to maintain airway patency.[24]

CONCLUSION

Airway management in oncology has been a challenge both managing during elective procedures or during their critical illness in ICU. Airway assessment and backup plan prior to anesthesia should be the corner stone in airway management. Usually, these patients are anticipated to have difficult airway. ATI is the technique of choice in most instances. Proper preoxygenation, topicalization, low sedation, and judicious performance should be the crux for ATI. However, during emergency procedures or during mechanical ventilation, RSI or DSI may be an alternate choice. No technique is without any complications so one has to be thorough with the troubleshoot. Individual disease with specific airway issues should be dealt as per the priority of airway issues.

REFERENCES

1. Cook TM, Woodall N, Harper J, Benger J; Fourth National Audit Project. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 2: intensive care and emergency departments. Br J Anaesth. 2011;106(5):632-42.
2. Abramian O, Kolman D, Abramian E. Oncological airway emergencies in the critical care unit. In: oncology critical care. Croatia: InTech Publications; 2016.
3. Schaeuble JC, Caldwell JE. Effective communication of difficult airway management to subsequent anesthesia providers. Anesth Analg. 2009;109(2):684-6.
4. Hillel AT, Diaz Voss Varela AD, Bhatti NI. The Difficult Airway in Conventional Head and Neck Surgery, 3rd edition. Netherlands: Elsevier Inc. 2013. pp. 813-23.
5. Pearce A. Evaluation of the airway and preparation for difficulty. Best Pract Res Clin Anaesthesiol. 2005;19(4):559-79.
6. Ernst A, Feller-Kopman D, Becker HD, Mehta AC. Central airway obstruction. Am J Respir Crit Care Med. 2004;169(12):1278-97.
7. Pfleger A, Eber, E., Assessment and causes of stridor. Paediatr Respir Rev. 2016;18:64-72.
8. Kheterpal S, Martin L, Shanks AM, Tremper KK. Prediction and outcomes of impossible mask ventilation: a review of 50,000 anesthetics. Anesthesiology. 2009;110(4):891-7.
9. Fernandez MW, Beattie LK. Assessment of the Difficult Airway, Atlas of Emergency Medicine Procedures. New York: Springer Science; 2016. pp. 89-91
10. Mallampati SR, Gatt SP, Gugino LD, Desai SP, Waraksa B, Freiberger D, et al. A clinical sign to predict difficult tracheal intubation: A prospective study. Can Anaesth Soc J. 1985;32(4):429-34.
11. De Jong A, Molinari N, Terzi N, Mongardon N, Arnal JM, Guitton C, et al. Early identification of patients at risk for difficult intubation in the Intensive Care Unit: Development and validation of the MACOCHA score in a multicenter cohort study. Am J Respir Crit Care Med. 2013;187(8):832-9.
12. Ahmad I, El-Boghdadly K, Bhagrath R, Hodzovic I, McNarry AF, Mir F, et al. Difficult Airway Society guidelines for awake tracheal intubation (ATI) in adults. Anaesthesia. 2020;75(4): 509-28.
13. Myatra SN, Ahmed SM, Kundra P, Garg R, Ramkumar V, Patwa A, et al. All India difficult airway association 2016 guidelines for tracheal intubation in the intensive care unit. Indian J Crit Care Med. 2017;21(3):146-5313.
14. Kuo GP, Torok CM, Aygun N, S. Zinreich SJ. Diagnostic imaging of the upper airway. Proc Am Thorac Soc. 2011;8(1):40-5.
15. Osman A, Sum KM. Role of upper airway ultrasound in airway management. J Intensive Care. 2016;4:52.
16. Wang J, Xia M, Jiang H. Advances in studies on imaging and artificial intelligence technology-assisted difficult airway assessment. Front Oral Maxillofac Med. 2021;3:8-18.
17. Myatra SN, Shah A, Kundra P, Patwa A, Ramkumar V, Divatia JV, et al. All India Difficult Airway Association 2016 guidelines for the management of unanticipated difficult tracheal intubation in adults. Indian J Anaesth. 2016;60(12):885-98.
18. Frerk C, Mitchell VS, McNarry AF, Mendonca C, Bhagrath R, Patel A, et al. Difficult Airway Society intubation guidelines working group, Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults. Br J Anaesth. 2015;115(6):827-48.
19. Kundra P, Garg R, Patwa A, Ahmed SM, Ramkumar V, Shah A, et al. All India Difficult Airway Association 2016 guidelines for the management of anticipated difficult extubation. Indian J Anaesth. 2016;60(12):915-21.
20. Merelman AH, Perlmutter MC, Strayer RJ. Alternatives to rapid sequence intubation: contemporary airway management with ketamine. West J Emerg Med. 2019;20(3):466-71.
21. Apfelbaum JL, Hagberg CA, Caplan RA, Blitt CD, Connis RT, Nickinovich DG, et al. Practice guidelines for management of the difficult airway: An updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology. 2003;98:1269-77.
22. Ciaglia P, Firsching R, Syniec C. Elective percutaneous dilatational tracheostomy. A new simple bedside procedure; preliminary report. Chest. 1985;87(6):715-9.
23. López F, Devaney KO, Hanna EY, Rinaldo A, Ferlito A. Metastases to nasal cavity and paranasal sinuses. Head Neck. 2016;38(12):1847-54.
24. Ost DE, Ernst A, Grosu HB, Lei X, Diaz-Mendoza J, Slade M, et al. Therapeutic bronchoscopy for malignant central airway obstruction: success rates and impact on dyspnea and quality of life. Chest. 2015;147(5):1282-98.

CHAPTER 71

Tissue Target Therapy and Associated Complications

Asif Ahmed, Bharat Parikh, Rahul Jaiswal

INTRODUCTION

"Tissue target" therapy drugs act by blocking the growth and spread of cancer by interfering with the molecular targets which are involved in the growth, division, and spread of cancer cells, whereas "standard" chemotherapy acts on all rapidly dividing normal and cancerous cells. These drugs are often cytostatic as compared to the standard chemotherapy agents which are cytotoxic. Targeted cancer therapies approved by the Food and Drug Administration (FDA) include hormonal therapies, gene expression modulators, signal transduction inhibitors, angiogenesis inhibitors, apoptosis inducers, toxin delivery molecules, and immunotherapy. With a better understanding of molecular biology, a lot of cancers that were considered incurable with short survival earlier, now have a better prognosis and quality of life with targeted therapies. Cancers having inherent or acquired mutations that were resistant to target drivers can also be treated with these newly designed specific drugs.[1-3]

MECHANISMS AND TYPES

Various mechanisms have been described for the action of tissue target therapies which are as follows:

- Hormone therapies prevent the production of hormones or interfere with the action of hormones. These have been approved for breast cancers, prostate cancers, and some endometrial cancers.
- Gene expression modulators act by modifying proteins that are responsible for controlling gene expression.
- Signal transduction inhibitors act by blocking the activities of molecules that are involved in signal transduction.
- Angiogenesis inhibitors act by blocking the growth of new blood vessels followed by tumor growth. Some targeted therapies interfere with the action of vascular endothelial growth factor (VEGF) and inhibit angiogenesis.
- Apoptosis inducers help in programed cell death of cancer cells.
- Monoclonal antibodies recognize the specific molecules on the surface of the cancer cells. Monoclonal antibodies bind to the target molecules resulting in immune-mediated destruction of cells, which express target molecules. These monoclonal antibodies carrying toxic molecules lead to the death of cancer cells specifically. When these antibodies bind to the target cells, the toxic molecules, such as radioactive or chemical substances, are taken up by the cell and destroyed.
- Immunotherapies are the latest drugs for cancer treatment and the basic mechanism of action is activation of cytotoxic T cells by inhibiting the inhibitory pathways which keep these cells in check. The usual inhibitory pathways are PD1/PDL1 and CTLA4.

INDICATIONS

Tumor tissues are tested to determine the presence of an appropriate target. The use of targeted therapy may be restricted to patients where the tumor has a specific gene mutation. Certain cancers release tumor cells in circulation called circulating tumor cells (CTCs) and cell-free DNA which can be tested in blood and is called liquid biopsy. This is a noninvasive method by which molecular targets can be tested if tissue blocks are exhausted or biopsy is difficult. These tests have their validation and quality control.

Food and Drug Administration sets the criteria for targeted therapy, i.e., a patient is taken up for targeted therapy only if the cancer is not responding to other therapies, is spreading, or cannot be operated upon. Recently many targeted therapies have got approval in adjuvant settings such as anti-epidermal growth factor receptor (EGFR) drugs in adenocarcinoma of the lung, immunotherapies in melanoma, anti-HER2 therapies in carcinoma of the breast, and PARP inhibitors (poly ADP ribose polymerase) in carcinoma of the ovary and breast.[1] The different target therapies in use and the indications are displayed in **Table 1**.[1-5]

TABLE 1: Various therapies for the organ specific malignancies.

S. No.	*Malignancy*	*Drugs*
1.	Bladder cancer	Atezolizumab, nivolumab, avelumab, pembrolizumab, and erdafitinib
2.	Brain cancer	Bevacizumab and everolimus
3.	Breast cancer	Everolimus, tamoxifen, trastuzumab, fulvestrant, anastrozole, exemestane, lapatinib, letrozole, pertuzumab, ado-trastuzumab emtansine, trastuzumab deruxtecan,[4] palbociclib, ribociclib, neratinib maleate, abemaciclib, olaparib, alpelisib, tucatinib, and sacituzumab
4.	Cervical cancer	Bevacizumab and pembrolizumab
5.	Colorectal cancer	Cetuximab, panitumumab, bevacizumab, aflibercept, regorafenib, ramucirumab, nivolumab, ipilimumab, encorafenib, and trastuzumab
6.	Dermatofibrosarcoma protuberans	Imatinib mesylate
7.	Endocrine/neuroendocrine tumors	Lanreotide acetate, avelumab, lutetium lu 177-dotatate, and iobenguane I 131
8.	Endometrial cancer	Pembrolizumab, lenvatinib mesylate, dostarlimab-Gxly, letrozole, and anastrozole
9.	Esophageal cancer	Trastuzumab, ramucirumab, pembrolizumab, and nivolumab
10.	Head and neck cancers	Cetuximab, pembrolizumab, and nivolumab
11.	Gastrointestinal stromal tumor	Imatinib mesylate,[5] sunitinib, regorafenib, avapritinib, ripretinib, cabozantinib, sorafenib, and dasatinib
12.	Giant cell tumor	Denosumab and pexidartinib hydrochloride
13.	Kidney cancer	Bevacizumab, sorafenib, sunitinib, pazopanib, temsirolimus, everolimus, axitinib, nivolumab, cabozantinib, lenvatinib mesylate, ipilimumab, pembrolizumab, and avelumab
14.	Leukemia	Tretinoin, imatinib mesylate,[3] dasatinib, nilotinib, bosutinib, rituximab, alemtuzumab, ofatumumab, obinutuzumab, ibrutinib, idelalisib, venetoclax, ponatinib hydrochloride, midostaurin, gemtuzumab, rituximab, acalabrutinib, blinatumomab, and nelarabine
15.	Liver and bile duct cancer	Sorafenib, regorafenib, nivolumab, lenvatinib mesylate, pembrolizumab, cabozantinib, ramucirumab, ipilimumab, atezolizumab, and bevacizumab
16.	Lung cancer	Bevacizumab, crizotinib, erlotinib, gefitinib, afatinib, ceritinib, ramucirumab, nivolumab, pembrolizumab, osimertinib, alectinib, atezolizumab, durvalumab, capmatinib, ipilimumab, lorlatinib, dabrafenib, trametinib, and trastuzumab
17.	Lymphoma	Brentuximab, rituximab, vorinostat, romidepsin, bortezomib, pralatrexate. ibrutinib, idelalisib, obinutuzumab, nivolumab, pembrolizumab, acalabrutinib, venetoclax, and crizotinib
18.	Malignant mesothelioma	Ipilimumab and nivolumab
19.	Microsatellite instability-high or mismatch repair-deficient solid tumors	Pembrolizumab and dostarlimab-Gxly
20.	Multiple myeloma	Bortezomib, carfilzomib, panobinostat, daratumumab, ixazomib, daratumumab, and melphalan flufenamide hydrochloride
21.	Myelodysplastic/myeloproliferative disorders	Imatinib mesylate, ruxolitinib, and fedratinib
22.	Neuroblastoma	Dinutuximab and naxitamab
23.	Ovarian epithelial/fallopian tube/primary peritoneal cancers	Bevacizumab, olaparib, rucaparib, and niraparib
24.	Pancreatic cancer	Erlotinib, everolimus, sunitinib, and olaparib
25.	Prostate cancer	Cabazitaxel, enzalutamide, abiraterone acetate, radium 223 dichloride, apalutamide, darolutamide, rucaparib, and olaparib
26.	Skin cancer	Vismodegib, ipilimumab, trametinib, dabrafenib, pembrolizumab, nivolumab, alitretinoin, avelumab, and atezolizumab
27.	Soft tissue sarcoma	Pazopanib and alitretinoin
28.	Solid tumors (tumor mutational burden-high)	Pembrolizumab
29.	Solid tumors (*NTRK* gene fusion)	Larotrectinib sulfate
30.	Stomach cancer	Pembrolizumab, trastuzumab, ramucirumab, fam-trastuzumab, and nivolumab
31.	Systemic mastocytosis	Imatinib mesylate and midostaurin
32.	Thyroid cancer	Cabozantinib, sorafenib, lenvatinib mesylate, trametinib, and dabrafenib

LIMITATIONS OF TARGET THERAPY[1,2]

Though many advantages have been documented but targeted therapies have their own limitations. These include:

- Cancer cells can develop resistance to targeted therapy by two different modalities. The "target" can acquire changes through mutation so that the targeted therapy fails to interact with it. The other mode is that tumor growth adopts a new pathway that is independent of the target.
- It is difficult to develop drugs for a few identified targets given their structure and functioning in the cell. Ras, a signaling protein that is mutated in cancers, and inhibitors of Ras signaling have still not been developed with the existing technologies.
- Targeted therapies need to be combined with chemotherapy, e.g., targeted therapy Trastuzumab is combined with chemotherapy drug docetaxel for treating metastatic breast cancer (that overexpresses the protein HER2/neu).

COMPLICATIONS OF TARGETED THERAPY AND MANAGEMENT

The increasing use of targeted agents requires monitoring with regards to surveillance for drug toxicities and assessments of therapeutic response. As for all, even target therapy is associated with complications. Knowledge of the toxicities specific to different targeted therapy can help in identifying and differentiating drug-related complications from disease progression. The side effects depend on the type of targeted therapy and how the body reacts to the therapy. The most common side effects of targeted therapy are as follows:[1,6,7]

- Anemia
- Autoimmune reactions especially with immunotherapies
- Bleeding and bruising (thrombocytopenia)
- Cardiac toxicity
- Delirium
- Effects on the eye such as conjunctivitis, retinitis, edema, and necrosis[6]
- Hypertension
- Neutropenia and infection
- Oral and throat problems such as mucositis, pharyngitis and candidiasis
- Immunotherapy and organ-related inflammation
  Pain and peripheral neuropathy
- Skin and nail changes such as rashes, dry hair, color change, and hand foot syndrome
- Urinary and bladder problems
- Bowel perforation

Close monitoring, early recognition, and treatment of complications can lead to improved clinical outcomes. Patient awareness about the same can also be beneficial. Management is based on the need and specific complications related to the therapy used. It could include prophylactic treatment for oral and skin-related complications. Hypertension should be treated with the combination of angiotensin-converting enzyme inhibitors and calcium channel blockers. Dose reduction of therapy may also be required in severe cases. Thyroid-stimulating hormone (TSH) should be monitored and need-based replacement provided. Monitoring of hematological and biochemical parameters including electrolytes should be done regularly (as early as bimonthly) for early detection of complications. Complications related to specific medications should be identified and differentiated from other medical conditions and treated accordingly.

CONCLUSION

For years, cancer has been treated by cytotoxic chemotherapy, where the drugs targeted rapidly dividing cells irrespective of cancer cells or certain normal tissues. These were also associated with classical complications such as gastrointestinal symptoms, alopecia, and myelosuppression.

Target therapy has brought about a dramatic shift in cancer therapy in recent times. The traditional cytotoxic chemotherapy remains the treatment of choice for many malignancies, but targeted therapy is now being used for many cancers such as lung, breast, colorectal, and pancreatic cancers and for leukemia, lymphoma, and multiple myeloma also.[8]

Trials related to targeted therapy have shown a clear benefit from the combination of new molecules with chemotherapy. Monotherapy seem to have benefits, but they cannot equate to the efficacy of combination therapy, hence targeted therapy cannot be substituted completely for chemotherapy.[9]

Recent research has also highlighted the use of nanoparticles with antibody fragments, which enables them to deliver drugs and target the EGFR on cancer cells, and this technology in combination with the conventional therapy may add to the future of tissue target therapy for cancer.[10]

REFERENCES

1. National Cancer Institute. 'Targeted Therapy to Treat Cancer.' Maryland: National Cancer Institute; 2021.
2. Mahadevan D. Targeted Cancer Therapy: Medscape, Drugs & Diseases; 2021.

3. Deininger M, Buchdunger E, Druker BJ. The development of imatinib as a therapeutic agent for chronic myeloid leukemia. Blood. 2005;105(7):2640-53.
4. Modi S, Saura C, Yamashita T, Park YH, Kim SB, Tamura K, et al. Trastuzumab deruxtecan in previously treated HER2 positive breast cancer. N Engl J Med. 2020;382(7): 610-21.
5. Verweij J, Casali PG, Zalcberg J, LeCesne A, Reichardt P, Blay JY, et al. Judson Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet. 2004;364(9440):1127-34.
6. Ho WL, Wong H, Yau T. The ophthalmological complications of targeted agents in cancer therapy: what do we need to know as ophthalmologists? Acta Ophthalmol. 2013;91(7): 604-9.
7. Watters AL, Epstein JB, Agulnik M. Oral complications of targeted cancer therapies: A narrative literature review. Oral Oncol. 2011;47(6):441-8.
8. Kumar M, Nagpal R, Hemalatha R, Verma V, Kumar A, Singh S, et al. Targeted cancer therapies: the future of cancer treatment. Acta Biomed. 2012;83(3):220-33.
9. Schütz F. Targeted therapy: Can it substitute for chemotherapy? Heidelberg: Universitätsfrauenklinik; 2008.
10. Balfour H. (2020). Nanoparticle drug delivery could be the future of targeted cancer therapies. [online] Available from: https://www.europeanpharmaceuticalreview.com/news/113823/nanoparticle-drug-delivery-could-be-the-future-of-targeted-cancer-therapies/#:~:text=A%20research%20collaboration%20has%20produced,for%20targeted%20anti%2Dcancer%20treatments. [Last accessed February, 2022].

CHAPTER 72

Hemophagocytic Lymphohistiocytosis Syndrome: Current Status

Arun K Baranwal, Lalit Takia

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a clinicopathological syndrome characterized by aggressive, life-threatening dysfunctional general activation of the immune system.[1] It manifests with fever, pancytopenia, hepatosplenomegaly along with liver dysfunction.[1,2] It is observed in all ages, however, infants are most frequently affected. It is triggered by a multitude of conditions, the most common being infections, disrupting immune homeostasis, and can occur as a familial or sporadic disorder.[2] Patients with familial (primary/genetic) variety most often have autosomal recessive biallelic genetic defects in the perforin-dependent cytotoxic pathway or mutations affecting activation of the inflammation. Sporadic (secondary/acquired) cases often occur secondary to infections, malignancies, or autoinflammatory/autoimmune diseases.[2] HLH induced by autoimmune disease is termed macrophage activation syndrome (MAS).

The incidence of HLH in the general and critical care population is largely unknown.[2] Early identification and prompt management are crucial. However, the rarity of the syndrome, variable clinical presentations, clinical overlap with other hyperinflammatory disorders, and poor specificity of clinicolaboratory findings delay its diagnosis. Delayed diagnosis continues to be the most significant obstacle to a successful outcome.[3] Intensivists play a crucial role in its diagnosis among critically ill patients.

TERMINOLOGY

Primary/Familial Hemophagocytic Lymphohistiocytosis

Primary/familial HLH refers to underlying presumed or demonstrated inherited defect.

Secondary/Acquired Hemophagocytic Lymphohistiocytosis

Secondary/acquired HLH is an acquired form of immune dysregulation that is triggered by an infection, malignancy, autoimmune disease, or other immune challenges without an inherited defect.

Macrophage Activation Syndrome

Symptoms and signs of HLH due to persistent immune stimulation primarily in patients with autoimmune disease or malignancy.

PATHOPHYSIOLOGY

Immune Dysregulation

In response to a trigger, macrophages and/or lymphocytes get activated and secrete excessive cytokines, causing inflammation, tissue damage, and ultimately organ failure if remain unabated. Normally, natural killer (NK) cells and/or cytotoxic T-cells (CTLs) downregulate activated macrophages and lymphocytes, and eliminate them. However, among patients with HLH, NK cells, and/or CTLs fail to downregulate and remove activated macrophages and thus permit uncontrolled activation of macrophages, highly elevated interferon-γ and other cytokines leading to excessive inflammation.[4,5] In the normal population, NK cells and CTLs eliminate activated macrophages through perforin-dependent cytotoxicity. However, among patients with familial HLH, genetic defects involve genes encoding proteins responsible for perforin-dependent cytotoxicity.

Toll-like receptors (TLRs) are nonantigen-specific receptors found in NK cells and get activated by bacteria, fungi, viruses, or mycoplasma. Their overactivation is also implicated in the causation of HLH. Genes associated with the signaling of TLR/interleukin-1 receptor (IL-1R) are upregulated in patients with autoinflammatory disorders[6] and may contribute to HLH. The pathophysiology of HLH is summarized in **Figure 1**.

Hemophagocytosis

In addition to antigen presentation and cytokine production, overactivated macrophages phagocytize host cells as well. Hemophagocytosis is characterized by the presence of red

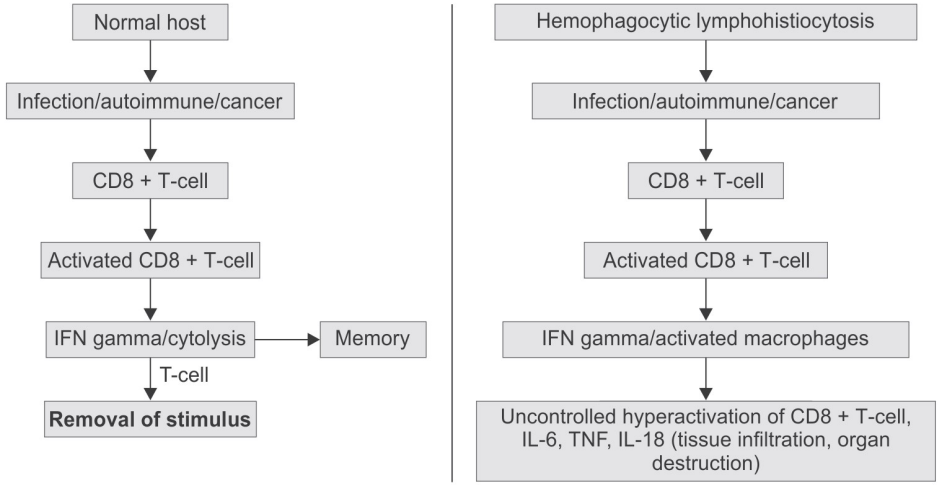


Fig. 1: Comparison of immunologic response in the usual host versus patients with hemophagocytic lymphohistiocytosis (HLH).[12] (IFN: interferon; IL: interleukin; TNF: tumor necrosis factor)

blood cells, platelets, or white blood cells in their cytoplasm. It can be demonstrated in lymph nodes, spleen, liver, or bone marrow. Though "hemophagocytosis" is a component of the term "HLH," suggests excess macrophage activation and is included in the diagnostic criteria, it is neither pathognomonic of, nor required for, the diagnosis of HLH.[6]

Cytokine Storm

Persistent overactivation of macrophages, NK cells, and CTLs leads to cytokine storm which is responsible for multiorgan failure and consequent high mortality. Extremely high levels of interferon-γ and chemokine CXCL9 (which is regulated by interferon-γ); tumor necrosis factor-α; ILs (e.g., IL-6, IL-10, and IL-12); and soluble IL-2 receptor (CD25). High levels of IL-16 may be responsible for the TH1-type response that recruits macrophages and other immunologically active cells.[7]

Triggers

Trigger is mostly an infection, or alteration in immune homeostasis. These may be either immune activators or those leading to immune deficiency. Immune activation due to an infection, the most common being a viral one, is a common trigger for both primary and secondary cases. Primary Epstein–Barr virus (EBV) infection can trigger HLH in patients with a defect in perforin-dependent cytotoxicity, as well as in those without a known predisposition. Other causative organisms include cytomegalovirus (CMV), parvovirus, herpes simplex virus, varicella-zoster virus, measles, human herpesvirus 8, H1N1 influenza virus, parechovirus, human immunodeficiency virus (HIV), SARS-CoV-2, bacteria, *Mycobacterium tuberculosis,* and fungi. Excessive cytokine release in patients with the chronic granulomatous disease and Kawasaki disease can also trigger HLH. Common immunodeficiency triggers include inherited syndromes, malignancy, rheumatologic disorders, or HIV infection. Patients with X-linked lymphoproliferative disease are also at high risk.[2]

Genetics

"HLH-associated" genes encode proteins responsible for perforin-dependent cytotoxicity, and get inherited in an autosomal recessive manner.[7] They play a significant role in pediatric cases and are increasingly being implicated in adults as well. Genetic information may help determine likelihood of future recurrences, the need for hematopoietic cell transplantation, and risk in other family members.

Mutations at Familial Hemophagocytic Lymphohistiocytosis Loci

Mutations at loci responsible to code for proteins involved in cytotoxic granule formation and release pathway are labeled as FHL loci, which are as follows:

- *FHL1*: Unknown (9q21.3–2)
- *FHL2*: PRF1, perforin (10q21–2)
- *FHL3*: MUNC13D, Munc13-4 (17q25)
- *FHL4*: STX11, Syntaxin11 (6q24)
- *FHL5*: STXBP2, Munc18-2 (19p)

Primary immunodeficiency syndromes, due to mutations, are also associated with a higher incidence of HLH. These include chronic granulomatous disease, X-linked lymphoproliferative disease, Chédiak–Higashi syndrome, Griscelli syndrome, XMEN disease (X-linked immunodeficiency with magnesium defect, EBV infection, and neoplasia), IL-2-inducible T cell kinase, Hermansky–Pudlak syndrome, and lysinuric protein intolerance.[8-11]

CLINICAL FEATURES

Initial Clinical Presentation

Hemophagocytic lymphohistiocytosis usually presents as an acute or subacute febrile illness and multiorgan dysfunction.

Symptoms and signs of HLH resemble common infections, sepsis, pyrexia of unknown origin, hepatitis, or encephalitis. Incidence of various clinical findings are as follows (cooperative HLH-2004 study; n = 369):[13]

- Fever (95%)
- Splenomegaly (89%)
- Bicytopenia (92%)
- Hypertriglyceridemia or hypofibrinogenemia (90%)
- Hemophagocytosis (82%)
- Ferritin >500 µg/L (94%)
- Low/absent NK cell activity (71%)
- Soluble CD25 elevation (97%)

Laboratory Findings

Cytopenias

Anemia and thrombocytopenia are seen in >80% of patients at presentation. It may occur late in patients with MAS, especially among patients with juvenile idiopathic arthritis, as they often have elevated counts before the development of MAS.

Hyperferritinemia

Macrophages are primary storage sites of ferritin, and account for very high ferritin levels in HLH. Significant hyperferritinemia is common in HLH, and has high sensitivity and specificity, especially in children. A study revealed ferritin levels >500 ng/mL, >5,000 ng/mL, and >10,000 in 93, 42, and 25 of HLH patients, respectively; the median ferritin level was 2,950 ng/mL.[14] Such high ferritin levels are rare in children and seen in the setting of iron overload syndromes, e.g., patients with multiple transfusions. Ferritin levels over 10,000 ng/mL can be seen in neonatal hemochromatosis or fulminant liver failure; however, the presence of fever, cytopenias, elevated soluble IL-2 receptor (sIL-2R), and soluble CD-163 (sCD163) help in excluding these possibilities.[15] Though a very high ferritin level is common in HLH, low ferritin (e.g., ferritin <500 ng/mL) does not exclude the same. Relatively normal ferritin may be seen during a disease flare among patients with HLH genetic syndromes, and disease activity may correlate better with elevated sIL-2R or sCD25.[15]

Liver Function and Coagulation Abnormalities

Almost all patients have liver dysfunctions, manifesting as transaminitis (>3 times the upper reference level, 50–90%), hyperbilirubinemia (3–25 mg/dL, >80%), elevated lactate dehydrogenase (LDH) (85%), hypertriglyceridemia, and coagulopathy. γ-glutamyl transferase level is elevated due to infiltration of the biliary tract by lymphocytes and macrophages. γ-glutamyl transferase and triglycerides serve as sensitive markers for monitoring disease activity.[16,17] Evidence of disseminated intravascular coagulopathy, especially elevated D-dimer, is frequently seen.

Neurologic Abnormalities

Neurologic abnormalities are observed in a third of patients and include seizures, altered mentation (including coma), and ataxia. Neurologic abnormalities may dominate the clinical picture, and/or may develop before the appearance of other signs and symptoms. About 50% of patients have cerebrospinal fluid abnormalities and may be associated with increased risk for mortality and neurologic sequelae. Patients are also at risk of developing posterior reversible encephalopathy. Magnetic resonance imaging (MRI) of the brain may show hypodense or necrotic area.

Other Abnormalities

- Respiratory abnormalities may acute respiratory distress syndrome requiring ventilator support, and death. It may be due to worsening HLH, or due to superadded infection.
- Shock requiring vasoactive drugs
- Renal dysfunction may present with hyponatremia, probably due to syndrome of inappropriate antidiuretic hormone (SIADH) mechanism. Many patients require dialysis.
- Skin manifestations include generalized rashes, erythroderma, edema, petechiae, and purpura.
- Bleeding is common and may be due to coagulopathy, thrombocytopenia, or platelet dysfunction associated with an underlying genetic defect in platelet granule processing.

Triggering Conditions

Infection, malignancy, rheumatologic and immunodeficiency syndromes are common triggers and thus associated with HLH, especially among adults. Their early identification and prompt specific therapy may improve HLH itself and may help avoid more toxic therapy (e.g., hematopoietic cell transplant). However, investigations for these conditions should not delay diagnostic evaluation for HLH and/or the initiation of anti-HLH therapy in critically ill patients.

Infections

Hemophagocytic lymphohistiocytosis is often associated with viral infections as mentioned above. HLH is reported to occur shortly after initiation of antiretroviral therapy for HIV/acquired immunodeficiency syndrome (AIDS). HLH may also occur with infections due to bacteria (e.g., *Brucella*, gram-negative bacteria, and tuberculosis), parasites (e.g., leishmaniasis and malaria), and fungi.[2,18]

Malignancy

Hemophagocytic lymphohistiocytosis is reported in association with malignancies, mostly with lymphomas and leukemias, and less commonly with solid tumors. Prognosis is poor irrespective of the patient's age at presentation.[19]

Rheumatologic Disorders/Macrophage Activation Syndrome

Hemophagocytic lymphohistiocytosis is reported to develop any time during a rheumatologic disorder, e.g., at presentation, during therapy, or in association with a concurrent infection.[20]

Immunodeficiency

In addition to inherited and acquired immunodeficiency disorders, acquired immunodeficiency is also reported to be associated with HLH, including HIV/AIDS, hematopoietic cell transplantation, kidney, and liver transplantation.[2]

EVALUATION AND DIAGNOSIS

Most patients with HLH are critically ill with cytopenias and multiorgan dysfunctions. A rapid evaluation for dysfunctions of bone marrow, liver, nervous system, and immune activation should be performed, to start treatment at the earliest once the diagnosis of HLH is strongly suspected or confirmed. The diagnostic approach is similar among infants, children, and adults.

History regarding parental consanguinity, familial disorders, antecedent infections, recurrent fevers, and pre-existing immunologic defects (e.g., HIV infection, rheumatologic disorders, and immunosuppressive medications) should be enquired from patients and family. Thorough physical examination to detect rashes, bleeding, lymphadenopathy, hepatosplenomegaly, neurologic abnormalities, and signs of other organ involvement should be performed.[2]

Initial Investigations

- Complete blood count
- Coagulation profile, including fibrinogen, and D-dimer
- Liver function tests
- Serum triglycerides (fasting)
- Serum ferritin
- Cultures of blood, urine, cerebrospinal fluid, and other relevant body fluids
- Bone marrow aspiration/biopsy for cytopenias, hemophagocytosis, infectious organisms, and malignancy
- Titers for EBV, CMV, adenovirus, and other suspected viruses

Specialized Investigations

Immunologic Profile

Immunologic and cytokine studies should be done based on the results of the initial assessment.[2,3]

- sCD25 or sIL-2R, IL-18, and CXCL9
- Tests of NK cell function/degranulation [CD107-α, also called LAMP-1 (lysosomal-associated membrane protein 1)]
- Flow cytometry for cell surface expression of perforin and granzyme B proteins
- Serum levels of soluble CD163
- Immunoglobulin levels (IgG, IgA, and IgM)
- Lymphocyte subsets to detect underlying immunodeficiency diseases

Genetic tests to detect HLH gene mutation in patients suspected to have familial HLH.

Diagnostic Criteria (Hemophagocytic Lymphohistiocytosis—2004)[2,13]

Diagnosis is established with either (A) or (B) being fulfilled.

A. Molecular diagnosis consistent with HLH
B. Presence of at least five of the following eight criteria:
   1. Fever (≥38.5°C) for ≥7 days
   2. Splenomegaly (≥3 finger breadths below left subcostal margin)
   3. Cytopenias affecting ≥2 of 3 lineages in peripheral blood
      - Hemoglobin <9 g/L
      - Platelets $<100 \times 10^9$/L
      - Absolute neutrophil count $<1 \times 10^9$/L
   4. Hypertriglyceridemia (fasting triglycerides ≥265 mg/dL) and/or hypofibrinogenemia (fibrinogen ≤1.5 g/L)
   5. Hemophagocytosis in the bone marrow/spleen/lymph node
   6. Low or absent NK cell activity (according to the local laboratory reference)
   7. Ferritin ≥500 μg/L
   8. sCD25 (sIL-2 receptor) ≥2,400 U/mL

Differential Diagnosis

- Sepsis
- Liver disease/liver failure
- Multiple organ dysfunction syndrome
- Encephalitis
- Autoimmune lymphoproliferative syndrome (ALPS)
- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- Kawasaki disease
- Cytophagic histiocytic panniculitis
- Thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), or drug-induced thrombotic microangiopathy
- Transfusion-associated graft-versus-host disease (ta-GVHD)

MANAGEMENT

Clinically Stable Patients

Clinically stable patients with a known trigger may respond to treatment of the triggering condition. Infection should be

diagnosed rapidly, and appropriate empiric antimicrobial therapy should be initiated depending on the suspected organism.[21] For EBV infection, rituximab (375 mg/m^2 weekly for 1–4 weeks depending on the rapidity with which EBV DNA level drops) or intravenous immunoglobulin may be initiated. Some patients with a rheumatological condition associated with MAS will respond to disease-specific therapy alone.

Critically Ill/Deteriorating Patients

Patients with deteriorating organ functions should be treated promptly with adequate supportive and HLH-specific treatment. Treatment should not be delayed while awaiting genetic or specialized immunologic testing. Supportive care includes close monitoring of organ dysfunctions, respiratory and circulatory support, appropriate transfusions, prevention and treatment of opportunistic infections.

Specific Therapy

HLH-2004 protocol included etoposide plus dexamethasone regimen used in HLH-94 but incorporated cyclosporine as part of initial therapy. The efficacy of etoposide and dexamethasone is proven, however, the benefit of incorporating cyclosporine as part of initial therapy is not clear.[13,21]

Dexamethasone is the preferred corticosteroid as it crosses the blood–brain barrier. Dexamethasone is given intravenously or orally and tapered over 8-week induction:

- *Weeks 1 and 2*: 10 mg/m^2 daily
- *Weeks 3 and 4*: 5 mg/m^2 daily
- *Weeks 5 and 6*: 2.5 mg/m^2 daily
- *Week 7*: 1.25 mg/m^2 daily
- *Week 8*: Taper dose to zero

Etoposide at a dose of 150 mg/m^2 for adults and 5 mg/kg for children weighing <10 kg. It is given twice weekly for the first 2 weeks, followed by once weekly for 8 weeks.

Central nervous system (CNS) involvement, based on clinical assessment, cerebrospinal fluid analysis, and MRI of the brain, is treated with weekly intrathecal chemotherapy with a combination of methotrexate and hydrocortisone. Doses are as follows:

- *<1 year*: Methotrexate 6 mg and hydrocortisone 8 mg
- *1–2 years*: Methotrexate 8 mg and hydrocortisone 10 mg
- *2–3 years*: Methotrexate 10 mg and hydrocortisone 12 mg
- *>3 years*: Methotrexate 12 mg and hydrocortisone 15 mg

Intrathecal therapy is continued for at least 1 week after resolution of CNS involvement, as monitored by clinical assessment and CSF analyses.

Allogeneic Hematopoietic Cell Transplant

Hematopoietic cell transplant is indicated in patients with the following underlying conditions for their high mortality and high risk of relapse:[22,23]

- Homozygous/compound heterozygous HLH gene mutations
- Lack of response to chemotherapy
- CNS involvement
- Underlying hematologic malignancy

PROGNOSIS

Without therapy, patients with HLH have high mortality.[24,25] Following conditions predict poor prognosis:

- Infants <6 months, and older age
- Higher level of serum ferritin and its slower fall with therapy
- Neurologic involvement
- Underlying malignancy
- Familial disease without allogeneic hematopoietic cell transplant

CONCLUSION

Hemophagocytic lymphohistiocytosis is a clinical syndrome characterized by aggressive and life-threatening severe generalized immune system activation in the setting of immune dysfunction. Hypersecretion of cytokines and invasion of organs with overactive immune cells results in multiple organ failures. Delayed diagnosis is often the greatest barrier to treatment. Survival may be improved dramatically with HLH-specific therapy. HLH-2004 diagnostic criteria may be used to increase clinical suspicion and confirm the diagnosis. Apart from supportive therapy, management includes chemotherapy and allogeneic hematopoietic cell transplant. The prognosis of HLH among adult patients is poor compared to children, due to a lack of awareness among physicians. The high degree of clinical suspicion in patients with multiorgan failure, early diagnosis, and prompt treatment are the keys to improved outcomes.

REFERENCES

1. Filipovich AH. Hemophagocytic lymphohistiocytosis and other hemophagocytic disorders. Immunol Allergy Clin North Am. 2008;28(2):293-313.
2. Kim YR, Kim DY. Current status of the diagnosis and treatment of hemophagocytic lymphohistiocytosis in adults. Blood Res. 2021;56(S1):S17-25.
3. Jordan MB, Allen CE, Greenberg J, Henry M, Hermiston ML, Kumar A, et al. Challenges in the diagnosis of hemophagocytic lymphohistiocytosis: Recommendations from the North American Consortium for Histiocytosis (NACHO). Pediatr Blood Cancer. 2019;66(11):e27929.
4. Filipovich A, McClain K, Grom A. Histiocytic disorders: recent insights into pathophysiology and practical guidelines. Biol Blood Marrow Transplant. 2010;16(1 Suppl):S82.
5. Pachlopnik Schmid J, Côte M, Ménager MM, Burgess A, Nehme N, Ménasché G, et al. Inherited defects in lymphocyte cytotoxic activity. Immunol Rev. 2010;235(1):10-23.

6. Risma K, Jordan MB. Hemophagocytic lymphohistiocytosis: updates and evolving concepts. Curr Opin Pediatr. 2012; 24(1):9-15.
7. Ishii E, Ueda I, Shirakawa R, Yamamoto K, Horiuchi H, Ohga S, et al. Genetic subtypes of familial hemophagocytic lymphohistiocytosis: correlations with clinical features and cytotoxic T lymphocyte/natural killer cell functions. Blood. 2005;105(9):3442-8.
8. Dalal BI, Vakil AP, Khare NS, Wang SY, Richards MJ, Chen LYC. Abnormalities of the lymphocyte subsets and their immunophenotype, and their prognostic significance in adult patients with hemophagocytic lymphohistiocytosis. Ann Hematol. 2015;94(7):1111-7.
9. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. Cell. 2010;140(6):805-20.
10. Behrens EM, Canna SW, Slade K, Rao S, Kreiger PA, Paessler M, et al. Repeated TLR9 stimulation results in macrophage activation syndrome-like disease in mice. J Clin Invest. 2011;121(6):2264-77.
11. Ivashkiv LB, Donlin LT. Regulation of type I interferon responses. Nat Rev Immunol. 2014;14(1):36-49.
12. Aricò M, Danesino C, Pende D, Moretta L. Pathogenesis of haemophagocytic lymphohistiocytosis. Br J Haematol. 2001;114(4):761-9.
13. Bergsten E, Horne A, Aricó M, Astigarraga I, Egeler RM, Filipovich AH, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. Blood. 2017;130(25):2728-38.
14. Trottestam H, Horne A, Aricò M, Egeler RM, Filipovich AH, Gadner H, et al. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. Blood. 2011;118(17):4577-84.
15. Wu JR, Yuan LX, Ma ZG, Chen XX, Gu L, Gao J. GDF15-mediated upregulation of ferroportin plays a key role in the development of hyperferritinemia in children with hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2013;60(6):940-5.
16. Stapp J, Wilkerson S, Stewart D, Coventry S, Mo JQ, Bove KE. Fulminant neonatal liver failure in siblings: probable congenital hemophagocytic lymphohistiocytosis. Pediatr Dev Pathol. 2006;9(3):239-44.
17. Okamoto M, Yamaguchi H, Isobe Y, Yokose N, Mizuki T, Tajika K, et al. Analysis of triglyceride value in the diagnosis and treatment response of secondary hemophagocytic syndrome. Intern Med. 2009;48(10):775-81.
18. Brito-Zerón P, Bosch X, Pérez-de-Lis M, Pérez-Álvarez R, Fraile G, Gheitasi H, et al. Infection is the major trigger of hemophagocytic syndrome in adult patients treated with biological therapies. Semin Arthritis Rheum. 2016; 45(4):391-9.
19. Strenger V, Merth G, Lackner H, Aberle SW, Kessler HH, Seidel MG, et al. Malignancy and chemotherapy induced haemophagocytic lymphohistiocytosis in children and adolescents-a single centre experience of 20 years. Ann Hematol. 2018;97(6):989-98.
20. Davì S, Minoia F, Pistorio A, Horne A, Consolaro A, Rosina S, et al. Performance of current guidelines for diagnosis of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. Arthritis Rheumatol. 2014;66(10): 2871-80.
21. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. Blood. 2011;118(15):4041-52.
22. Hartz B, Marsh R, Rao K, Henter JI, Jordan M, Filipovich L, et al. The minimum required level of donor chimerism in hereditary hemophagocytic lymphohistiocytosis. Blood. 2016;127(25):3281-90.
23. Cooper N, Rao K, Goulden N, Webb D, Amrolia P, Veys P. The use of reduced-intensity stem cell transplantation in haemophagocytic lymphohistiocytosis and Langerhans cell histiocytosis. Bone Marrow Transplant. 2008;42 Suppl 2:S47.
24. Otrock ZK, Eby CS. Clinical characteristics, prognostic factors, and outcomes of adult patients with hemophagocytic lymphohistiocytosis. Am J Hematol. 2015;90(3):220-4.
25. Henter JI, Elinder G, Söder O, Ost A. Incidence in Sweden and clinical features of familial hemophagocytic lymphohistiocytosis. Acta Paediatr Scand. 1991;80(4):428-35.

CHAPTER 73

Metabolic Crisis in Oncology Patients

Rakesh Garg, Priyanka Singhani, Sulagna Bhattacharjee

INTRODUCTION

Cancer patients undergo various modalities of treatment including surgery, chemotherapy, and radiotherapy alone or in combination. Crises may be seen in these cancer patients requiring acute interventions in critical care setup. These crises may be related to metabolic, neurological, cardiorespiratory conditions in these patients. Some of these metabolic crises may be life-threatening or functional capacity. Timely recognition, appropriate assessment, and management are paramount for an optimal outcome. In this chapter, we discuss some of the important metabolic crises in cancer patients in intensive care unit (ICU) settings and their management.

TUMOR LYSIS SYNDROME

Tumor lysis syndrome (TLS) is a clinical condition seen in cancer patients due to metabolic and electrolyte derangements as a result of cancer destruction in response to chemotherapy. It may at times may be life-threatening and increases various morbidities in cancer patients, even to the extent of mortality. It occurs in the context of chemotherapy of high-grade malignancies such as Burkitt lymphoma and acute myeloid leukemia (AML).[1] These malignancies are at increased risk of TLS due to their large tumor bulk, destructive potential in response to chemotherapy, and have a high proliferative potential.

Tumor lysis syndrome is defined based on clinical and laboratory criteria (Cairo and Bishop's classification)[2] **(Table 1)**.

The laboratory diagnosis of TLS requires confirmation of two or more metabolic abnormalities (hyperuricemia, hyperkalemia, hypocalcemia, and hyperphosphatemia) within 3 days before or up to 7 days after starting chemotherapy initiation of therapy. The clinical diagnosis requires in addition to laboratory findings, the presence of increased creatinine levels, seizures, dysrhythmias, and death. Any symptomatic hypocalcemia is also considered as clinical TLS.

TABLE 1: Cairo and Bishop's definition of tumor lysis syndrome (TLS).

Metabolic abnormality	*Laboratory criteria*	*Clinical criteria*
Hyperuricemia	Uric acid >8 mg/dL or 25% rise from baseline	
Hyperphosphatemia	Phosphorus >4.5 mg/dL or 25% rise from baseline	
Hypocalcemia	Calcium <7 mg/dL or 25% fall from baseline	Seizures, neuropathy, muscle twitching, and carpopedal spasm
Hyperkalemia	Potassium >6 mmol/L or 25% rise from baseline	Sudden cardiac death, electrophysiological disturbances including lethal arrhythmias

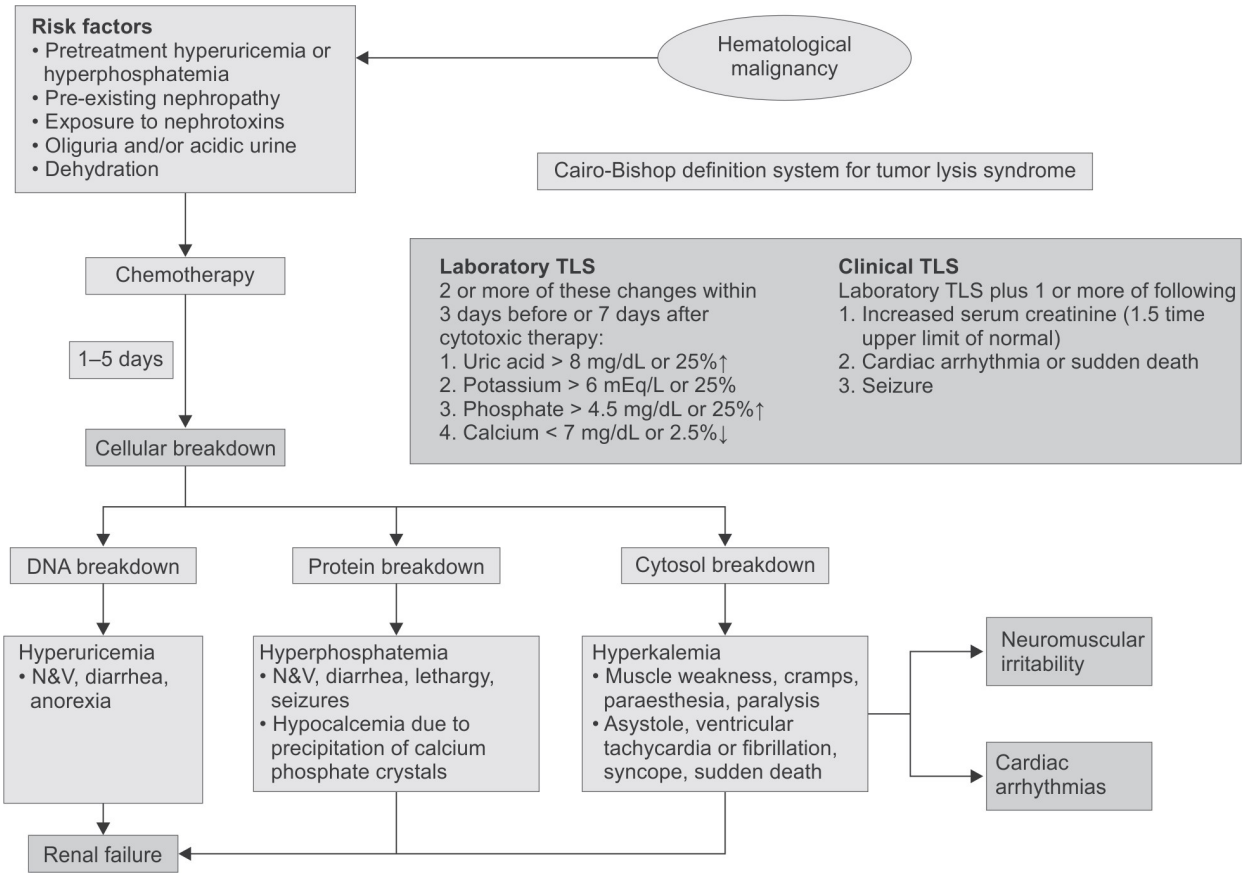
Pathophysiology

The pathophysiology of TLS involves action and consequences at multiple cellular and organ levels **(Flowchart 1)**. Cell death releases intracellular contents into the blood. This causes levels of uric acid, potassium, and phosphorus to rise at a rate higher than kidneys can remove them. It overwhelms the body's homeostasis and leads to the accumulation of these potentially toxic metabolites in the body. This leads to metabolic and electrolyte derangements which are frequently fatal. Hyperkalemia may lead to dysrhythmias. Hyperphosphatemia can lead to hypocalcemia, numbness, paresthesias, and tetany. The deposition of calcium crystals affects the functioning of various organ systems, especially kidneys, heart, brain, muscles, and gastrointestinal tract. This may have an impact on various organ systems, seen leading to multiorgan failure.

Symptoms

The manifestation of TLS varies with the severity and the organ involvement. The usual symptoms include nausea, vomiting, loss of appetite, fatigue, reduced urine output,

Flowchart 1: Pathophysiology of tumor lysis syndrome (TLS) and Cairo–Bishop definition of TLS.



(DNA: deoxyribonucleic acid; N&V: nausea and vomiting)

neurological symptoms (such as neural involvement leading to decrease sensation, hallucinations, and convulsions), muscle cramps, spasms, heart palpitations, renal failure, and death, if left untreated.

Outcome

Tumor lysis syndrome if not recognized well in time and can have a worse prognosis.[1] Mortality rates can vary from 21 to 32%.[3-5] The most important and independent predictor of outcome in TLS is the development of acute kidney injury (AKI). AKI occurs primarily due to the deposition of calcium and urate crystals in renal tubules, thereby leading to toxicity.

Prevention

High-risk patients should be pre-emptively identified for the occurrence of TLS and all preventive measures taken to prevent TLS in these cancer patients. Preventing the development of electrolyte abnormalities and renal failure before starting chemo or radiotherapy significantly reduces both the risk of developing TLS and the severity of the disease. Early identification of these complications aids in prompt management. Serum electrolytes, blood urea nitrogen, creatinine levels, uric acid levels, calcium, and phosphorus should be measured regularly at an appropriate time coinciding with their derangements. All the assessment and laboratory measurements should be made at the administration of chemotherapy, then every 4–6 hours for 2–3 days.[6]

Prevention and Treatment of Tumor Lysis Syndrome

The mainstay of management of TLS is prompt identification of causes and risk factors predisposing to TLS, appropriate prophylactic measures, intensive monitoring of electrolytes and input–output, and initiation of active treatment measures as early as possible. Patients may require admission to ICU. The various modalities for its treatment include the following mentioned below.

Aggressive Hydration and Diuresis

Aggressive hydration and diuresis form the mainstay of prevention and management of TLS. Intravenous fluids should be given for up to 2–3 L per day to achieve a urine output of 100–200 mL/hr. In patients with adequate renal function, the output should be equal to the input. Daily and intensive monitoring of input and output ensures adequate hydration. Loop diuretics and mannitol can also be used to

obtain a good urine output in patients with compromised renal function. This helps in preventing urate nephropathy.

Allopurinol

Allopurinol is a xanthine oxidase inhibitor, which prevents the conversion of xanthine and hypoxanthine to uric acid. Thus, it reduces the amount of newly formed uric acid without having any influence on already present uric acid. Administration of allopurinol before the onset of chemotherapy reduces the incidence of AKI subsequently.[7] Intravenous formulation is also available for patients with reduced oral intake. The use of allopurinol leads to the accumulation of xanthine, which itself is a cause of renal dysfunction.

Rasburicase (Recombinant Uric Acid Oxidase)

Rasburicase is a recombinant enzyme derived from *Aspergillus flavus*. It promotes the formation of allantoin from uric acid. Allantoin has 10 times higher solubility in urine as compared to uric acid. It has superior efficacy in both treatment and prevention of TLS as compared to allopurinol (29, 30, and 37 of cancer network journal). It is administered in a dosage of 0.15–0.2 mg/kg in 50 mL saline given slowly over 30 minutes. Even a single dose of rasburicase is also considered quite effective in reducing uric acid levels in patients at risk of developing TLS.[8-10] However, treatment with rasburicase has its problems.

Urinary Alkalinization

Traditionally, soda bicarbonate has also been used to increase the excretion of uric acid in urine. It helps in increasing the alkalinity of urine. However, excess levels of purine metabolites may get accumulated in renal tubules leading to obstructive uropathy. Hence, their use is currently not recommended.

Dialysis

Dialysis is often indicated in patients with worsening renal function, severe metabolic derangements unresponsive to medical management. Intermittent and continuous modality is preferred over peritoneal dialysis as uric acid and solute clearance are superior. Dialysis can reduce uric acid levels to <10–12 mg/dL. Uric acid clearance is reduced by 50% in 6-hour sessions. Uric acid clearance is 70–100 mL/hr.

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE

Syndrome of inappropriate antidiuretic hormone (SIADH) secretion is the most common cause of hyponatremia in cancer patients.[11,12] The diagnostic criteria for SIADH are presented in **Box 1**.[13]

BOX 1: Diagnostic criteria for syndrome of inappropriate antidiuretic hormone (SIADH).[13]

Essential criteria:
- Decreased serum osmolality (<275 mOsm/kg)
- Urine osmolality >100 mOsm/kg
- Clinically euvolemic
- Urine sodium >30 mEq/L on a normal daily sodium intake
- Normal thyroid and adrenal function
- No recent use of diuretics

Supplementary criteria:
- Plasma uric acid <4 mg/dL
- Blood urea nitrogen <10 mg/dL
- Failure to correct hyponatremia (or worsening hyponatremia) after 1–2 L of 0.9% saline
- Correction of hyponatremia with fluid restriction
- An abnormal result on the test of water load (<80% excretion of 20 mL water/kg body weight throughout 4 hours) or inadequate urinary dilution (>100 mOsm/kg H_2O)
- Plasma arginine vasopressin level elevated relative to plasma osmolality

TABLE 2: Anticancer drugs known to cause syndrome of inappropriate antidiuretic hormone (SIADH).[14,15]

Mechanism	*Drugs*
Increased hypothalamic AVP production	• Vinca alkaloids (vincristine and vinblastine) • Platinum compounds (cisplatin and carboplatin) • Alkylating agents (cyclophosphamide, ifosfamide, and melphalan) • Others (methotrexate, interferon γ, α) • Palliative (antipsychotics, antidepressants, and antiepileptics)
Potentiation of AVP secretion	• Anticancer-alkylating agents • NSAIDs, antiepileptics, antidiabetic agents, targeted therapies such as tyrosine kinase inhibitors

(AVP: arginine–vasopressin; NSAID: nonsteroidal anti-inflammatory drug)

Etiology

The etiology of SIADH in malignancy is multifactorial. It may be associated with one or more of the following factors:[12]

- Ectopic vasopressin [antidiuretic hormone (ADH)] secretion
- Antineoplastic agents (chemotherapy, targeted drugs) **(Table 2)**.
- Other medications are antidepressants or antiepileptics.
- Pulmonary infections due to therapy-related immunosuppression, postobstructive, or malnourishment
- Central nervous system and pulmonary metastasis can interdependently cause SIADH.
- Pain or nausea caused by the tumor or as a side effect of therapy can also lead to SIADH.

Malignancy is reported to cause 73% of the cases, while 27% of cases result from other causes. Small cell lung cancer

is the most common malignancy associated with SIADH, with 10–15% of patients presenting with hyponatremia, and elevated plasma vasopressin in up to 70% of patients. Adenocarcinoma, squamous cell, and undifferentiated lung cancers have also been associated with SIADH. Other cancers include colon, lymphoma, breast, and pancreatic cancers.[12]

Classification of Syndrome of Inappropriate Antidiuretic Hormone

Syndrome of inappropriate antidiuretic hormone has been classified into four types (A to D) using plasma vasopressin levels. Type A characterized by erratic vasopressin secretion, type B by a reset osmostat, type C is a constant nonsuppressible leak, and type D is increased sensitivity to vasopressin or presence of vasopressin substance. Small cell lung carcinoma (SCLC) patients were found to be associated with not just ectopic vasopressin secretion but all other types of SIADH. Copeptin, a C-terminal peptide of the precursor vasopressin molecule, has been used as a surrogate marker of vasopressin, for its correlation with vasopressin levels and its ease of measurement. Analyzing copeptin levels and plasma osmolality, type A (ectopic ADH secretion) and type C (low-level ectopic ADH secretion) are most associated with malignancy, with 80% of type A associated with lung cancer and 32% of type C with solid tumors.[16]

Management of Syndrome of Inappropriate Antidiuretic Hormone in Cancer Patients (Flowchart 2)

Treatment of the underlying cause of SIADH may or may not be possible in the case of malignancy. Hyponatremia can be refractory to treatment due to:

- Incurable cancer or ongoing antineoplastic drug **(Table 3)**
- Poor intake and gastrointestinal losses
- Use of isotonic/hypotonic fluids along with chemotherapy

Hyponatremia can be classified based on:

- *Symptoms*: Asymptomatic, mild (nausea and headache), moderate (lethargy, confusion, and disorientation), and severe (seizures, stupor, and coma)
- *Onset*: Acute (<48 hours) or chronic (≥48 hours)
- *Sodium levels (mEq/L)*: Mild (130–135), moderate (120–129), and severe (<120)

Therapeutic Options

The various management strategies include the following **(Flowchart 3)**:[16,17]

- Fluid restriction is considered the first line for chronic asymptomatic hyponatremia due to SIADH. However, 60–70% of patients with cancer-associated SIADH do not respond to fluid restriction alone. Fluid restriction may not be effective as:
  - Urine Na >130 mEq/L and urine osmolality >500 mOsm/kg have very high specificity (91.3 and 87%, respectively) to predict nonresponsiveness of SIADH patients to fluid restriction. Urine to plasma electrolyte ratio >1 is also another strong negative predictor.
  - Many patients may not tolerate fluid restriction.
- *Salt and loop diuretics*: Lop diuretics cause free water excretion by interfering with the medullary concentration gradient. Salt tablets are given to replace the salt losses. A recently published randomized controlled trial revealed that furosemide with salt tablets (NaCl 6 g/day) along with fluid restriction is not significantly beneficial to Fr alone. AKI has been reported with the use of this regimen. Salt tablets alone have also been shown to cause a mild but significant elevation of serum sodium levels in SIADH.

Flowchart 2: Steps to diagnose syndrome of inappropriate antidiuretic hormone (SIADH).

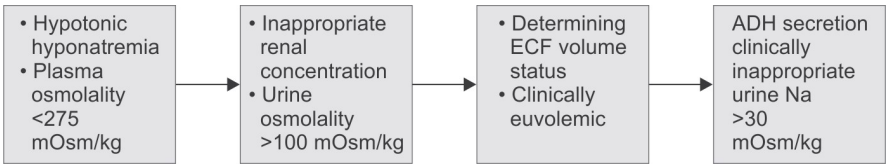
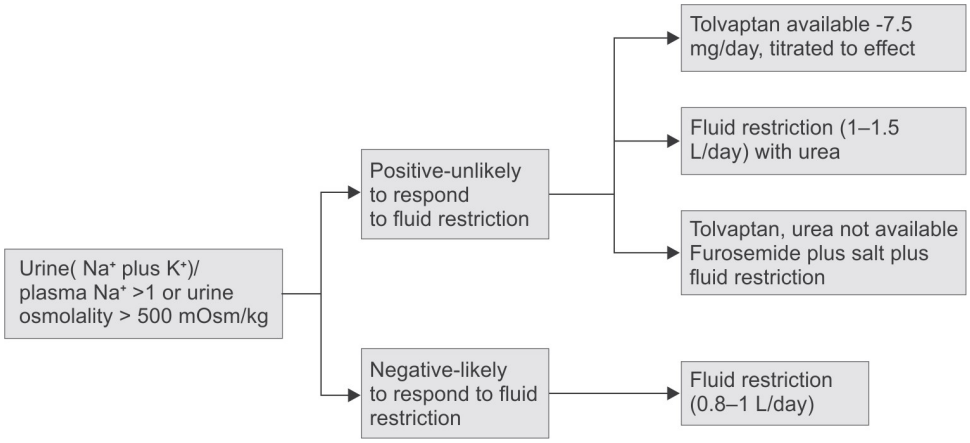


TABLE 3: Treatment of syndrome of inappropriate antidiuretic hormone (SIADH) in cancer patients.[6,7]

Severity	*Therapy*
Acute and/severe hyponatremia (clinically severe or serum Na <120 mEq/L	• 3% hypertonic saline bolus 100 mL, repeated till symptoms persist • ↑ serum Na to 4–6 mEq/L in initial 1–2 hours • Slower correction over next 48 hours • ↑ up to 8–10 mEq/L over 24 hours, 18 mEq/L over 48 hours
Mild/moderate hyponatremia (serum Na >120 mEq/L)	• Water restriction up to 800–1,000 mL/day • V_2 antagonist • Loop diuretics and salt tablets • Urea

Flowchart 3: Algorithm for treating cancer-associated syndrome of inappropriate antidiuretic hormone (SIADH).[16]



- *Vaptans*: Vaptans such as tolvaptan and conivaptan are vasopressin receptor type 2 antagonists, which increase free water excretion through the collecting duct. The SALT 1 and SALT 2 trials have demonstrated the efficacy and safety of tolvaptan in hyponatremia, including malignancy-related hyponatremia. Data from a small, randomized placebo-controlled trial (N = 48) as well as small observational studies suggest that tolvaptan is an effective therapy in this scenario. Major side effects such as liver injury and rapid correction of serum sodium, causing osmotic demyelination syndrome (ODS) and minor like polydipsia, dry mouth, and polyuria, remain. The United States Food and Drug Administration (US FDA) has restricted its use for not >30 days. Starting tolvaptan at a low dose with gradual titration can reduce the chances of ODS.[11]
- *Urea*: It increases urinary solute load and promotes free water excretion. Usual dose is 0.25–0.5 g/kg. Side effects include nausea and distaste. Multiple case series have reported an increase of serum sodium and normonatremia with urea. ODS has not been reported with the use of urea.

Prognosis

Patients with malignancy-associated SIADH (primary paraneoplastic or tumor-related) had lower short-term serum sodium levels, and lower rates of sodium correction had significantly shorter median survival and survival rates than SIADH due to other etiologies. Thus, malignancy-associated SIADH may be used as a prognostic marker to assist clinical decision-making.[12]

Summary

Being the most common cause of hyponatremia in malignancy, SIADH has important prognostic implications. Early detection of the type and etiology, and appropriate management can shorten hospitalization, improve quality of life and survival.

URIC ACID NEPHROPATHY

Acute uric acid nephropathy (UAN) typically results in acute oliguric or anuric renal failure due to uric acid crystals deposition in the distal and collecting tubules. This is commonly associated with rapid cell turnover in malignancies such as leukemia, lymphoma, myeloproliferative disorders, and less frequently with seizures or treatment of solid tumors. Chemo- or radiotherapy-induced rapid cell lysis leads to the release of nucleic acid which is converted to uric acid. It is also seen in the condition of TLS which may be seen after chemotherapy for rapidly growing tumors.

Diagnosis

Uric acid nephropathy has no specific symptoms. Flank pain can occur in the case of renal pelvic or ureteral obstruction. Diagnosis is made in the setting of acute renal failure with significant hyperuricemia that is serum or plasma urate >15 mg/dL. This contrasts with other causes of AKI where the urate level is usually <12 mg/dL, except for prerenal causes which can have significant proximal tubular reabsorption of urate.[18] Urine analysis may show multiple uric acid crystals or absent crystals in case no output is generated from obstructed nephrons. Uric acid to creatinine ratio in a random urine specimen if >1 signifies UAN, as other forms of AKI have a usual ratio of 0.60–0.75.[19]

Prevention and Treatment[1]

Prevention is the key in UAN. Strategies in high-risk patients include:

- Hydration to expand intravascular volume
- Use of recombinant urate oxidase (rasburicase) to convert urate to more water-soluble allantoin) or a xanthine oxidase inhibitor (allopurinol or febuxostat) to reduce the production of urate. It should be started several days before chemotherapy in high-risk cases.

Therapy after the Onset of Uric Acid Nephropathy

- Intravenous fluids with loop diuretics to flush out urate crystals
- Allopurinol, febuxostat, or rasburicase
- Hemodialysis to remove excess urate in persistently oliguric or anuric patients

Sodium bicarbonate should be avoided if not associated with metabolic acidosis as it can cause precipitation of calcium phosphate.

HYPERCALCEMIA OF MALIGNANCY

Hypercalcemia is one of the most frequent metabolic emergencies seen in cancer patients. Hypercalcemia is seen in cancer patients, such as patients having multiple myelomas, lung cancer, breast, kidney, and head and neck cancers.[20] Most commonly it is attributed to raised levels of parathyroid hormone-related protein. In patients with calcium levels between 10 and 14 mg/dL, nonspecific clinical features such as nausea, vomiting, bone pain, and fatigue are seen. Gastrointestinal, renal, and neurologic abnormalities are one of the earliest symptoms of hypercalcemia seen in cancer patients. When serum calcium levels increase to >14 mg/dL, neurological symptoms such as confusion, lethargy, and even coma are seen. Medications such as thiazide diuretics, lithium, vitamin D, and antiestrogens, which precipitate hypercalcemia should be discontinued. The treatment includes fluid resuscitation and bisphosphonates **(Table 4)**.

ELECTROLYTE DISORDERS IN CANCER PATIENTS

Electrolyte imbalances are seen in cancer patients and are related to variable diseases and treatment-related factors.[21] The usual alterations include imbalances with sodium, potassium, calcium, and magnesium body levels. Many times, these imbalances remain asymptomatic; however, awareness of these possible alterations should be kept in mind while treating cancer patients. These abnormalities can be life-threatening at times, increase morbidity, delay oncology treatment, and negatively impact overall outcomes. These disorders require timely identification and optimal management.

The underlying etiologies for such imbalances are related to treatment-related toxicity, paraneoplastic syndrome of inappropriate antidiuresis, TLS, and nutrition-related concerns. Usually, the electrolyte imbalances remain multifactorial and get precipitated by some acute event such as infection and drug toxicity.

The treatment requires understanding the underlying pathophysiology for such imbalances and prompt management with a high index of suspicion as early diagnosis may be missed. Treatment of underlying precipitating factors should also be considered while managing these abnormalities.

Glucose Disorder

The imbalance of glucose levels is seen in cancer patients because of variable etiology.[22-24] Certain cancer such as multiple myeloma, non-Hodgkin lymphoma, and Hodgkin disease have been observed to have manifestations of hypoglycemia primarily related to the production of insulin-like substances by cancer cells. Also, other mechanisms include the production of autoantibodies to insulin or its receptor, insulin-like growth factor-1 (IGF-1) tumor secretion by the cancer cells.[23,24] Also, increase glucose consumption with decreased nutritional intake also leads to episodes of hypoglycemia. The treatment of hypoglycemia is primarily aimed at treating the underlying condition, monitoring

TABLE 4: Management strategy of hypercalcemia in malignancy.

Intervention	*Dose*	*Adverse effects*
Hydration with isotonic saline	• Initial 1–2 L bolus • Then, 200–500 mL/hr (maintain a urine output of 100–150 mL/hr)	Fluid overload over heart, heart failure
Furosemide (diuretics)	20–40 mg intravenously (up to 120 mg) every 2–4 hourly	Dehydration, hypokalemia
Pamidronate (bisphosphonate)	• 60–90 mg in 100 mL of saline (or 5% dextrose) intravenously over 2 hours • To be repeated every 3–4 weeks	Transient flu-like symptoms like aches, chills, and fever, and renal failure (raised creatinine)
Zoledronic acid (bisphosphonate)	• 4 mg in 50 mL saline (or 5% dextrose) intravenously over 15 minutes • To be repeated every 3–4 weeks	
Clodronate (bisphosphonate)	1,500 mg intravenous over 2 hours	
Prednisolone (corticosteroids)	20–30 mg 12 hourly	
Calcitonin	4 units/kg every 12 hourly for 4–6 doses (IV or SC or IM)	
Hemodialysis	In refractory hypercalcemia	

blood sugar levels and sugar supplementations. At times, with chronic recurrent hypoglycemia, the patient may require steroids, glucagon, and even octreotide, diazoxide, or growth hormone.

Hyperglycemia may also be seen and lead to sequelae of its acute and chronic complications including diabetic ketoacidosis and remains a crisis.[24] The underlying mechanism includes related to the tumor, use of steroids, immunosuppression, infections, etc., even well-controlled diabetic patients with cancer may have worsening of sugar status during intercurrent infections and stressful situations. This further can lead to other metabolic disturbances such as metabolic acidosis. The usual therapy includes optimal hydration, optimization of electrolyte imbalance, and insulin replacement.

CONCLUSION

Cancer patients may present with various clinical manifestations at various stages of the disease and may be related to the disease itself or related to cancer therapy. Immediate recognition and prompt management of life-threatening metabolic emergencies are important to improve the patients' outcomes and provide a better quality of life to cancer patients. This ensures the return of definitive therapy from an oncology point of view.

REFERENCES

1. Matuszkiewicz-Rowinska J, Malyszko J. Prevention and treatment of tumor lysis syndrome in the era of onco-nephrology progress. Kidney Blood Press Res 2020;45(5):645-60.
2. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol. 2004;127(1):3-11.
3. Montesinos P, Lorenzo I, Martín G, Sanz J, Pérez-Sirvent ML, Martínez D, et al. Tumor lysis syndrome in patients with acute myeloid leukemia: identification of risk factors and development of a predictive model. Haematologica. 2008;93(1):67-74.
4. Durani U, Shah ND, Go RS. In-hospital outcomes of tumor lysis syndrome: A population-based study using the national inpatient sample. Oncologist. 2017;22(12):1506-9.
5. Darmon M, Guichard I, Vincent F, Schlemmer B, Azoulay E. Prognostic significance of acute renal injury in acute tumor lysis syndrome. Leuk Lymphoma. 2010;51(2):221-7.
6. Pession A, Barbieri E. Treatment and prevention of tumor lysis syndrome in children. Experience of Associazione Italiana Ematologia Oncologia Pediatrica. Contrib Nephrol. 2005;147:80-92.
7. Smalley RV, Guaspari A, Haase-Statz S, Anderson SA, Cederberg D, Hohneker JA. Allopurinol: Intravenous use for prevention and treatment of hyperuricemia J Clin Oncol. 2000;18(8):1758-63.
8. Bosly A, Sonet A, Pinkerton CR, McCowage G, Bron D, Sanz MA, et al. Rasburicase (recombinant urate oxidase) for the management of hyperuricemia in patients with cancer: report of an international compassionate use study. Cancer. 2003;98(5):1048-54.
9. Coiffier B, Mounier N, Bologna S, Fermé C, Tilly H, Sonet A, et al. Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma: results of the GRAAL1 (Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma) study. J Clin Oncol. 2003;21(23):4402-6.
10. Pui CH, Mahmoud HH, Wiley JM, Woods GM, Leverger G, Camitta B, et al. Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients with leukemia or lymphoma. J Clin Oncol. 2001;19(3):697-704.
11. Kitchlu A, Rosner MH. Hyponatremia in patients with cancer. Curr Opin Nephrol Hypertens. 2019;28(5):433-40.
12. Goldvaser H, Rozen-Zvi B, Yerushalmi R, Gafter-Gvili A, Lahav M, Shepshelovich D. Malignancy associated SIADH: characterization and clinical implications. Acta Oncol. 2016;55(9-10):1190-5.
13. Rosner MH, Dalkin AC. Electrolyte disorders associated with cancer. Adv Chronic Kidney Dis. 2014;21(1):7-17.
14. Castillo JJ, Vincent M, Justice E. Diagnosis and management of hyponatremia in cancer patients. Oncologist. 2012;17(6):756-65.
15. Verzicco I, Regolisti G, Quaini F, Bocchi P, Brusasco I, Ferrari M, et al. Electrolyte disorders induced by antineoplastic drugs. Front Oncol. 2020;10:779.
16. Workeneh BT, Jhaveri KD, Rondon-Berrios H. Hyponatremia in the cancer patient. Kidney Int. 2020;98(4):870-82.
17. De las Peñas R, Escobar Y, Henao F, Blasco A, Rodríguez CA; Spanish Society for Medical Oncology. SEOM guidelines on hydroelectrolytic disorders. Clin Transl Oncol 2014;16(12):1051-9.
18. Feinstein EI, Quion-Verde H, Kaptein EM, Massry SG. Severe hyperuricemia in patients with volume depletion. Am J Nephrol. 1984;4(2):77-80.
19. Kelton J, Kelley WN, Holmes EW. A rapid method for the diagnosis of acute uric acid nephropathy. Arch Intern Med. 1978;138(4):612-5.
20. Cervantes A, Chirivella I. Oncological emergencies. Ann Oncol. 2004;15:299-306.
21. Beradi R, Torniai M, Lenci E, Pecci F, Morgese F, Rinaldi S. Electrolyte disorders in cancer patients: a systematic review. Cancer Metastasis Treat. 2019;5:79.
22. Nauck MA, Reinecke M, Perren A, Frystyk J, Berishvili G, Zwimpfer C, et al. Hypoglycemia due to paraneoplastic secretion of insulin-like growth factor-I in a patient with metastasizing large-cell carcinoma of the lung. J Clin Endocrinol Metab. 2007;92(5):1600-5.
23. Bodnar TW, Acevedo MJ, Pietropaolo M. Management of nonislet-cell tumor hypoglycemia: a clinical review. J Clin Endocrinol Metab. 2014;99:713-22.
24. Beltran G. Diabetic emergencies: new strategies for an old disease. Emerg Med Pract. 2014;16(6):1-19.

CHAPTER 74

Intelligent Interpretation of the Hemogram

Farhad Kapadia, Ritika Sharma, Jagannath Jare

INTRODUCTION

The complete blood count (CBC) or hemogram is a basic test that gives useful information to an intensivist. When interpreting a CBC, the first question the intensivist should ask herself or himself is whether one is dealing with a patient with a pre-existing hematological problem, or if the patient previously was normal. The next step is to reach an appropriate diagnosis and make appropriate therapeutic decisions.

We will first discuss the hematologist's approach to a pre-existing disease and then the intensivist's approach to the critical illness.

HEMATOLOGISTS APPROACH

For most intensive care unit (ICU) patients, the critical illness [e.g., sepsis with systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS)] will alter the CBC. Many of these patients could have a pre-existing hematological condition that could be missed. *In this situation, it is best to analyze the first CBC at the time of admission, or the most recent CBC, before the current illness.* A systematic and careful analysis can give a working diagnosis that can be confirmed with appropriate tests.

Hemoglobin

One should first look at the hemoglobin, hematocrit (HCT), and red blood cell (RBC) count as a group. After making an initial evaluation with these three parameters, one should then look at the RBC indices, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). This two-step approach allows a more systematic evaluation of any underlying abnormality.

The normal range of hemoglobin in males is 14–17 g/dL and in females is 12–16 g/dL. The normal value of HCT is 37–47% and the normal RBC count is $3.8–5.8 \times 10^{12}$/L. These normal reference values may differ between laboratories and with different ethnic groups.

If the hemoglobin, HCT, and RBC count all move upward, one is dealing with pre-existing polycythemia, isolated vascular volume depletion, or combined vascular and extravascular volume depletion. In hemoconcentration or pure intravascular fluid depletion, the hemoglobin and HCT will increase, but the RBC count will be normal or marginally increased. The hemoglobin, HCT, and RBC count will be proportionately high in the extravascular volume loss (dehydration).[1] Of course, this diagnosis of volume depletion is more of an academic exercise in an ICU patient. The fluid status will change rapidly because of the reversal of the underlying disease and because of the administration of either fluid, blood products, or diuretics as indicated.

In polycythemia, the hemoglobin, HCT, and RBC count, all are proportionately high. A relatively high RBC count with low or normal hemoglobin and HCT suggests thalassemia syndromes or polycythemia with iron deficiency. One then separates primary from secondary polycythemia by checking the erythropoietin (EPO) levels. This will be low or normal in polycythemia vera and further genetic tests (JAK2 mutation) should be done to confirm the diagnosis. A normal or high EPO level denotes secondary polycythemia usually seen secondary to chronic hypoxemia. This is seen in smokers, those with chronic respiratory diseases and is also seen in congenital cyanotic heart diseases.

If the hemoglobin is low, one is dealing with anemia. Further information can be obtained by looking at the RBC indices. The MCV (76–96 fL), MCH (27–32 pg), and MCHC (30–35 g/dL).

Low hemoglobin with a low MCV is either thalassemia, iron deficiency, or anemia of chronic diseases. If the MCH and MCHC are both low, it suggests iron deficiency while if the MCHC is normal, it suggests thalassemia. In thalassemia, the RBC count will be relatively high, while it will be proportionately low in iron deficiency anemia. In any context, a low MCHC indicates iron deficiency. Iron deficiency anemia can be distinguished from anemia of chronic disease with further testing [iron, total iron-binding capacity (TIBC), transferrin saturation, ferritin, soluble

transferrin receptor assay, and reticulocyte hemoglobin equivalent]. Thalassemia is confirmed by blood tests such as hemoglobin electrophoresis or HPLC and then by further genetic testing.

Low hemoglobin with a high MCV suggests vitamin B_{12} or folate deficiency and this can be confirmed by measuring the serum or RBC B_{12} and folate levels. In vitamin B_{12} deficiency, it is worth testing for antiparietal cell antibodies and intrinsic factor blocking antibodies.

Other causes of low hemoglobin with a high MCV are hypothyroidism, and certain drugs such as antiretroviral therapy (ART) or chemotherapy, chronic liver disease, and myelodysplasia.

Low hemoglobin with a high MCHC invariably points to hemolysis that may be extravascular (spleen or bone marrow) or intravascular. A very high MCHC is usually associated with cold agglutinins disease.

Low hemoglobin with normal RBC indices seen in bone marrow disease, hemolysis, hemorrhage, or anemia of chronic disease. Conditions such as renal disease, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) are associated with anemia of chronic disease. Bone marrow disease is accompanied by low white blood cell (WBC) or platelets count. If this pattern is seen along with high lymphocyte count and very low platelet count, the diagnosis invariably points toward aplastic anemia.

Reticulocyte count or reticulocyte production index helps evaluate the etiology of anemia. A normal reticulocyte count and a reticulocyte production index <2.5 indicate bone marrow hypoproduction. A high reticulocyte count or reticulocyte production index of >2.5 is associated with acute anemia due to blood loss or hemolysis. It is also seen in the recent correction of iron, B_{12}, or folate deficiency anemia.

If the hemoglobin is low along with a bi-cytopenia, or pancytopenia, one should suspect a primary hematological or bone marrow problem. This could be nutritional deficiency (Fe, B_{12}, or folate), or a primary bone marrow problem such as aplastic anemia and myelodysplastic syndrome (MDS).

White Blood Cell

When interpreting the WBC in an ICU patient, it is again important to see the first CBC or the most recent CBC before the illness. A low WBC suggests bone marrow hypofunction seen in B_{12} and folate deficiency, MDS, or aplastic anemia. It can also be seen in myelofibrosis and infiltrative bone marrow disease such as metastatic malignancy. It can also be seen in the leukemic phase of leukemia phase or in patients receiving chemotherapy or other drugs that suppress the bone marrow.

A very high WBC (>30–50,000/mm^3) is usually due to leukemia or myeloproliferative neoplasm but could be seen in a leukemoid reaction. In the latter, there is a high number of neutrophilic granules also known as toxic granules and the leukocyte alkaline phosphatase (LAP) score is high. This is because the neutrophils are in overdrive trying to clear the invading pathogen. In leukemia, the granules are reduced and the LAP score is low, and immature cells such as myelocyte, promyelocyte, and blasts are seen on peripheral smear. A high basophil count is seen in chronic myeloid leukemia (CML). High lymphocyte count was seen in viral infection, tuberculosis, brucellosis, toxoplasmosis, and in chronic lymphocytic leukemia (CLL) (absolute lymphocyte count >10,000/μL). High eosinophils count is seen in allergic conditions and parasitic infestation.

Platelet Counts

A high platelet count is either reactive or because of underlying bone marrow disease such as myeloproliferative neoplasms such as CML and essential thrombocythemia. Counts >10,00,000/mm^3 may suggest underlying essential thrombocythemia and should be confirmed by appropriate genetic testing like *JAK* 2 (V617F), *JAK*2 Exon 12, MPL, and *CALR* mutation. Peripheral smear examination and other reactive markers such as C-reactive protein (CRP), ferritin also is very useful for differentiating between reactive thrombocytosis and essential thrombocythemia.

A low platelet count is seen in chronic liver disease, immune thrombocytopenic purpura (ITP), a presenting hematologic illness, chemotherapy, other drugs, pregnancy including HELLP (syndrome of hemolysis, elevated liver enzymes, and low platelets), and immune disease [thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome (HUS), and SLE].

Peripheral Smear

When interpreting the CBC, additional information can be acquired from the peripheral smear. Fragmented RBCs are seen in sepsis and disseminated intravascular coagulation (DIC), but could indicate a pre-existing microangiopathic hemolytic anemia (MAHA) such as TTP and HUS (>1% schistocytes). In iron deficiency anemia, anisocytosis, poikilocytosis, target cells, pencil-shaped, or cigar-shaped cells are seen. In vitamin B_{12} and folate deficiency macro-ovalocyte, polychromatic RBCs, teardrop cell, or hypersegmented neutrophils are seen. Target cell and basophilic stippling are seen in the thalassemia trait. Bite cells, blister cells, and Heinz bodies are seen in glucose-6-phosphate-dehydrogenase (G6PD) deficiency. Sickled crescent-shaped RBCs, Howell–Jolly bodies (if the patient has autosplenectomy), and target cells are seen in sickle cell anemia. Spherocytes are seen in hereditary spherocytosis and autoimmune hemolytic anemia. In essential thrombocytosis, platelets anisocytosis is seen. In marrow fibrosis teardrop cells, poikilocytosis, leukoerythroblastic picture, and giant abnormal platelets are seen. Blast cells are increased in leukemias. In CLL, smudged lymphocytes are seen.

We would like to stress that the above discussion is in the context of a pre-existing hematological condition and that the earliest CBC should be used. In the presence of a critical illness, without an earlier CBC, it is best to assume that the changes seen are due to the critical illness itself. An abnormal CBC does not necessarily warrant a hematological workup in the presence of a clear diagnosis such as pneumonia, dengue, or malaria. Any persisting abnormality can be evaluated after the critical illness is reversed. Occasionally, a critical illness may be the first presentation of a hematological illness, like a G6PD or sickle crisis, or a thrombotic event due to increased RBCs or platelets.

AN INTENSIVIST'S APPROACH

The Effect of Critical Illness on the Complete Blood Count

The most common indication for ICU admission is shock and multiorgan failure (MOF). These could be triggered by sepsis, trauma, surgery, or by tissue damage due to ischemia or autoimmune responses. This syndrome of sepsis and MOF can directly cause changes in the CBC.

Hemoglobin

The hemoglobin invariably falls during a critical illness. This could be because of decreased production, hemodilution, or peripheral destruction.[2] This hemodilution may be an evolutionary adaptive response to improve the microcirculatory flow.[3] A very rapid fall of hemoglobin suggests bleeding or massive hemolysis. Serial hemoglobin values are an important way of monitoring the ongoing blood loss and the adequacy of replacement. Very early in the blood loss, the hemoglobin may not fall, but as fluid resuscitation and physiological fluid retention occur, the hemoglobin starts falling.

The hemoglobin may go up in volume depleted or dehydrated patients.

White Blood Cell

The WBC may show an increase in the total count with neutrophilic predominance, with the shift to the left of granulocytic cells. This most commonly occurs in infections and sepsis. A high WBC count is also seen in noninfectious causes such as pancreatitis, burns, or myocardial infarction. Appropriate cultures, procalcitonin (PCT), and peripheral smear may identify the pathogen. The more recent DNA-based tests (e.g., GeneXpert, BCID panel, and Bio-Fire) are useful in reaching a rapid diagnosis and detecting the presence of resistance genes. Imaging studies are needed to identify the site of the infection.

In certain illnesses, there may be a significant fall in the WBC. This is usually seen with viral illness but is also seen in malaria and typhoid. It can also be seen in profound sepsis or adverse drug effects.

Platelets

The platelets too may fall, once again attributed to decreased production or peripheral destruction. This peripheral destruction can precede the onset of DIC. The most common cause of low platelet in ICU patients is sepsis, including some tropical illnesses such as dengue and malaria.

If an ICU patient with a previously normal CBC shows the above typical changes of sepsis and MOF, no further hematological investigations or interventions are required. The platelet count has been called the erythrocyte sedimentation rate (ESR) of the ICU. Tracking the platelet count gives a good indication of the worsening or resolution of the underlying sepsis. An unexpected fall of platelets should prompt a search for a new septic episode.

A platelet count that remains low persistently or is out of proportion to the illness warrants further investigation. Though sepsis is the most common cause of thrombocytopenia in ICU, other causes should be considered. These include drugs, mechanical circulatory support devices [intra-aortic balloon pump (IABP), prosthetic valve, extracorporeal membrane oxygenation (ECMO), left ventricular assist device (IVAD)], heparin-induced thrombocytopenia (HIT), and macrophage activation syndrome (MAS).

Pancytopenia

Preexisting pancytopenia could be due to many of the above-mentioned causes of anemia, leukopenia, or thrombocytopenia. The MAS can lead to pancytopenia. The MAS is invariably a hyperinflammatory reaction to an underlying illness. Hemophagocytic lymphohistiocytosis (HLH) is a specific genetic condition, that primarily leads to hemophagocytosis. In both HLH and MAS, the ferritin and triglycerides are raised and the bone marrow shows hemophagocytosis. In MAS, the treatment should be focused on treating the underlying illness and replacing products as needed. HLH needs immune-suppressive treatment that may be detrimental if used in the context of sepsis and MAS.

THERAPEUTIC DECISIONS

The above two sections have discussed hematologist's and an intensivist's approach to the interpretation of the CBC. It is important to arrive at a comprehensive diagnosis. This should include the primary disease causing the critical illness, the presence of any pre-existing hematological condition, and additional effects of the critical illness, such as the effect of drugs, DIC, bleeding, or more complex complications such as the MAS. Once this diagnosis is made, the focus should be on reversing the primary disease, removing other inciting factors, and giving appropriate blood products. It is important to be clear of the goals of these therapies. In stable patients, outside the hospital or the ICU, one would normally correct anemia till the hemoglobin normalizes.

In critically ill patient, the aim is to improve clinical outcomes, rather than simply improve or normalize the laboratory values. A growing trend in critical care trials is to move away from therapies that show improvement in surrogate values, to those that show clinical benefit to the patient. A good example of the dangers of chasing physiological targets is the PATCH trial.[4] In this randomized trial, patients on antiplatelet drugs and intracranial hemorrhage (ICH) had worse functional outcomes if they received platelet transfusions. This study should make clinicians aware that simply following physiological principles can lead to unanticipated harm.

Therapeutic Decisions Based on Abnormal Complete Blood Count

The main decisions are regarding the use of blood products or growth factors.

Low Hemoglobin

The transfusion target is now fairly firmly established at 7 g/dL.[5-12] Some data suggest a possible benefit of using a higher threshold of 9 g/dL.[13] The use of fresh versus old packed red blood cells (PRBCs)[14,15] is not associated with improved clinical outcomes.

The use of EPO[16] in the critically ill has been shown to improve the hemoglobin value without improving clinical outcomes.

The use of intravenous iron[17] has not been shown to improve clinical outcomes.

Low White Blood Cell

The use of colony-stimulating factors in critically ill non-hematological patient has been shown to improve only WBC counts without improving clinical outcomes.[18]

The use of transfused WBCs has not been studied in the context of critically ill patients with the nonhematological illnesses.

Low Platelets (And Other Coagulation Factors)

Platelet transfusion is now recommended if the value is <5,000—10,000/μL.[19] Platelet targets of >50,000/μL[19] are suggested for bleeding patients or for those due to undergo an invasive procedure. A higher threshold of 100,000/μL[19] has been suggested for patients undergoing a brain or spine surgical procedure. In ICU patients, a review paper found that platelet transfusion was associated with higher rates of thrombotic events.[20]

Clinicians should avoid using therapies that have improved the CBC values but not improved the clinical outcomes.

CONCLUSION

An intelligent analysis of the CBC helps the clinician diagnose pre-existing hematological conditions, as well as evaluate the critical illness and its complications. Therapeutic decisions should however be based on clinical outcomes and not on normalizing the CBC values.

ACKNOWLEDGMENT

We would like to thank Drs Farah Jijina, Balkrishna Padate and Shahnaz Khodaiji (Consultant Hematologists, PD Hinduja Hospital Mumbai) for their valuable inputs.

REFERENCES

1. Gautam B, Eric GN. Volume depletion versus dehydration: How understanding the difference can guide therapy. Am J Kidney Dis. 2011;58(2):302-9.
2. Rawal G, Kumar R, Yadav S, Singh A. Anemia in Intensive Care: A Review of Current Concepts. J Crit Care Med. 2016; 2(3):109-114.
3. Messmer K. Haemodilution. Surg Clin North Am. 1975;55(3): 659-78.
4. Baharoglu MI, Cordonnier C, Salman RA, de Gans K, Koopman MM, Brand A, et al. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. Lancet. 2016;387(10038): 2605-13.
5. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, et al. A multicentre, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999; 340(6):409-17.
6. Desjardins P, Turgeon AF, Tremblay MH, Lauzier F, Zarychanski R, Boutin A, et al. Hemoglobin levels and transfusions in neurocritically ill patients: a systematic review of comparative studies. Crit Care. 2012;16(2):R54.
7. Villanueva C, Alan C, Alba B, Concepción M, Hernandez-Gea V, Aracil C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013;368(1):11-21.
8. Jairath V, Kahan BC, Gray A, Doré CJ, Mora A, James MW, et al. Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open label, cluster randomised feasibility trial. Lancet. 2015; 386(9989):137-44.
9. McIntyre L, Hebert PC, Wells G, Fergusson D, Marshall J, Yetisir E, et al. Is restrictive transfusion strategy safe for resuscitated and critically ill traumatic patients? J Trauma. 2004;57(3):563-8.
10. Jeffrey LC, Michael L, Helaine N, Sanders DW, Chaitman BR, Rhoads GG, et al. Liberal or restrictive transfusion in high-risk patient after hip surgery. N Engl J Med. 2011;365(26): 2453-62.
11. Hajjar LA, Vincent JL, Galas FR, Nakamura RE, Silva CMP, Santos MH, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. JAMA. 2010;304(14):1559-67.

12. Holst BL, Haase N, Wettersley J, Wernerman J, Guttormsen AB, Karlsson S, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med. 2014;371(15):1381-91.
13. Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K, et al. Restrictive or liberal red-cell transfusion for cardiac surgery. N Engl J Med. 2017;377:2133-44.
14. Jacques L, Paul CH, Dean AF, Tinmouth A, Cook DJ, Marshall JC, et al. Age of transfused blood in critically ill adults. N Engl J Med. 2015;372(15):1410-8.
15. Cooper DJ, McQuilten ZK, Nichol A, Ady B, Aubron C, Bailey M, et al. Age of red cell for transfusion and outcomes in critically ill adults. N Engl J Med. 2017;377(19):1858-67
16. Corwin HL, Gettinger A, Rodriguez RM, Pearl RG, Gubler KD, Enny, C, et al. Efficacy of recombinant human erythropoietin in the critically ill patient: a randomized, double-blind, placebo-controlled trial." Critical Care Medicine. 1999;27(11):2346-50.
17. IRONMAN Investigators; Litton E, Baker S, Erber WN, Farmer S, Ferrier J, et al. Intravenous iron or placebo for anaemia in intensive care: the IRONMAN multicentre randomized blinded trial. Intensive Care Med. 2016;42(11):1715-22.
18. Nelson S, Belknap SM, Carlson RW, Dale D, DeBoisblanc B, Farkas S, et al. A randomized controlled trial of filgrastim as an adjunct to antibiotics for treatment of hospitalized patients with community-acquired pneumonia. CAP Study Group. J Infect Dis. 1998;178(4):1075-80.
19. Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinmouth AT, Capocelli KE, et al. AABB. Platelet transfusion: a clinical practice guideline from the AABB. Ann Intern Med. 2015;162(3):205-13.
20. Refaai MA, Phipps RP, Spinelli SL, Blumberg N. Platelet transfusions: impact on haemostasis, thrombosis, inflammation and clinical outcomes. Thromb Res. 2011;127(4):287-91.

SECTION

14

Transplant/Organ Donation

CHAPTER 75

Liver Transplantation: A Critical Care Perspective

Vaishali Solao

INTRODUCTION

Liver intensive care is a rapidly evolving specialized branch due to the progress in surgical techniques and the availability and safety of liver transplantation all across India.

As the field has reached a consolidation phase across the country, demand for intensivists who have an understanding and experience of handling patients peri-liver transplant has increased. Increasingly sicker patients with more comorbidities are undergoing transplants. Appropriate critical care is required to support prompt graft recovery and prevent systemic complications. Preoperative optimization and postoperative stabilization have a crucial role to play in the final outcome. Recipient evaluation pretransplant requires an exhaustive workup to assess multiple systems. The model for end-stage liver disease-sodium (MELD-Na) and frailty index have emerged as the two biggest markers of prognosis post-liver transplant (LT). Preoperative cardiac and pulmonary assessment and optimization is an important aspect of the workup. Infections in the perioperative period can impact outcomes adversely and remain a major challenge. This chapter will cover preoperative relevant issues and early postoperative management in the intensive care under following headings:

- Severity of liver disease
- Frailty
- Cardiac and pulmonary assessment
- Transplantation in acute-on-chronic liver failure (ACLF) and acute liver failure (ALF)
- Perioperative management in the first week

SEVERITY OF LIVER DISEASE

Preoperative liver dysfunction and its severity has been shown to correlate with postoperative outcomes. Multiple scoring systems have been postulated to grade the severity of dysfunction all over the world. Of all the scores MELD-Na has stood the test of time and remains the most well-established scoring system that accurately predicts patients 3-month waitlist mortality.[1] Originally designed to assess patient's fitness for transjugular intrahepatic portosystemic shunt, MELD rapidly got wider acceptance and now is most commonly used criteria for organ allocation in USA, UK, and other developed nations. In India too, some states follow MELD-based organ allotment system. There are some standardized MELD exceptions like hepatocellular carcinoma, hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH). Although MELD is the most frequently used criteria, it has its challenges of not being able to capture patients with predominantly severe portal hypertension and refractory ascites, hyponatremia, and recurrent bleeds. MELD score of >35 is associated with significant post-transplant mortality and morbidity.[2]

FRAILTY

Frailty has emerged as a strong predictor of post-transplant survival in the last one decade. Cirrhosis leads to considerable muscle mass loss and consequent frailty. Recent studies measuring sarcopenia by the psoas muscle index or skeletal muscle index have shown very low muscle mass in cirrhotics. The liver frailty index is a simple bedside test used to quickly assess frailty.[3] A score of >4 has been shown to be associated with adverse post-transplant outcomes. Although it is not entirely possible to reverse the frailty preoperatively, attention to nutrition, physiotherapy, and regular exercise regimes have been shown to prevent deterioration. Sarcopenic obesity is also identified as a risk factor for mortality.

LUNG IN LIVER TRANSPLANT

Hepatopulmonary syndrome and POPH are two most common pulmonary complications of cirrhosis. Workup must be exhaustive to rule out both. Apart from this underlying chronic obstructive pulmonary disease (COPD) or interstitial lung disease (ILD) has to be thoroughly evaluated as well. HPS is diagnosed on arterial blood gas (ABG) showing a PaO_2 of <60 and a bubble echo showing extracardiac shunt. No levels of hypoxia however are a strict

contraindication to transplant. PaO_2 <45, i.e., severe HPS can be quite difficult to handle intra- and postoperatively and transplant is usually avoided. Transient deterioration of hypoxia in the postoperative period is expected which needs meticulous management of fluid balance, early extubation and use of high-flow nasal cannula/bilevel positive airway pressure (HFNC/BiPAP). Extreme cases may need veno-venous extracorporeal membrane oxygenation (VV-ECMO) to tide over the hypoxic crisis. Hypoxia improves gradually post-transplant, but patients may need oxygen therapy for months post-transplant.

Portopulmonary hypertension is a rare complication with a prevalence of 2–6% of patients with end-stage liver disease. A routine echo showing right heart pressures above 50–55 mm Hg must undergo a right heart catheterization to evaluate the underlying nature of pulmonary hypertension. POPH is defined as mean pulmonary arterial pressure (MPAP) > 25 with pulmonary vascular resistance index (PVRI) > 250 dynes/sec^4 with normal wedge (<15). POPH needs to be medically optimized before transplant to an MPAP > 35 is a contraindication to transplant. Also transplant should be undertaken for a liver indication as POPH may not reverse completely with transplant.

HEART IN LIVER TRANSPLANT

A detailed discussion of cardiac assessment is beyond the scope of this chapter. Patients with nonalcoholic steatohepatitis (NASH) tend to have the metabolic syndrome and are at an increased risk of coronary artery disease. Every center has its protocol for assessing risk of coronary artery disease. In general, more than two risk factors for coronary artery disease (CAD) are an indication for coronary angiography.

KIDNEYS IN LIVER TRANSPLANT

Kidney plays a key role in evaluation and management of the recipient. Many patients have acute kidney injury (AKI) pretransplant and then are at a risk of postoperative AKI. Risk factors include several modifiable and nonmodifiable parameters.[5] Donor-associated risk factors are an added complication in deceased donor liver transplant (DDLT). Calcineurin inhibitors (CNIs) remain the major contributory factor to postoperative AKI and newer regimes are more inclined toward CNI minimization in order to prevent short-term and long-term kidney failure post-LT.

SPECIAL SCENARIOS IN ACUTE LIVER FAILURE AND ACUTE-ON-CHRONIC LIVER FAILURE

The survival in acute liver failure patients has drastically improved with transplantation.

Acute liver failure patients comprise 5% of all LTs in the US. Indications vary between the east and the west. ALF poses a unique circumstance where a timely early transplant can be lifesaving. King's College criteria are the most extensively used even today to decide who needs transplantation. Those fulfilling the criteria are likely to die without transplant (sensitivity of 58% and specificity of 88%).[4] Cerebral edema poses a unique challenge in managing ALF and preventing and controlling intracranial hypertension is central to perioperative course of ALF.

Once considered a contraindication to transplant ACLF is now been offered transplants but only in carefully selected cases. Even in the Moreau study only 10% of the total number of ACLF patients underwent transplant.[6] The chronic liver failure-sequential organ failure assessment (CLIF-SOFA) score grades ACLF into 3 grades with increasing 1 month and 3-month mortality from grade 1 to 3. Mortality of ACLF grade is very high without transplant albeit very few can be considered for transplant. So, it is very essential to evaluate the futility of transplantation in ACLF.

POSTOPERATIVE MANAGEMENT

Immediate postoperative management in the intensive care unit is again a multidisciplinary team effort.

Hemodynamic Monitoring

Invasive hemodynamic monitoring is integral to transplantation intraoperative as well as postoperative. Tools used vary from center to center. Instead of protocolized fluid therapy, individualized fluid and vasopressor therapy have now become the method of choice. Various tools available, each has its unique advantages and disadvantages. The goal is to maintain intravascular volume, perfusion pressure and act rapidly on the changes before organ perfusion gets affected. Some centers have now started relying on echo-guided monitoring, but echo training, interobserver variability as well as lack of continuous nature all are impediments. Ideally, the method should be least invasive, objective, reproducible, continuous and standardized (thermodilution), and give dynamic variables as well as static. Pulse index continuous cardiac output (PiCCO) has all these characteristics, albeit is invasive in nature and needs femoral access. The aim of using dynamic variables and continuous cardiac output is to optimize filling so as to avoid underfilling or pulmonary edema and maintain adequate perfusion pressures.

Fluid and Electrolytes

Choice of intravenous (IV) fluids in intensive care has been a subject of debate over the last decade. Advocates of chloride low-balanced fluids have been winning the battle so far. Basics trial in 2021 however showed that nature of IV fluid normal saline (NS) versus balanced fluids made no difference in renal or patient outcomes after major abdominal surgery.[7] The bottom line is in patients at risk of AKI who are already on

inotropes, balanced fluids may have an edge over NS. In not very sick patients who are not at risk of AKI, NS probably is just as good. The amount of fluid has also been a subject of many trials comparing positive balances postoperative to net zero balance 5 days postoperative. The current recommendation is to give individualized therapy with caution to avoid large positive balances in first few postoperative days. Albumin is usually given in the postoperative phase especially if the drains are high. Albumin 5% can be used to replace half the drain volume. Synthetic colloids like delousing also can be used with same intent. 20% albumin can replace 5% when availability is an issue. Practically all electrolyte abnormalities are possible post-LT, of which the most important is hyponatremia. Hyponatremia peri-LT and its appropriate management has tremendous impact on outcomes for if not managed well, it may lead to osmotic demyelination is a very morbid complication causing prolonged hospital stay. Usually, patients are hyponatremic pretransplant, sodium of <120 mEq/L would be a relative contraindication to transplant considering the likelihood of sudden rise by >10 intraoperative or in the postoperative phase. It is desirable to have a sodium of >12 5 mEq/L before transplant with a strategy of strict monitoring intra- and postoperatively and controlling sodium levels if <130 mEq/L to begin with.

Postoperative Mechanical Ventilation and Weaning

Enhanced recovery after surgery (ERAS) protocol post-LT [especially living donor liver transplantation (LDLT)] has not received much support. The reason being long surgical time, need to observe graft function before extubation and chances of hemorrhage. Usually, patients come ventilated to ICU, provided hemodynamics, and graft functions are good efforts to wean and extubate follow in the next 12 hours. Some patients may have respiratory failure post-transplant due to cardiac issues, fluid overload, transfusion-related acute lung injury (TRALI) or bibasal collapse. In these scenarios, patient will need low tidal volume and positive end-expiratory pressure (PEEP) strategy but high PEEP > 10 mm Hg has been shown to be detrimental to graft function. Regardless hypoxia should be avoided to preserve the graft. Noninvasive ventilation/high-flow nasal cannula (NIV/HFNC) is an option to support such patients temporarily.

Infections and Prophylaxis

Postoperative infections can be a major cause of morbidity and prolong ICU stay. Preoperative colonization with multi-drug resistant organism (MDRO) has been shown to be associated with postoperative MDRO infections. Donor-derived infections are also possible in the DDLT scenario. Screening the deceased donor for infections by blood and urine and ET cultures is always a good strategy to follow. Prophylaxis will depend on local and patient factors. A high MELD patient with recent (within 3 months) hospital admissions and treated with antibiotics will need a carbapenem depending on local flora. A straightforward low MELD hepatocellular carcinoma with no hospitalization or colonization a β-lactam/β-lactamase inhibitor (BL/BLI) with gram-positive cover for 48 hours postoperative suffices. Antifungal prophylaxis is indicated for ALF and ACLF as they are at a very high risk of both *Candida* and mold infections in the first 3–4 weeks post-transplant. An echinocandin for 2–3 weeks post-transplant is recommended as per the European Association for the Study of the Liver (EASL) guidelines. Herpes simplex virus (HSV) and cytomegalovirus (CMV) are two viral reactivations causing mortality and morbidity post-transplant. CMV prophylaxis is an exhaustive topic in itself but it suffices to say high-risk patients should be on valganciclovir prophylaxis.

Post-transplant Graft-related Complications

Detailed discussion of graft-related complications is beyond the scope of this chapter.

Postoperative hemorrhage, primary nonfunction, small for size syndrome, acute cellular rejection, hepatic artery thrombosis, portal vein thrombosis, outflow obstruction, and bile leaks are possible complications in first phase post-LT. Each of them requires early identification and brisk correction to save the graft function in the long run. Daily Doppler for first 3–5 days in LDLT setting is imperative to pick up vascular complications early. Daily or twice daily liver enzymes can help in early recognition of acute cellular rejection. Primary nonfunction will require urgent relisting and retransplantation although it is one of the rarer complications.[8]

Neurological Complications

The spectrum of neurological complications post-LT is wide. Tacrolimus-induced posterior reversible encephalopathy syndrome (PRESS), seizures and encephalopathy, tacrolimus-induced tremors and hyperirritability, visual hallucinations, and cortical blindness. Osmotic demyelination occurs with a frequency of 1–3.5% post-LT, especially in alcoholics. It is essential to be cautious of drug interactions of CNI to avoid sudden surges in their levels, even though neurotoxicity is not dose related but idiosyncratic in nature. Changing from tacrolimus to cyclosporine is the most common remedy for tacrolimus-related neurotoxicity and vice versa.

Acute Kidney Injury

Incidence of AKI ranges from 20 to 50% post-LT depending on the definition used in various studies. AKI remains a major issue to tackle post-LT. Many patients have hepatorenal

syndrome (HRS) AKI preoperative, and are more prone to postoperative AKI. Multiple modifiable and nonmodifiable factors predispose to postoperative AKI. There is increased mortality associated with AKI. Recent survey involving 13,400 LT patients across continents showed incidence of AKI as 40% and AKI needing RRT about 7%. Both groups had higher mortality and higher graft loss. 30-day mortality was 16% and 1-year mortality was 31%. Odds ratio for mortality in patients with AKI was 2.9 and 8.9 for those on RRT.[5]

CONCLUSION

Meticulous intensive care is needed perioperatively for LT patients. Acute liver failure is the most challenging condition one can handle in an ICU. Proper management in the ICU to control intracranial pressure sepsis and hemodynamics followed by a successful transplant in indicated cases has improved survival of ALF drastically in the last one decade. ACLF is now an emerging challenge for transplantation. Patients are sicker and frailer and case selection is very important for acceptable results post-transplant. Diabetes mellitus (DM), CAD, obesity, and chronic kidney disease (CKD), increasingly coexisting in these patients, make perioperative management complex, requiring a truly multidisciplinary coordinated effort for eventual success.

REFERENCES

1. Ruf AE, Kremers WK, Chavez LL, Desclazi VI, Podesta LG, Villamil FG. Addition of serum sodium into MELD score predicts waiting list mortality better than MELD alone. Liver Transplant. 2005;11(3):336-43.
2. Artru F, Louvet A, Ruiz I, Levesque E, Labreuche J, Ursic-Bedoya J, et al. Liver transplantation in the most severely ill cirrhotic patients: a multicenter study in acute-on-chronic liver failure grade 3. J Hepatol. 2017;67:708-15.
3. Kardashian A, Ge J, McCulloch CE, Kappus MR, Dunn MA, Duarte-Rojo A, et al. Identifying an optimal liver frailty index cutoff to predict waitlist mortality in liver transplant candidates. Hepatology. 2021;73:1132-9.
4. Thongprayoon C, Cheungpasitporn W, Lertjitbanjong P, Aeddula NR, Bathini T, Watthanasuntorn K, et al. Incidence and Impact of Acute Kidney Injury in Patients Receiving Extracorporeal Membrane Oxygenation: A Meta-Analysis. J Clin Med. 2019;8(7):981.
5. McPhail MJ, Wendon JA, Bernal W. Meta-analysis of performance of Kings's College Hospital Criteria in prediction of outcome in non-paracetamol-induced acute liver failure. J Hepatol. 2010;53(3):492-9.
6. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013;144(7):1426-37,e1-9.
7. Zampieri FG, Machado FR, Biondi RS, Freitas FGR, Veiga VC, Figueiredo RC, et al. Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients: The BaSICS Randomized Clinical Trial. JAMA. 2021;326(9):818-29.
8. Feltracco P, Barbieri S, Galligioni H, Michieletto E, Carollo C, Ori C. Intensive care management of liver transplanted patients. World J Hepatol. 2011;3(3):61-71.

CHAPTER 76

Heart Transplant: What Intensivist Must Know?

Bhagyesh Shah, Dhiren Shah, Niren Bhavsar

INTRODUCTION

In the era of organ transplantation being explored for all the possible reasons, end-stage heart failure has been the major reason for heart transplant throughout the world being well sought after in certain class of symptomatic patients despite of well-optimized mechanical and medical support.[1] Orthotopic heart transplant is done when a brain-dead donor's family donate his/her heart to an eligible recipient with heart failure. Long-term outcomes after transplantation have improved with the advances made in transplant candidate selection, surgical techniques, immunosuppressive modalities, and postoperative care. With 1 year survival at 85–90% and median survival of 12–14 years, heart transplant has proven its worth. Worldwide >125,000 heart transplants have been performed with North America being the leader. Heart transplantation In India has been on rise since last 8–10 years. In India till date, we have performed around 1,100 heart transplants, with annually around 150 transplants. For better outcomes in heart transplantation, the role of intensivist is of paramount importance, both preprocedural (during brain-dead donor identification and optimization) and postsurgery while recipient is in the ICU.

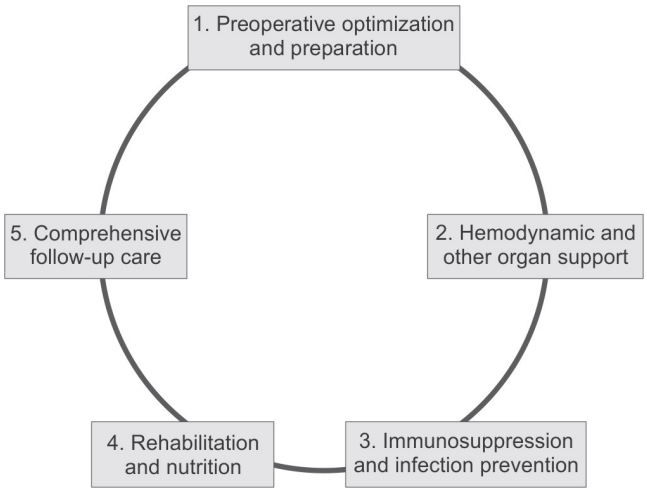


Fig. 1: Multipronged role of intensivist in heart transplant patient care.

INDICATION OF HEART TRANSPLANT AND RECIPIENT EVALUATION

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines include the following indications for cardiac transplantation:[2]

- Refractory cardiogenic shock requiring intra-aortic balloon pump (IABP) counter pulsation or left ventricular assist device (LVAD)
- Cardiogenic shock requiring continuous intravenous (IV) inotropic therapy (i.e., dobutamine, milrinone, etc.)
- Peak VO_2 (VO_{2max}) <10 mL/kg per min
- New York Heart Association (NYHA) class of III or IV despite maximized medical and resynchronization therapy
- Recurrent life-threatening left ventricular (LV) arrhythmias despite an implantable cardiac defibrillator, anti-arrhythmic therapy, or catheter-based ablation
- End-stage congenital heart failure with no evidence of pulmonary hypertension.

Similarly, the European Society of Cardiology describes a series of features that must be met before consideration for heart transplant which are more specific and include, functional, structural, and symptoms parameters.[3]

- Severe symptoms, with dyspnea at rest or with minimal exertion (NYHA class III or IV).
- Episodes of fluid retention (pulmonary or systemic congestion, peripheral edema) or of reduced cardiac output at rest (peripheral hypoperfusion).
- *Objective evidence of severe cardiac dysfunction (at least one of the following)*: LV ejection fraction <30%, pseudonormal or restrictive mitral inflow pattern on Doppler echocardiography, high left and/or right ventricular (RV) filling pressure severely impaired functional capacity demonstrated by one of the following: Inability to exercise, 6-minute walk test distance <300 m

(or less in women or patients who are age of 75 years and older), or peak oxygen intake <12–14 mL/kg/min.
- One or more hospitalizations for heart failure in the past 6 months.

ABSOLUTE CONTRAINDICATION FOR HEART TRANSPLANT[4]

- Advanced irreversible renal failure with Cr >2 or creatinine clearance <30–50 mL/min without plans for concurrent renal transplant
- Advanced irreversible liver disease
- Advanced irreversible pulmonary parenchymal disease or [forced expiratory volume in the first second (FEV1) <1 L/min]
- Advanced irreversible pulmonary arterial hypertension (PAH) (pulmonary artery systolic pressure >60 mm Hg, pulmonary vascular resistance >4–5 wood units despite vasodilators) due to risk of acute RV failure soon after transplant from insufficient accommodation of the donor heart to high pulmonary vascular resistance pressures
- History of solid organ or hematologic malignancy within the last 5 years due to probability of recurrence.

RELATIVE CONTRAINDICATION FOR HEART TRANSPLANT[4]

- Severe peripheral vascular disease
- Severe cerebrovascular disease
- Severe obesity [body mass index (BMI) >35 kg/m^2] or cachexia
- Acute pulmonary embolism
- Active infection (excluding LVAD-related infections)
- Advanced age (>70 years old)
- Psychological instability [e.g., post-traumatic stress disorder (PTSD)]
- Active or recent (within 6 months) substance abuse (alcohol, cocaine, opioids, tobacco products, etc.)
- Diabetes mellitus with end organ damage
- Lack of social support or sufficient resources to permit ongoing access to immunosuppressive medication and frequent medical follow-up.

MANAGEMENT OF POTENTIAL HEART DONORS

Traditional Cardiac Donor Selection Criteria[5]

Age <55 years old:
- No history of chest trauma or cardiac disease
- No prolonged hypotension or hypoxemia
- Appropriate hemodynamic—Mean arterial pressure (MAP) >60 mm Hg, central venous pressure (CVP) 8–12 mm Hg
- Inotropic support <10 mg/kg/min (dopamine or dobutamine)
- Normal electrocardiogram
- Normal echocardiogram
- Normal cardiac angiography (if indicated by donor age and history)
- Negative serology (hepatitis B surface antigen, hepatitis C virus and human immunodeficiency virus).

Preoperative Recipient Evaluation

A patient of heart failure is considered for heart transplant first on the bases of maximum exercise capacity assessed by VO_{2max}. Once the patient is considered for heart transplant. Thorough preoperative planning and preparation is must with immunizations, nutritional plans to avoid perioperative complications. At all steps a family counseling with patient by the whole transplant team is done with audio-visual informed consents matching the legal framework of the country.

A well-planned multiorgan or whole-body screening is done which involves:
- Cardiac imaging and right heart catheterization is done. Unfavorable pulmonary hypertension presents a significant risk for right heart failure after transplantation.
- Respiratory evaluation for diseases such as chronic obstructive pulmonary disease (COPD), PAH, pulmonary embolism, and collected data from pulmonary function test (PFT) including diffusing capacity of the lungs for carbon monoxide (DLCO).
- Renal issues such as diabetic nephropathy or renal arterial stenosis, etc. along with renal function tests
- Hepatobiliary diseases either primary or secondary to heart disease should be evaluated.
- Rule out history of solid organ or hematologic malignancy within the last 5 years or active malignancy.
- Nutritional assessment and medication history
- Immunization history
- Recent infections if any
- Neurological and psychiatric history.

INTENSIVE CARE MANAGEMENT POSTHEART TRANSPLANT

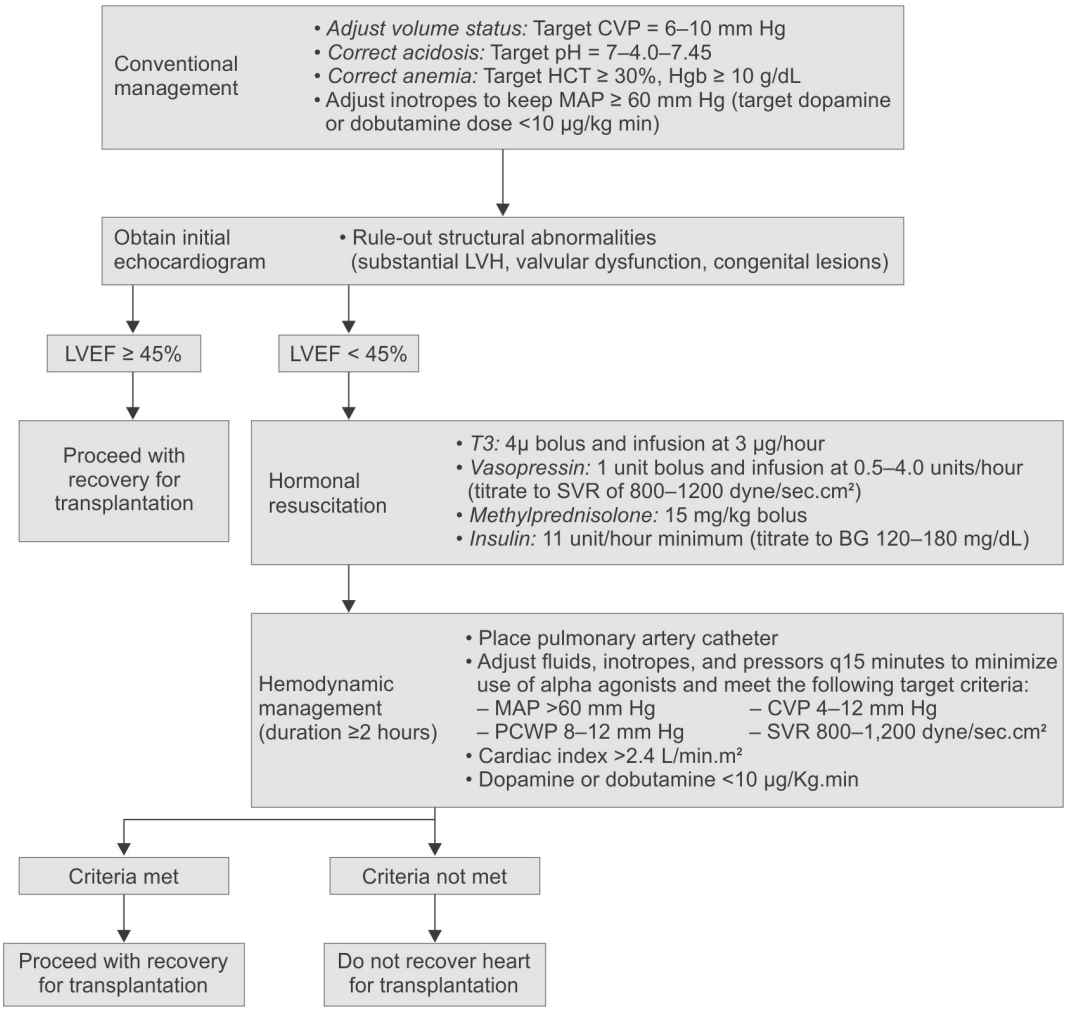
Heart transplant recipient should be received in an isolated room and should be nursed with strict aseptic care. Once received patient is monitored with invasive arterial, pulmonary, and CVPs with continuous cardiac output (CCO) monitoring in addition to standard cardiopulmonary monitoring.

Frequent blood gas analysis with serum lactate measurement must be done as high lactate with normal bicarbonate and PH is common after first 12–24 hours postheart transplant as this was preheart transplant-related low cardiac output-related lactate and now coming into circulation.

Hemodynamic Management

Primary challenge after heart transplant is RV dysfunction. It is important to prevent, identify, and treat RV dysfunction early. Acute RV failure can cause trouble immediately

Flowchart 1: The Crystal City Guidelines for an algorithm for the management of potential heart donors.[6]



(CVP: central venous pressure; HCT: hematocrit; LVH: left ventricular hypertrophy; LVEF: left ventricular ejection fraction; MAP: mean arterial pressure; PCWP: pulmonary capillary wedge pressure; SVR: systemic vascular resistance)

post-transplant due to pre-existing PAH or due to temporary or acute vasospasm of pulmonary vasculature or tricuspid or pulmonary valve malfunction after RV dilation in post-operative period. Size mismatch can be a rare phenomenon nowadays due to meticulous donor selection supported by transesophageal echocardiogram (TEE) guided data and measurements. Additional factors that may contribute to postoperative RV dysfunction include a prolonged donor heart ischemic time, inadequate myocardial protection, and surgical manipulation of the heart.

Findings suggesting RV dysfunction can be rising CVP, pulmonary arterial (PA) pressures, and higher transpulmonary pressure gradient. Goal is to keep pulmonary vascular resistance (PVR) less than six woods unit and transpulmonary gradient (TPG) <5–10 mm Hg. RV dysfunction can be treated with increasing FiO_2, avoiding high positive end-expiratory pressure (PEEP), correcting acidosis, hyperventilation, inotropes such as dobutamine, milrinone, epinephrine and isoprenaline, inhaled nitric oxide (iNO), IV or oral sildenafil, and other selective pulmonary vasodilators. Refractory RV dysfunction may sometimes need mechanical circulatory supports (MCPs) such as right ventricular assist device (RVAD) or extracorporeal membrane oxygenation (ECMO).

Left ventricular function issues can be more common in donors who were already on higher inotropic supports. Surgical manipulation lasting longer or prolonged ischemia time can be the reason for surgery-related risk factors for LV dysfunction with very rare chances of intracoronary air embolism. You will need to support with adrenaline or dobutamine along with noradrenaline for longer time. IABP if normal systemic vascular resistance (SVR) and severe LV dysfunction refractory to medical management. Consider LVAD or venoarterial extracorporeal membrane oxygenation (VA ECMO) if refractory LV dysfunction. It can be a sign of rejection also.

Arrhythmias: Transplanted hearts are autonomically denervated and bradyarrhythmias only respond to directly acting drugs such as catecholamine and may require temporary atrioventricular (AV) pacing which may

sometimes require permanent pacemaker if persist for >2 weeks. Any sustained tachyarrhythmias should be evaluated for potential rejection. Tachyarrhythmias can be treated with direct-current (DC) cardioversion or amiodarone and rate control can be achieved with beta-blockers.

As per 2014 International Consensus Conference classification,[7] there can be two types of graft dysfunctions:

1. *Primary graft dysfunction (PDG):* Can be of variable degrees involving either side of heart during first 24 hours of transplant. There can be severe low cardiac output or low systolic function without obvious acute graft rejection signs. If rejection is suspected, endomyocardial biopsy (EMB) should be taken for diagnosis. Treatment starts with vasoactive and inotropic support followed by IABP and if needed ECMO at last.
2. *Secondary graft dysfunction (SDG):* It is mostly due to reasons such as acute rejection, surgical complications, or pulmonary hypertension and needs treatment according to the specific reason found.

Perioperative Mechanical Circulatory Support after Heart Transplantation

Mechanical circulatory support is needed whenever there is circulatory failure compromising the weaning from cardiopulmonary bypass (CPB) or there are signs of heart failure worsening in perioperative period. Continuous cardiac monitoring if reveals that cardiac index or MVO_2 is decreasing with increasing lactate should prompt the clinician to consider MCS along with IABP.

Ventricular assist devices may provide temporary but adequate support for the failing heart when the expertise is available. Various centers in India have used them successfully already.

Overall graft recovery will should happen within 3–4 days with adequate quantitative exclusion criteria for rejection and slow weaning from MCS should start later.

Use of ECMO or VAD devices carry a risk of infection, coagulation-related abnormalities, and significant cost along with limited mobility. The expert centers have slowly learned to overcome all of this with multidisciplinary approach where intensivists have played a big part.

Respiratory Management

Once patient starts getting hemodynamically stable with all hemodynamic targets well within control, the weaning process is started. The weaning is done as done in any ICU case while keeping in mind to avoid anything which can lead to increased PVR such as hypercapnia, hypoxia with ventilator pressures, and measures in normal range such as PEEP <8 and plateau pressures under 30. If nitric oxide inhalation was used, then switch to IV or oral pulmonary vasodilator is must before weaning. If weaning is not done in 5–7 days, tracheostomy is preferred to facilitate ventilator weaning. Aggressive physiotherapy with incentive spirometry or vibrating devices for clearance of secretions and early mobilization even with minimal inotropes is desirable.

Renal Dysfunction

There may be pre-existing low output state aggravated by stress, intravascular volume depletion, long CPB time, overuse of colloids, use of unbalanced fluid solutions, and active cytokine release-related hemodynamic fluctuations. Most important cause for acute kidney failure (ARF) can be right heart failure leading to high CVP and decrease renal perfusion pressure (RPP) as RPP = MAP – CVP. It is very important to maintain high MAP and decrease CVP by early diuresis and or continuous renal replacement therapy (CRRT)/sustained low-efficiency dialysis (SLED) and management of RV dysfunction with pulmonary vasodilators and inotropes. Early application of CRRT is desired for better fluid balance and improving cardiac and renal function.

If still renal insufficiency persists or there is deterioration happening, it is better to hold for starting calcineurin inhibitor therapy. In such a case, it is advisable to consider giving second dose of basiliximab, especially when renal dysfunction is established or anticipated.

Antibiotics

Antibiotic therapy must be based on multiple factors including local antibiogram, surgical time, presence of tubes, and catheters in patient body along with the background history of donor and/or recipient. Donor blood culture should be collected, and antibiotics should be optimized if required. On second or third postoperative day, send peripheral blood cultures and cultures from all invasive lines. Keep as minimal invasive lines as possible. In Indian Scenario, it is hard to keep a fine balance between immunosuppression and infection prevention and intensivist plays a definitive role in this subset of patients. Maintain proper oral hygiene of patient and ensure hand hygiene being followed by health workers. To optimize pharmacokinetics and pharmacodynamics proper monitoring of antibiotic dosing and their levels in plasma along with help from intensivist, nephrologist and infectious disease specialist's input is being more and more followed across our country.

Prophylaxis for cytomegalovirus (CMV), *Pneumocystis jirovecii*, and *Aspergillus* infections are routinely given when on immunosuppression.

Immunosuppression

Immunosuppression is managed by transplant team with regards to patient profile as per locally approved

treatment plans. Usually, it starts with high dose bolus of methyl-prednisolone and basiliximab in operation theater (OT). In ICU, methylprednisolone is given for first few days in tapering doses and switched to oral prednisolone. MMF (mycophenolate mofetil) is started on the first day and tacrolimus is added on second or third day if renal function is preserved. Intensivist must take active part in dosing as he/she is the one who has to strike a fine balance between avoiding sepsis and optimizing immunosuppression. Immunosuppression is monitored with complete blood counts, CD4 and CD25 cell counts along with renal function. Blood pressure and sugar can go high due to steroids and tacrolimus needing watchfulness and drugs to control same. Few patients may require antihypertensives and insulin on discharge. Hyperkalemia is common with tacrolimus.

Bleeding and Hemostasis

All transplant recipients must receive irradiated and leukoreduced red blood cells (RBCs) to avoid any sensitization. Significant blood loss must be addressed, and any coagulopathy must be treated under guidance of thromboelastogram (TEG). Use of cell saver can be considered if significant blood loss is present. Use of large amount of blood and blood product can lead to respiratory complications and rise in PVR.

Nutrition and Rehabilitation

Early enteral feeding is the norm nowadays. It is initially given via nasogastric (NG) tube in continuous feeding or as intermittent feeding. The average target range will be to achieve 25–30 kcal/kg/day and then switch to self-feeding is done once there is no more gastroparesis or intolerance. Protein supplements and micronutrient support is usually well tolerated and helps in early recovery.

Albumin level should be maintained >3–3.5 g/dL to maintain oncotic pressure in order to maintain MAP. Albumin shall be given only if IVC diameter is <20 mm to avoid fluid overload.

Early aggressive passive and active whole-body physiotherapy along with mobilization is prudently needed and to be ensured. Gadgets to improve lung capacity (spirometer, Acapella, and Aerobika) and assist active mobilization must be used in transplant unit. Reversible recurrent laryngeal nerve palsy with hoarseness of voice, poor cough, cough while taking oral feeds are common in early few days after heart transplant. Even injury to phrenic nerve and diaphragmatic palsy has also been noted. Early mobilization even with inotropes is encouraged in this era of mobilization with even ECMO.

Regular clinical counsellor visits will avoid psychological issues for long term.

REFERENCES

1. Metra M, Ponikowski P, Dickstein K, McMurray JJV, Gavazzi A, Bergh CH, et al. Advanced chronic heart failure: A position statement from the study group on advanced heart failure of the heart failure association of the European Society of Cardiology. Eur J Heart Fail. 2007;9(6-7):684-94.
2. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: Developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009;119(14):1977-2016.
3. Hunt SA, Kouretas PC, Balsam LB, Robbins RC. Heart transplantation. In: Zipes DP, Libby P, Bonow RO, Braunwald E (Eds). Braunwald's Heart Disease, 7th edition. Philadelphia: Elsevier Saunders; 2005.
4. Mancini D, Lietz K. Selection of cardiac transplantation candidates in 2010. Circulation. 2010;122(2):173-83.
5. Kilic A, Emani S, Sai-Sudhakar CB, Higgins RS, Whitson BA. Donor selection in heart transplantation. J Thorac Dis. 2014;6(8):1097-104.
6. Zaroff JG, Rosengard BR, Armstrong WF, Babcock WD, D'Alessandro A, Dec GW, et al. Consensus conference report: maximizing use of organs recovered from the cadaver donor: cardiac recommendations, March 28-29, 2001, Crystal City, VA. Circulation. 2002;106(7):836-41.
7. Kobashigawa J, Zuckermann A, Macdonald P, Leprince P, Esmailian F, Luu M, Mancini D, et al. Consensus Conference participants. Report from a consensus conference on primary graft dysfunction after cardiac transplantation. J Heart Lung Transplant. 2014;33(4):327-40. doi: 10.1016/j.healun.2014.02.027. Epub 2014 Mar 5. PMID: 24661451.

77

CHAPTER

Lung Complications after Hematopoietic Stem Cell Transplant

Mrinal Sircar, Sanket Shah

INTRODUCTION

Since the first successful bone marrow transplant (BMT) in 1956 by Dr Donald Thomas, numbers have seen 7% annual increase,[1] to estimated 90,000 global and 2,500 Indian transplants annually.[1,2] Stem cells may be also obtained from peripheral blood or cord blood and hence the new name: Hematopoietic stem cell transplantation (HSCT). Improvement in overall knowledge, drugs and supportive care, use of haploidentical (half match) transplants, reduced intensity conditioning, etc., have increase in number of transplantation but at the same time increase in the recognition of various complications. Pulmonary complications (infectious and noninfectious) are major contributors to mortality and morbidity. Less myeloablative conditioning and newer antibiotics have decreased infections while use of peripheral blood stem cells and growth factors has increased certain noninfectious complications. The 100-day mortality rates after allogeneic HSCT is 17–19% for noninfectious and 12–17% for infectious complications.[3]

PULMONARY COMPLICATIONS

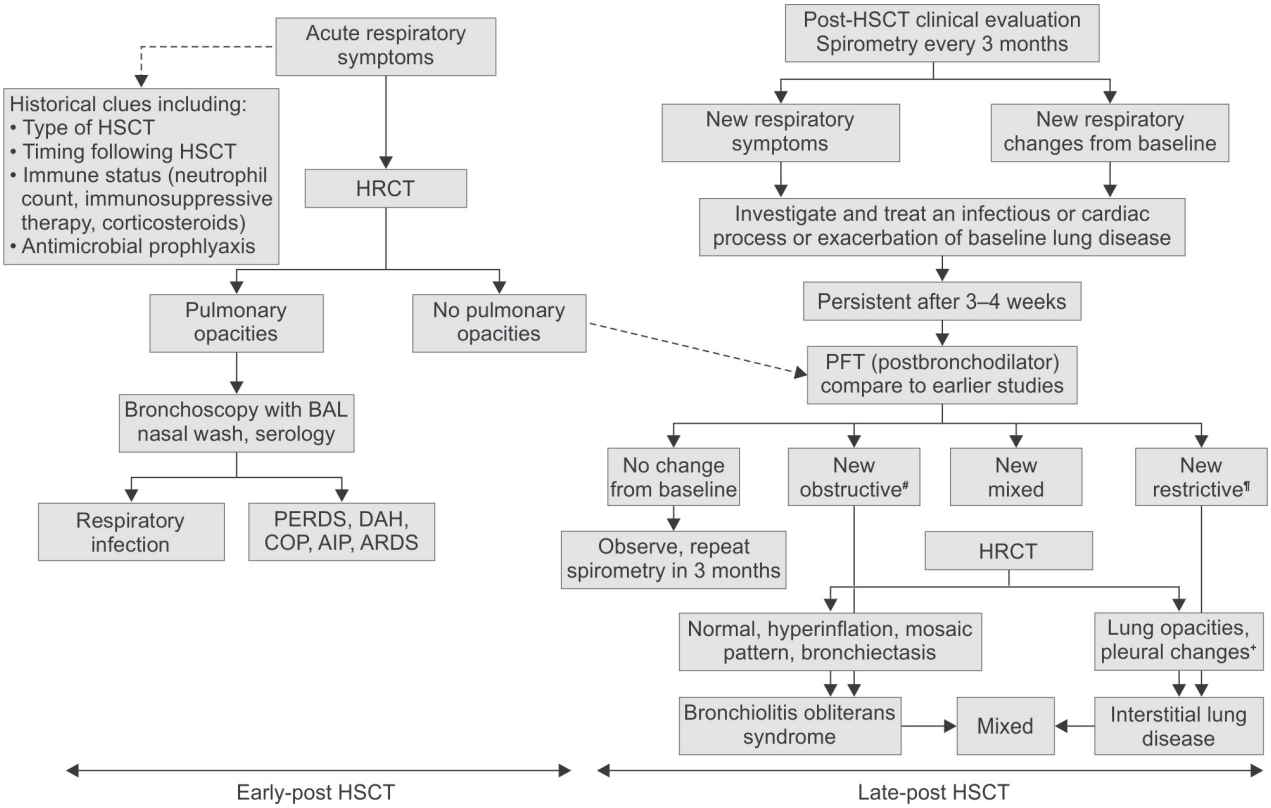
Pulmonary complications depend on factors such as intensity of conditioning regimen, source of stem cells, use of radiation, pre-existing pulmonary dysfunction, previous episodes of pulmonary infections, smoking, older age, and graft versus host disease (GVHD).[3] Broadly, depending on time of onset, we can classify pulmonary complications into the following:

- *Early complications (from day of transplant to 100 days)*: Pulmonary edema, idiopathic pneumonia syndrome (IPS), periengraftment respiratory distress syndrome (PERDS), diffuse alveolar hemorrhage (DAH), acute radiation pneumonitis, infections, delayed pulmonary toxicity, and acute GVHD.
- *Delayed complications (beyond 100 days)*: Chronic GVHD, bronchiolitis obliterans syndrome (BOS), cryptogenic organizing pneumonia (COP), interstitial lung disease (ILD) or pulmonary fibrosis, post-transplant lymphoproliferative disorders (PTLD), and infections.

An initial diagnostic algorithm is provided in **Flowchart 1**. We describe some of the pulmonary complication below.

- *Pulmonary edema*: Perhaps the most common complication of HSCT and can be asymptomatic or a life-threatening condition due to cardiac or renal dysfunction or increase vascular permeability or direct drug toxicity. Most common cause is fluid overload resulting from hyperhydration to prevent chemotherapeutic drug toxicity. Use of strict input–output charting, weight monitoring, and low-dose diuretics are useful preventive measures.
- *IPS*: IPS term is used collectively for several conditions like PERDS, DAH, acute respiratory distress syndrome, noncardiogenic edema, capillary leak syndrome, delayed pulmonary toxicity syndrome (DPTS), and COP. It is diffuse alveolar injury with no identifiable cause. It is mostly observed 4–6 weeks post-transplant with 3–15% incidence. It is common with allogenic transplant and higher intensity conditioning regimen. Paradoxically >grade 2 acute GVHD and >1,200 rads radiation provide better survival.[4] Exact mechanism is not known but can be direct injury to parenchyma or endothelium by chemotherapeutic agents or immune-mediated.
- *PERDS*: Respiratory distress accompanied by fever, chills, flushing, fluid retention, and decrease urine output may precede, coincide, or follow the neutrophil engraftment. Depending on type of conditioning, graft source and reporting methods frequency ranges from 2 to 25%.[3] It is postulated to occur due to sudden increase in neutrophil that are more sticky and bind to pulmonary vasculature with release of inflammatory cytokines.[5] It is more often seen with autologous and haploidentical than in matched donor transplant possibly due to greater use of granulocyte colony-stimulating factor (GCSF) in the former. Most cases are mild and can be managed by supportive care but severe cases may require use of steroids or agents such as tocilizumab to tide over inflammatory cytokine storm.

Flowchart 1: Algorithm of the initial diagnostic approach to hematopoietic stem cell transplantation (HSCT) patients presenting with new respiratory symptoms.



(HRCT: high-resolution computed tomography; BAL: bronchoalveolar lavage; PERDS: peri-engraftment respiratory distress syndrome; DAH: diffuse alveolar hemorrhage; COP: cryptogenic organising pneumonia; AIP: acute interstitial pneumonitis; ARDS: acute respiratory distress syndrome; PFT: pulmonary function test.)

#Spirometry showing forced expiratory volume/forced vital capacity < 0.7 and decrease in forced expiratory volume in 1s ≥10% from baseline.

¶Decline in total lung capacity ≥10% from baseline.

+Persistent multilobar opacities (ground-glass, consolidation, small linear and reticular) with increasing pleural thickening consistent with pulmonary and/or pleural fibrosis.

Source: Haider S, Durairajan N, Soubani AO. Noninfectious pulmonary complications of haematopoietic stem cell transplantation. Eur Respir Rev. 2020;29(156):190119.

- *Diffuse alveolar hemorrhage*: It is seen in 5–30 %.[6] More often with autologous than allogeneic BMT. Usually seen 2 weeks after engraftment and may be fatal. Diffuse opacities on lung imaging, hemoptysis, or bloody endotracheal aspirate (may be present) with drop in hemoglobin are suggestive but diagnosis depends on bronchoscopy.
- *Acute pulmonary GVHD*: Pulmonary involvement is rare as it mainly affects liver, skin, and gastrointestinal (GI) tract. It is rare in autologous transplant. It resembles pulmonary edema or acute lung injury. It is a major complication of BMT and may cause mortality.
- *Acute radiation pneumonitis*: It usually manifests from 4 weeks to 6 months after radiotherapy.[4,7] Clinical presentation is similar to infection but bronchoalveolar lavage (BAL) shows only inflammatory infiltrate. Some authors do not consider total body irradiation (TBI) as a risk factor.[7] It can be a localized involvement in area of radiation or diffuse involvement.
- *Delayed pulmonary toxicity*: It occurs usually around 6–8 week post-transplant and resembles idiopathic pneumonia syndrome[3] and is responsive to steroids. Common in patients who have received high-dose chemotherapy or autologous transplant.[8] Ground glass opacities are most common but may be absent in 30% cases.
- Infections:
  - *Bacterial infections*: Highest incidence of bacterial infections is seen during the first 2 weeks of transplant as it is the neutropenic phase. As high as 44% of all pneumonias are due to bacteria.[9] In India, gram-negative bacteria predominate and infection can be either primary or secondary to lung seeding from GI tract origin bacteremia. Drug-resistant infections are particularly troublesome. Some studies have advocated prophylactic fluoroquinolones during the neutropenic phase but this is not uniformly practiced.

Prevalence of TB is high in India and fluoroquinolones are reserve drug and their usage may potentially promote emergence of drug-resistant tuberculosis (TB) in these patients. Reactivation of TB is possible in high prevalence countries. Patients with long-standing chronic GVHD and on immunosuppression are also at increased risk of infection with capsulated organisms and some centers advocate post-transplant penicillin prophylaxis for 1 year.

- *Fungal infections*: It is the second most common infections but incidence increases in post-transplant period with prolongation of immunosuppression. *Aspergillus* are the most common agent followed by *candida*. Rarely zygomycetes may be isolated. Early diagnosis can be made based on increased galactomannan or fungal hyphae in BAL and typical HRCT thorax features. Patients undergoing allogenic transplant or pre-existing pulmonary diseases or previous fungal pneumonia and those who have GVHD are at increased risk. Prophylactic use of posaconazole is now approved in all guidelines for allo-HSCT. *Pneumocystis jirovecii* can also cause pneumonia but incidence have reduced to 1–2.5% with co-trimoxazole prophylactic.[10]
- *Viral infection*: Cytomegalovirus (CMV) reactivation is a major issue as most of the donors and recipients are CMV immunoglobulin (IgG) positive. Most vulnerable period is after engraftment and in the first 3 months period during the time of immune reconstitution. Delayed CMV reactivation happens in chronic GVHD patients on immunosuppression. Use of T cell depletion in vitro or in vivo by antithymocyte globulin/cyclophosphamide is associated with increased risk. Letermovir has now been recommended as a prophylaxis agent but is expensive. Pre-emptive use of ganciclovir is universally used treatment. Cidofovir, intravenous immunoglobulin (IVIg), or foscarnet are more commonly used as second line treatment after ganciclovir failure or toxicity. CMV-specific IgG is considered to be highly effective but has limited availability. Respiratory syncytial virus, adenovirus, influenza, and parainfluenza are also common and is associated with higher morbidity and mortality compared to general population.

- *COP*: It was previously termed as bronchiolitis obliterans organizing pneumonia. It is seen more often in allogenic transplant and in those who received radiotherapy. Patients have cough, fever, and dyspnea associated with restrictive lung function pattern. Imaging show nonspecific consolidation along with ground glass and nodules. Lung biopsy classically shows intra-alveolar granulations. BAL is needed to rule out any infections. Long-term steroid is the treatment of choice.
- *Bronchiolitis obliterans syndrome*: Patients commonly presents with new onset of dyspnea with cough after few months of allogenic transplant. Clinical course is variable. There is progressive decrease of forced expiratory volume in the first second (FEV1) which is not corrected by bronchodilators. Lung biopsy is confirmatory, epithelial damage to bronchioles leading to fibrosis and luminal obstruction, but not done routinely. This results from T-cell mediated chronic inflammation of bronchiolar epithelium. This may be secondary to busulphan, BCNU (1,3-bis(2-chloroethyl)-l-nitrosourea), radiation, chronic GVHD, viral infections, peripheral blood derived stem cell transplant, etc. Treatment includes steroid, calcineurin inhibitors and anti-TNF alpha agents, Igs, etc., but results are unsatisfactory. Prolonged use of azithromycin may be useful.[8]

- *Interstitial lung fibrosis*: It is a rare complication affecting 2–3% of patients of allogeneic transplantation.[3] Patients present with progressive dyspnea without any fever. Pulmonary function test (PFT) demonstrates mainly restrictive or less often mixed pattern. Prognoses of patients with ILD is poor.
- *PTLD*: It is abnormal proliferation of donor-derived lymphocyte induced by Epstein–Barr virus (EBV) infection. It is a rare event and incidence is around 1%.[7] Usually it is B cell but can be of T cell origin. It can be monomorphic, polymorphic, reactive plasma cells or vary rarely Hodgkin disease.[8] Mediastinal lymphadenopathy with uncommonly parenchymal mass or nodule or pleural effusion is the presentation. Condition is rare and usually happens in the initial months of transplant.[3] Diagnosis is best established by biopsy though often not possible. Indirect diagnosis using PET scan and quantitative EBV DNA titers may be possible.
- *Pulmonary alveolar proteinosis*: It is characterized by rapid onset of dyspnea in a postallogeneic transplant patients. It can also happen secondary to infection with *P. jirovecii* or parainfluenza. Surfactant gets accumulated in the alveoli and hampers the diffusion of gases. On chest X-ray, it produces diffuse infiltrate pattern, crazy paving pattern on CT chest, and BAL reveals presence of periodic acid Schiff positive amorphous material.[8] It is a rare and delayed complication but must be kept in mind as it has a very high mortality rate.

MANAGEMENT

Mild Cases

Patients may present to oncologist in outpatient setting with mild symptoms and need to be evaluated as to the cause and treated. Cross consultation with pulmonologist may be needed as also laboratory work up, PFT, and imaging.

Bronchiolitis Obliterans

Prolonged low-dose azithromycin in HSCT patients with BOS showed a mean increased in FEV_1 by 30 mL.[11] Other agents such as moneleukast,[12] inhaled formoterol/budesonide are useful.[13] There are ongoing trials of inhaled cyclosporine and oral neutrophil elastase inhibitor for treatment of post-HSCT bronchiolitis obliterans (ClinicalTrials.gov identifiers: NCT01273207 and NCT02669251). Nintedanib and pirfenidone are also under trial.

Hematopoietic stem cell transplantation-associated ILD is histologically varied but may be responsive to steroids. It may be a manifestation of HSCT-associated autoimmune disorder, which needs to be treated accordingly.

Lung involvement is complex, with a range of conditions that include BOS, ILD, and pleuroparenchymal fibroelastosis (PPFE) that could even coexist.[14]

Pleural effusion can be due to fluid over load (treat with diuretics and fluid restriction) or infections (treat after establishing diagnosis) or rarely serositis (treat with increasing GVHD treatment, repeated thoracentesis) or drug induced. Thoracic air leak syndrome (pneumomediastinum, spontaneous pneumothorax, subcutaneous emphysema, and pneumopericardium) results from the "Macklin effect," treatment is drainage. Both occurrence of pleural effusion and air leak are associated with increased mortality despite treatment.

Moderate-to-severe Presentation

Patient with respiratory complications can only present with cough, expectoration, dyspnea, and with or without respiratory failure; sometimes with hemoptysis. The initial evaluation must include detailed history taking and examination, arterial blood gas (ABG), X-ray of the chest plus most commonly HRCT of the chest, hemogram, liver and kidney function tests, blood cultures, and procalcitonin. If patient is expectorating, collect sputum specimen for staining [Gram, fungal, pneumocystis pneumonia (PCP), and AFB] and cultures. Do an electrocardiogram (ECG). Consider doing an echocardiogram, cardiac enzymes, and N-terminal pro-brain natriuretic peptide (NT-proBNP).

Microbiological evaluation is of utmost priority as it point toward either infectious or noninfectious complication. An early fiberoptic bronchoscopy [sometimes supported by noninvasive ventilation (NIV) or high flow nasal cannula (HFNC)] to obtain BAL. In case of intubated patients, nonbronchoscopic BAL is also an option. Lower respiratory specimens must be sent for stains and cultures. If BAL is blood stained (or DAH is suspected), serial small aliquot BAL must be obtained after wedging the bronchoscope—an increasing content of blood in latter aliquots suggests DAH. Bleeding from >30% alveolar surface may be seen. Also look for 20% or more hemosiderin-laden macrophages (siderophages) as demonstrated by Prussian blue staining of BAL. Consider BAL sending for multiplex polymerase chain reaction (PCR) (e.g., Biofire pneumonia plus panel). Latter when available can potentially provide microbiological diagnosis within an hour along with presence of genes for antibiotic resistance. BAL cytology with hypercellularity and >20% lymphocytosis and a decreased CD4/CD8 ratio is seen in COP. Transbronchial bronchoscopic biopsy can potentially aggravate the situation due to pneumothorax but are diagnostic for COP and DPTS.[15-18]

First step in management is physiological stabilization (in tandem with diagnostic procedures). Start oxygen (after checking SpO_2 and immediate ABG) with nasal prongs or face mask. If patient is still distressed, consider NIV with full face mask or helmet interphase. If there is no hypercarbia, HFNC is a good alternative. Patient needs to be moved into a respiratory high-dependency unit (HDU) or intensive care unit (ICU) early for careful monitoring.

Hemodynamic status must be evaluated early. If blood pressure (BP) is low or arterial lactate >4 mmol/L or urine output <0.5 mL/kg/hr, evaluate volume status [clinical, ultrasonography (USG) to look at inferior vena cava and lungs, X-ray of the chest] and give titrated fluid resuscitation. If after initial bolus fluids patients BP, mentation, urine output, and lactates, do not normalize quickly start noradrenaline. If more than a small dose is needed, add vasopressin early. Monitor arterial BP, target mean arterial pressure (MAP) >65 mm Hg.

If respiratory distress persists or worsens or patient has altered sensorium or needs more than minimal inotropic support, early intubation and mechanical ventilation (MV) needs to be instituted. Apply lung protective ventilation. Add sedatives (midazolam and propofol) and pain reliever (fentanyl). Patients with acute respiratory distress syndrome (ARDS) may also need neuromuscular paralysis.

Severe lung injury in long-term >240 days postallogeneic HSCT recipients, otherwise eligible for aggressive interventions, may benefit from ECMO (survival 46%).[19]

Attention to mouth care, prevention of pressure sores, early enteral feeding, delirium assessment and treatment, etc., are useful. Standard nursing care and attention to nosocomial infection prevention are needed.

Specific Treatment

- *Antibiotics*: Start empirical antibiotics early based on possible etiological agents (depends on duration since transplant, prophylaxis being received, recent use of antibiotics, level of immunosuppression used, and neutropenia). Make every attempt to obtain microbiological specimens before first antibiotic dose. Deescalate or modify once microbiological information is available.

In case of secondary deterioration (presumed infection induced), obtain fresh specimens of blood, lower respiratory tract specimen, and even urine for stains and cultures and add broader spectrum empirical antibiotics based on institution guidelines to be modified based on laboratory results. Co-trimoxazole should be considered even based on radiological evidence (diffuse opacity with peripheral sparing) and clinical likelihood even before microbiological confirmation.

- *Corticosteroids*: They are very useful for PERS and moderately for DAH. High dose like 1–2 mg/kg methylprednisolone twice a day for 3 days and then taper off over next few days. For DPTA, a dose of 1 mg/kg of methylprednisolone is used. Also, low-dose steroids may help in case of persistent hypotension. If patient was already on long-term steroids, similar of slightly higher doses must be continued during the acute disease. Steroids also help in case of PCP pneumonia. For COP 0.5–1.0 mg/kg, prednisolone is to be initiated and tapered over several months. Drug-induced lung injury (cyclosporine, fludarabine, and sirolimus) may also respond to steroids.
- In case of DAH treatment may include platelet transfusions, therapies such as aminocaproic acid and recombinant factor VIIa and cytokine antagonists (etanercept and cyclophosphamide) with variable success.
- Most cases of venous thromboembolism occur within 6–12 months of HSCT. Treatment has to be decided on case-to-case basis.
- Treatment options include reduction of immunosuppression alone as pre-emptive therapy, administration of rituximab, or a combination of both may stop rapidly progressive multiorgan failure and death.[20]

CONCLUSION

Hematopoietic stem cell transplantation number and indications have been increasing over the years and so have recognition of associated pulmonary complications. With better techniques and ability to deal with infections, noninfectious complications have been relatively growing faster. Initial stabilization needs to happen in tandem with definitive diagnosis which then allows specific treatment and prognostication. Collaboration is needed between hematologist, oncologist, pulmonologist, and intensivist to manage these cases.

REFERENCES

1. Baldomero H, Niederwieser D, Bazuaye N, Bupp C, Chaudhri N, Corbacioglu S, et al. One and half million hematopoietic stem cell transplants (HSCT). dissemination, trends and potential to improve activity by telemedicine from the worldwide network for blood and marrow transplantation (WBMT). Blood. 2019;134(Suppl 1):2035.
2. Indian Society for Blood and Marrow Transplantation. ISBMT registry data (unpublished). [online] Available from: https://www.isbmt.org/. [Last accessed February 2022].
3. Haider S, Durairajan N, Soubani AO. Noninfectious pulmonary complications of hematopoietic stem cell transplantation. Eur Respiratory Rev. 2020;29(156):190119.
4. Khurshid I, Anderson LC. Non-infectious pulmonary complications after bone marrow transplantation. Postgrad Med J. 2002;78(919):257-62.
5. Capizzi SA, Kumar S, Huneke NE, Gertz MA, Inwards DJ, Litzow MR, et al. Peri-engraftment respiratory distress syndrome during autologous hematopoietic stem cell transplantation. Bone Marrow Transplant. 2001;27(12):1299-303.
6. De Lassence A, Fleury-Feith J, Escudier E, Beaune J, Bernaudin JF, Cordonnier C. Alveolar hemorrhage: diagnostic criteria and results in 194 immunocompromised hosts. Am J Respir Crit Care Med. 1995;151(1):157-63.
7. Peña E, Souza CA, Escuissato DL, Gomes MM, Allan D, Tay J, et al. Noninfectious pulmonary complications after hematopoietic stem cell transplantation: Practical approach to imaging diagnosis. Radiographics. 2014;34(3):663-83.
8. Soubani AO, Pandya CM. The spectrum of noninfectious pulmonary complications following hematopoietic stem cell transplantation. Hematol Oncol Stem Cell Ther. 2010;3(3):143-57.
9. Aguilar-Guisado M, Jiménez-Jambrina M, Espigado I, Rovira M, Martino R, Oriol A, et al. Pneumonia in allogeneic stem cell transplantation recipients: A multicenter prospective study. Clin Transplant. 2011;25(6):E629-38.
10. Cordonnier C. Pneumonia after hematopoietic stem cell transplantation. In: Ljungman P, Snydman D, Boeckh M. (Eds). Transplant Infections. Switzerland: Springer, Cham; 2016.
11. Yadav H, Peters SG, Keogh KA, Hogan WJ, Erwin PJ, West CP, et al. Azithromycin for the treatment of obliterative bronchiolitis after hematopoietic stem cell transplantation: a systematic review and meta-analysis. Biol Blood Marrow Transplant. 2016;22(12):2264-9.
12. Or R, Gesundheit B, Resnick I, Bitan M, Avraham A, Avgil M, et al. Sparing effect by montelukast treatment for chronic graft versus host disease: a pilot study. Transplantation. 2007;83(5):577-81.
13. Bergeron A, Chevret S, Chagnon K, Godet C, Bergot E, de Latour RP, et al. Budesonide/formoterol for bronchiolitis obliterans after hematopoietic stem cell transplantation. Am J Respir Crit Care Med. 2015;191(11):1242-9.
14. Greer M, Riise GC, Hansson L, Perch M, Hämmäinen P, Roux A, et al. Dichotomy in pulmonary graft-versus-host disease evident among allogeneic stem-cell transplant recipients undergoing lung transplantation. Eur Respir J. 2016;48(6):1807-10.
15. Sircar M, Jha OK, Chabbra GS, Bhattacharya S. Noninvasive ventilation assisted bronchoscopy in high risk hypoxemic patients. Indian J Crit Care Med. 2019;23(8):363-7.
16. Jha O, Kumar S, Mehra S, Sircar M, Gupta R. Helmet NIV in acute hyoxemic respiratory failure due to Covid- 19: Change in PaO_2/FiO_2 ratio a predictor of success. Indian J Crit Care Med. 2021;25(10):1135-44.

17. Sircar M, O Jha, Singh J, Yadav S, Kaur R. Prospective cohort study of Impact of BAL Biofire Filmarray pneumonia panel on microbial diagnosis and antibiotic prescription in ICU. Crit Care. 2020;24 (Suppl 1):446.
18. Sircar M, Ranjan P, Gupta R, Jha OK, Gupta A, Kaur R, et al. Impact of bronchoalveolar lavage multiplex polymerase chain reaction on microbiological yield and therapeutic decisions in severe pneumonia in intensive care unit. J Crit Care. 2016;31(1):227-32.
19. Wohlfarth P, Beutel G, Lebiedz P, Stemmler HJ, Staudinger T, Schmidt M, et al. Characteristics and outcome of patients after allogeneic hematopoietic stem cell transplantation treated with extracorporeal membrane oxygenation for acute respiratory distress syndrome. Crit Care Med. 2017;45:e500-7.
20. Xuan L, Jiang X, Sun J, Zhang Y, Huang F, Fan Z, et al. Spectrum of Epstein–Barr virus-associated diseases in recipients of allogeneic hematopoietic stem cell transplantation. Transplantation. 2013;96(6):560-6.

CHAPTER

78

Approach to Donor-derived Infection and Colonization in the Intensive Care Unit

Parikshit S Prayag, Vasant Nagvekar

INTRODUCTION

Transplantation, both solid organ as well as bone marrow, is on the rise across the globe, especially in India. Successful prevention and management of infections forms the cornerstone of a transplant program. It is important to recognize colonization of the donor with bacteria as well as infections (bacterial, fungal, viral, and parasitic) in a timely manner. Proper protocols must be established to identify, prevent, and treat donor-derived infection and colonization. It is important to know which organs can be accepted in this setting. This also includes putting into place robust screening protocols. This chapter will deal with important issues in the peritransplant setting such as screening donors, identifying infected organs, accepting or refusing organs, which are colonized and reducing the risk of donor-derived infections, with a focus on the intensive care unit (ICU) setting.

DONOR-DERIVED INFECTIONS

Numerous infections can be transmitted from the donor to the recipient, and hence, a detailed donor evaluation must be conducted. This is important from the point of view of identifying these infections and preventing transmission to the recipient **(Table 1)**.

BACTERIAL INFECTION/COLONIZATION IN THE DONOR

In an Indian setting, bacterial infection or colonization of the donor can be commonly found. This is further compounded by the fact that many of the isolates, especially gram-negative organisms found in this setting can be multidrug resistant. Hence, it is important to recognize which organs can be transplanted and to have the proper antimicrobial protocols in place. The approach is different for different scenarios:

Donor with Bacteremia

In general, bacteremia in the donor is not a contraindication for transplantation. In a study assessing the outcome of transplantation of organs procured from bacteremic donors, the outcomes of transplantation were not affected by the presence of donor bacteremia.[1] In a study from Italy, there were 14 recipients who received an organ from a high-risk donor (bacteremia or colonization of the transplanted organ with carbapenem-resistant gram-negative organisms). Proven transmission occurred in 4 out of the 14 high-risk recipients because donor infection was either not identified or there was no prompt communication. These recipients did not receive optimum post-transplant antibiotic therapy.

TABLE 1: Potential donor-derived infections in the transplant setting.

Bacteria	*Viruses*	*Fungi*	*Parasites*
• Gram-negative infections including multidrug-resistant pathogens • Gram-positive infections including *Staphylococcus*, *Enterococcus* (vancomycin-resistant *Enterococcus*), *Listeria* • Mycobacterial infections • Rickettsial infections, *Borrelia*, *Brucella* species • *Nocardia* • Syphilis	• HIV • Hepatitis viruses B, C, and E • Influenza • Adenovirus • CMV • HSV • ? COVID-19	• Candida • *Aspergillus* • Mucorales • *Cryptococcus* • Histoplasma	• Malaria • Toxoplasma • Schistosoma • Strongyloides

(CMV: cytomegalovirus; HIV: human immunodeficiency virus; HSV: herpes simplex virus)

Transmission did not occur in any high-risk recipient who received the optimum antimicrobials for at least 7 days.[2]

If feasible, delaying transplantation till the donor has received at least 48 hours of the appropriate antimicrobial therapy (based on susceptibility results) is prudent. Also, in the setting of bacteremia, a reasonable protocol is to administer the appropriate antibiotics (with demonstrated sensitivity) to the recipient for at least 7 days. Decisions to prolong this therapy to 14 days should be made on a case-to-case basis.

Donor with Bacterial Meningitis

A donor with bacterial meningitis is not a contraindication for transplantation. Several studies have shown that organs from donors with bacterial meningitis can be transplanted without adverse outcomes.[3-5] Donors should be on the appropriate antibiotics for at least 24–48 hours prior to procuring the organs and these should be continued in the recipient for about 7–10 days. Efficient communication is an integral part of this protocol and microbiologists as well as infectious diseases physicians should be consulted. Susceptibility as well as penetration into the central nervous system should be considered before choosing the antimicrobials.

When meningitis is caused by highly virulent pathogens such as *Listeria* or *Mycobacterium tuberculosis*, some transplant centers consider it to be a contraindication for organ transplant.

Donor with Colonization or Infection of the Transplanted Organ

As described above, in the study from Italy, transmission occurred in recipients when they were treated with inappropriate or short courses of therapy.[2] Hence, if an organ with bacterial colonization is transplanted, it is imperative to communicate properly and involve experts, to optimize the management of recipients. A transplant infectious diseases physician should be involved in this process.

Donor with Colonization Elsewhere (Other Than the Transplanted Organ)

This will not be a contraindication for transplantation. Also, in this situation, unnecessary usage of antibiotics must be avoided. This should be assessed on a case to case basis. Most donors in the ICU are at a risk for colonization, and this increases with other factors such as prolonged ICU stay, multiple antibiotics, indwelling devices, and duration of mechanical ventilation. Donor colonization (proven or suspected) at a site other than the transplanted organ needs careful evaluation by a transplant infectious diseases physician to see if targeted therapy is needed in the perioperative period for the recipient. This information should be clearly relayed to the treating teams.

Donor with Evidence of Syphilis

Both treponemal and nontreponemal tests should be used as a part of an algorithm to determine the presence of syphilis in the donor. Current evidence suggests that a donor with active syphilis need not be excluded as long as the recipient gets adequate therapy in the post-transplant setting.[6]

Tuberculosis

Donors with active tuberculosis (TB) are generally a contraindication for transplantation. Thorough assessment of donors in the ICU must be conducted to rule out active TB and should involve a transplant infectious diseases physician.

VIRAL INFECTION IN THE DONOR

Human Immunodeficiency Virus

A donor who is human immunodeficiency virus (HIV) positive remains a contraindication for a seronegative recipient.

There are research trials underway to assess whether a seropositive patient can be a donor for a seronegative recipient.

Hepatitis Viruses

Donors infected with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) should not be excluded. However, to determine the feasibility of such transplants, various factors need to be considered and this should be done by a relevant expert.

In addition, donors who are currently negative, but have risk factors for acquisition of HIV/HBV or HCV should not be excluded, but the risk should be communicated to the recipient so that enhanced surveillance can be practiced. Such adult donors include:

- Donors with high-risk sexual behavior
- Long-standing hemodialysis patients
- Donors who have injected drugs for nonmedical reasons.
- Donors who have been treated for other sexually acquired infections in the preceding 12 months.

Coronavirus Disease (COVID-19)

There is a theoretical risk of transmission of COVID-19 from the donor to the recipient is based on the fact that viral ribonucleic acid (RNA) is detected in organs that can be transplanted (e.g., lung, heart, kidney, and intestine) and in other sites (i.e., blood and urine).[7,8] Donors who have active COVID-19 (clinically, proven by testing or radiographically) or who have had infection in the preceding 21 days should be excluded.[9] Also, donors who have been exposed to individuals with known or suspected COVID-19 in the preceding 14 days should be excluded.[9]

Donor with Vaccine-induced Thrombosis and Thrombocytopenia

There is insufficient data to conclude whether a donor with thrombosis secondary to COVID-19 vaccination can be included as an organ donor. In a study involving donors with vaccine-induced thrombosis and thrombocytopenia (VITT), 21 of 27 (78%) allografts had satisfactory function after a median follow-up of 19 days post-transplantation.[10] Every effort must be made to exclude thrombosis in the graft, and can involve the use of Doppler as well as histopathological evaluation with a biopsy. Anti-PF4 antibodies can induce platelet activation and thrombosis, and hence, platelet transfusion should be avoided as far as possible. Anticoagulation regimens should generally include agents other than heparin. However, detailed counseling and consenting has to be a part of such protocols where there is inadequate clarity.

Donors with unexplained encephalitis should generally be excluded.

Dengue Virus

Cases of transmission of the dengue virus from the donor to the recipient have been described.[11] Although there are no official recommendations at this point of time, in endemic areas such as India, the transplant teams should be aware of the possibility of such transmissions. Donors with active dengue infection are best avoided.

Though cytomegalovirus and Epstein-Barr virus are not contraindications for organ donation, the serostatus helps in planning further prophylaxis in the recipients.

FUNGAL INFECTIONS IN THE DONOR

Candida

Donors with untreated candidemia should be excluded. Donors who have had adequate treatment and documented eradication of candidemia are usually considered to be low risk, and can be included, though the data is sparse. It would be reasonable to include these and administer appropriate antifungal therapy to the recipient in the peritransplant period. In the absence of documented infection in the recipient, empiric antifungal therapy can be discontinued at 2 weeks, and routine prophylactic guidelines (which may vary across centers) should be followed.

Candida isolated from the preservation fluid, or in the donor urine cultures in cases of kidney transplants, should be treated for 2 weeks in the recipients, unless there is evidence of continued infection or a robust reason to prolong antifungal therapy.

Colonization at distant sites need not always be treated, and decisions should be taken after consulting a transplant infectious diseases physician.

Renal and urinary penetration of antifungal agents should be considered, especially when dealing with fluconazole resistant species.

Usually, lung transplant centers use at least 3 months of antifungal prophylaxis. If candida isolated in the donor respiratory cultures is not covered as a part of the routine post-lung transplant antifungal prophylaxis, then anti-Candida therapy should be used till bronchoscopy has confirmed the integrity of the bronchial anastomosis. A more prolonged course can be used for recipients of bilateral or right lung transplants and in patients receiving depleting induction agents.

Mold Infections

Mold infections, such as *Aspergillus* and mucormycosis in the donor are generally considered to be a contraindication for transplantation.

Contamination of the preservation fluid can be a mode of transmission, leading to invasive mold infections in the recipients. Steps to identify and prevent such occurrences must be taken and appropriate communication must ensue, so that the recipient receives mold active therapy.

Donor with Cryptococcal Infection

The chances of transmission to the recipient are considerable, and hence, a donor with active cryptococcal disease is usually avoided. In cases, where the donor has been treated adequately and fungal eradication has been documented, transplantation can be considered. This should be done in consultation with a transplant infectious diseases expert.

PARASITIC INFECTIONS IN THE DONOR

Certain parasitic infections can be transmitted from the donor to the recipient. Local knowledge of the endemic parasites is crucial. Appropriate screening protocols can be then put into place.

Donors can be screened for strongyloides, which can be transmitted to the recipient, and can cause severe disease. Antibody results should not delay transplantation, but if positive, preventive ivermectin is a safe and effective approach for the recipient. Donors in the ICU with active malaria should be excluded. Donors with a strong suspicion for visceral leishmaniasis (VL) or proven VL should be generally excluded. These discussions should involve all the concerned teams.

SUMMARY OF THE APPROACH TO DONOR INFECTION/COLONIZATION

- Active bacteremia/meningitis in the donor is not a contraindication as long as the donor has received the appropriate antibiotics for 48 hours, and the information is relayed properly so that the recipient is treated.

- Approach to an organ colonized with bacteria which is transplanted should be similar to donor bacteremia.
- Donor colonization at a site other than the transplanted organ is not a contraindication and unnecessary antibiotic use should be avoided.
- Donors with active TB, severe malaria, dengue, mold infections should generally be avoided.
- Donors with active COVID-19 within the preceding 21 days or potential exposures within the prior 14 days are usually excluded.
- Donors with VITT should be included only after a thorough evaluation, multidisciplinary consultation, and extensive counseling.
- Donors with candidemia can be included if they have received adequate therapy with eradication of infection.
- Each center must develop a clear protocol in accordance with the local transplant authorities.
- Involvement of a transplant infectious diseases expert is invaluable, if such expertise is available.

CONCLUSION

It is important to recognize infections and colonizations promptly in the donor. This is a fine balance between not rejecting an organ in a set up where recipients have to endure long waiting periods and ensuring safety of transplantation. Local authorities, treating teams, and infectious diseases specialists have to act as a team and ensure prompt communication and an evidence-based approach.

REFERENCES

1. Freeman RB, Giatras I, Falagas ME, Supran S, O'Connor K, Bradley J, et al. Outcome of transplantation of organs procured from bacteremic donors. Transplantation. 1999;68:1107-11.
2. Mularoni A, Bertani A, Vizzini G, Gona F, Campanella M, Spada M, et al. Outcome of transplantation using organs from donors infected or colonized with carbapenem-resistant gram-negative bacteria. Am J Transplant. 2015;15(10):2674-82.
3. López-Navidad A, Domingo P, Caballero F, González C, Santiago C. Successful transplantation of organs retrieved from donors with bacterial meningitis. Transplantation. 1997;64:365-8.
4. Paig I JM, Lopez-Navidad A, Lloveras J, Mir M, Orfila A, Quintana S, et al. Organ donors with adequately treated bacterial meningitis may be suitable for successful transplantation. Transplant Proc. 2000;32:75-7.
5. Satoi S, Bramhall SR, Solomon M, Hastings M, Mayer AD, de Goyet JV, et al. The use of liver grafts from donors with bacterial meningitis. Transplantation. 2001;72:1108-13.
6. Screening of donor and recipient prior to solid organ transplantation. Am J Transplant. 2004;4(Suppl 10):10-20.
7. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA. 2020;323:1843-4.
8. Tavazzi G, Pellegrini C, Maurelli M, Belliato M, Sciutti F, Bottazzi A, et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. Eur J Heart Fail. 2020;22:911-5.
9. American Society of Transplantation. (2020). SARS-CoV-2 (Coronavirus, 2019-nCoV): Recommendations and guidance for organ donor testing. [online]. Available from: https://www.myast.org/sites/default/files/Donor%20Testing_100520_revised_ReadyToPostUpdated10-12.pdf [Last accessed December, 2021].
10. UK Donor VITT Transplant Study Group, Greenhall GHB, Ushiro-Lumb I, Pavord S, Currie I, Perera MTPR, et al. Organ transplantation from deceased donors with vaccine-induced thrombosis and thrombocytopenia. Am J Transplant. 2021;21(12):4095-7.
11. Cedano JA, Mora BL, Parra-Lara LG, Manzano-Nuñez R, Rosso F. A scoping review of transmission of dengue virus from donors to recipients after solid organ transplantation. Trans R Soc Trop Med Hyg. 2019;113(8):431-6.

CHAPTER 79

Antiviral Drugs in Transplant Recipients

Rajeev Soman, Sujata Rege, Geethu Joe

INTRODUCTION

Solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) recipients are uniquely predisposed to develop clinical illness, often with increased severity, due to a variety of common and opportunistic viruses. Patients may acquire viral infections from the donor (donor-derived infections), from reactivation of endogenous latent virus, or from the community. Treatment for viruses with proven effective antiviral drug therapies should be complemented by reduction in the degree of immunosuppression.[1] For others with no proven antiviral drugs for therapy, reduction in the degree of immunosuppression remains as the sole effective strategy for management. Prevention of viral infections is therefore of utmost importance, and this may be accomplished through vaccination, antiviral strategies, and aggressive infection control measures.[2]

Knowledge of nucleotide sequences, domains of structural, and enzyme proteins have enabled the design of antiviral drugs that target different steps of the viral-host interaction and replication cycle. A combination of such agents appear to be more effective in certain viral infections. Viruses can also be neutralized by antibodies and cell-mediated immunity which have found application in certain situations.

ANTIVIRAL DRUGS FOR CYTOMEGALOVIRUS[3]

Ganciclovir and Valganciclovir

Mechanism of Action

Ganciclovir (GCV) is converted intracellularly to monophosphate form by viral kinase. Cellular kinases catalyze the formation of di- and triphosphate [guanosine triphosphate (GTP)] forms which concentrate 10-fold greater in cytomegalovirus (CMV)-infected cells. GTP preferentially inhibits viral DNA polymerases as well as blocks chain elongation. Valganciclovir (vGCV) is an oral prodrug that is rapidly converted to GCV.

Resistance

Mutations in UL97 CMV phosphotransferase (conferring resistance to GCV/vGCV but not to cidofovir and foscarnet) and UL 54 CMV DNA polymerase (high level GCV resistance, cross-resistance to cidofovir).

Pharmacokinetics and Pharmacodynamics

Valganciclovir is absorbed orally with bioavailability of 60% (when administered with food) and hydrolyzed to GCV in the intestinal wall and liver.

Ganciclovir is excreted unmodified in urine and has higher intracellular half-life. Clearance of GCV correlates to glomerular filtration rate (GFR), hence dosage adjustment is required with impaired renal function. Hemodialysis decreases serum concentration by 50%, hence dosing postdialysis is recommended.

Administration and Dosage

- *Ganciclovir*: Intravenous (IV) and intraocular. IV: 5 mg/kg 12 hourly induction therapy followed by 24 hourly maintenance therapy.
- *Valganciclovir*: Oral 900 mg twice daily induction therapy followed by once daily maintenance.

Toxicity and Monitoring

- *Bone marrow suppression*: GCV and vGCV are associated with bone marrow suppression, particularly leukopenia, and are contraindicated when absolute neutrophil count (ANC) <500 cells/uL and/or platelet count <25,000/uL. Neutropenia is commonly observed in second week of treatment and is reversible in most patients within a week of drug cessation. Hematopoietic growth factors [granulocyte colony-stimulating factor (G-CSF)] are useful in counteracting myelosuppressive effect.
- *Nephrotoxicity*: It is potentiated by coadministration with other nephrotoxic drugs, e.g., cyclosporine.

- *Central nervous system (CNS) toxicity*: Ranges from headache to behavioral changes, seizures, and coma.

Hemogram and renal function test should be done twice weekly in induction therapy.

Drug Interactions

Increased risk of nephrotoxicity with coadministration of drugs such as cotrimoxazole, cyclosporine, and amphotericin B.

Foscarnet

Used in GCV resistant CMV infections.

Mechanism of Action

Foscarnet selectively inhibits CMV DNA polymerase by binding to pyrophosphate-binding site thereby blocking chain elongation.

Resistance

Mutations in CMV UL54 gene encoding DNA polymerase. These mutations can arise during therapy with foscarnet as well as with prolonged GCV exposure, after development of UL97 mutations.

Pharmacokinetics and Pharmacodynamics

Foscarnet has poor oral bioavailability, hence is given intravenously. It is eliminated renally and plasma clearance depends on glomerular function, so dosage adjustment is required in renal dysfunction. Hemodialysis removes around 40% drug, postdialysis dosing is recommended.

Administration

- Intravenous (IV)
- *Dosage*: 60 mg/kg/dose 8 hourly or 90 mg/kg/dose 12 hourly

Toxicity

- Foscarnet has a narrow therapeutic index.
- *Nephrotoxicity*: Azotemia, proteinuria, and acute tubular necrosis are major dose-limiting side effects, usually seen in second week of therapy. Saline hydration pre- and postdrug infusion reduces risk.
- *Metabolic abnormalities*: Being a potent chelator of divalent cations, hypocalcemia, hypomagnesemia, hypokalemia, and hypophosphatemia are commonly seen. Administering drug infusion at 1 mg/kg/min via infusion pump can help minimizing risk.
- *CNS effects*: Headache, acute dystonia, seizures, tremors, irritability, and hallucinations.

Drug Interactions

Coadministration with other nephrotoxic agents increases risk of renal toxicity. Administration with tacrolimus (TAC) increases risk of neurotoxicity.

Cidofovir

Mechanism of Action

Cidofovir undergoes cellular phosphorylation to its diphosphate form, which competitively inhibits viral synthesis via CMV DNA polymerase.

Resistance

Point mutations in UL54 gene encoding CMV DNA polymerase.

Pharmacokinetics and Pharmacodynamics

Cidofovir has poor oral bioavailability. Over 80% of the drug is excreted unchanged in the urine. Cerebrospinal fluid (CSF) penetration is low. High-dose probenecid (2 g 3 hours before and 1 g 2 hours before and 8 hours after infusion) blocks tubular secretion of cidofovir, thereby reducing renal clearance and increasing blood levels.

Toxicity

- *Nephrotoxicity*: Dose-related nephrotoxicity is the principal side effect of cidofovir. Preinfusion hydration and probenecid reduces risk. Cidofovir is contraindicated in persons with proteinuria 2+ or greater or creatinine clearance (CrCl) <55 mL/min.
- Neutropenia develops in around 30% patients, regular monitoring is necessary.

Antivirals for Cytomegalovirus Prophylaxis[4]

Approach to CMV prophylaxis in transplant recipients can be either:

- *Prophylactic*: Prophylaxing transplant recipients with high-risk of CMV reactivation with antivirals for 100 days.
- *Pre-emptive*: Serial quantitative CMV PCR testing and treating those who develop viremia (threshold 500–1,000 copies/mL).

Agents used for CMV prophylaxis include GCV/vGCV, high-dose acyclovir, letermovir, and maribavir.

Letermovir

Letermovir inhibits viral replication by targeting CMV DNA terminase enzyme complex and has been approved for CMV prophylaxis in HSCT recipients. It is currently unavailable in India.

Maribavir

Maribavir is a novel investigational drug for treatment of refractory/resistant CMV disease. It is presently unavailable in India.

ANTIVIRAL DRUGS FOR HERPES SIMPLEX AND VARICELLA ZOSTER

Acyclovir and Valacyclovir

Mechanism of Action

Acyclovir is activated by viral thymidine kinase which further competitively inhibits viral DNA synthesis. Acyclovir is approximately 10 times more potent against herpes simplex virus (HSV)-1 and HSV-2 than against varicella zoster virus (VZV), and even lesser against CMV. Valacyclovir is the L-valyl ester prodrug of acyclovir.

Resistance

- Absent/low production of viral thymidine kinase
- Altered thymidine kinase activity resulting in decreased acyclovir phosphorylation
- Altered viral DNA polymerase

Pharmacokinetics and Pharmacodynamics

Acyclovir has an oral bioavailability of 15–30%, which decreases with higher doses. IV formulations achieve higher steady state peak plasma concentrations, hence is preferred for serious infections.

Acyclovir achieves widespread tissue and fluid penetration including CSF. Excretion is predominantly renal, hence dosage modifications are required in the presence of renal insufficiency, which is a risk factor for acyclovir-related neurotoxicity.

Toxicity

- *Nephrotoxicity*: Acute renal failure produced by precipitation of relatively insoluble acyclovir crystals in renal tubules. Risk can be minimized by prior hydration and slow drug infusion.
- *Neurotoxicity*: Typically occurs in patients with underlying renal failure. Symptoms include agitation, delirium, hallucinations, and tremors.

Drug Interactions

Concomitant use of cyclosporine and other nephrotoxic agents increases risk of renal toxicity.

Role in Prophylaxis

Acyclovir/valacyclovir is used for HSV prophylaxis in seropositive HSCT recipients, to be initiated with the conditioning regimen and continued till recovery of white blood cell (WBC) count and resolution of mucositis. Duration of prophylaxis is extended in patients with frequent recurrences and graft versus host disease (GVHD).

Seropositive SOT recipients who do not require CMV prophylaxis but need HSV prophylaxis are given acyclovir till 3–6 months post-transplant and recovery of lymphodepletion associated with treatment of rejection.

Famciclovir and Penciclovir

Mechanism of Action

Penciclovir is activated into triphosphate form by HSV thymidine kinase which further inhibits HSV DNA polymerase. Compared to acyclovir, penciclovir has a lower affinity for viral DNA polymerase but a longer intracellular half-life.

Famciclovir is an oral prodrug that is converted by first-pass metabolism to penciclovir.

Resistance

- Similar to those conferring resistance to acyclovir
- Most acyclovir-resistant HSV/VZV strains exhibit cross-resistance to penciclovir

Pharmacokinetics and Pharmacodynamics

Famciclovir has an oral bioavailability of 77%. After first-pass metabolism in the liver and intestine, it is converted to penciclovir, which has a prolonged intracellular half-life (10–20 hours for HSV, 7–14 hours for VZV), hence requiring less frequent dosing.

Excretion is primarily renal, requiring dose reduction in patients with renal insufficiency.

Toxicity

Apart from nausea and fatigue, famciclovir is well tolerated.

Drug Interactions

No clinically important drug interactions have been identified for famciclovir.

ANTIVIRAL DRUGS FOR INFLUENZA, RESPIRATORY SYNCYTIAL VIRUS AND SARS-COV-2[5]

Oseltamivir: Influenza

Mechanism of Action

Oseltamivir is the ethyl ester prodrug, which is hydrolyzed to active form oseltamivir carboxylate (OC). OC is a 50-fold more potent specific inhibitor of the neuraminidase of influenza A and B viruses.

Resistance

Point mutations in viral hemagglutinin or neuraminidase genes.

Pharmacokinetics and Pharmacodynamics

Oral oseltamivir is rapidly absorbed and metabolized to active form in the gastrointestinal (GI) tract, liver, and blood. Drug achieves similar levels in tissue and blood. Excretion is primarily through kidneys, hence dosage modification is required at CrCl <30 mL/min.

Toxicity

- *GI side effects*: Dose-related nausea and vomiting is common and occurs within first 2 days of treatment.
- *Neuropsychiatric effects*: Rare events of confusion, delirium, and hallucination can occur, mechanism unknown.

Drug Interactions

No interactions with immunosuppressive agents.

Role in Influenza Prophylaxis

Prophylactic administration of once daily oral oseltamivir (75 mg) has shown efficacy in reducing the risk for development of febrile illness in unimmunized high-risk individuals such as transplant recipients (efficacy 80%).

Once daily oseltamivir for 7–10 days is also effective as postexposure prophylaxis in household contacts.

Aerosolized Ribavirin: Respiratory Syncytial Virus

Mechanism of Action

Inhibits replication of RNA and DNA polymerase activity and elongation of RNA fragments.

Resistance

No ribavirin-resistant respiratory syncytial virus (RSV) has been detected.

Pharmacokinetics and Pharmacodynamics

With aerosol administration, systemic absorption is low, and respiratory secretion levels exceed 1,000 μg/mL. A special aerosol generator is needed to produce particles of proper size to reach lower respiratory tract.

Toxicity

Aerosolized ribavirin may cause conjunctival irritation, rash, bronchospasm, and reversible deterioration in pulmonary function. No adverse hematological effects have been associated with aerosolized ribavirin.

Remdesivir: SARS-COV-2[6]

Mechanism of Action

Remdesivir (RDV) is a novel nucleotide which inhibits SARS-CoV-2 RNA-dependent RNA polymerase, essential for viral replication.

Dosage and Administration

Intravenous: 200 mg single dose day 1, followed by 100 mg once daily for 5 days.

Toxicity

Remdesivir is fairly well tolerated. Bradycardia, GI disturbances, increased hepatic transaminases, and prothrombin time have been seen occasionally.

Interactions

Remdesivir is a substrate of CYP3A4, hence strong inducers can decrease serum concentration of RDV.

ANTIVIRALS FOR EPSTEIN–BARR VIRUS

Primary Epstein–Barr virus (EBV) infections usually require symptomatic treatment. EBV reactivation in post-transplant setting occurs from endogenous reactivation, or transmission from allograft. It maybe asymptomatic, or cause a mononucleosis syndrome, or can progress to EBV-related post-transplant lymphoproliferative disorder (PTLD).

Antivirals such as acyclovir and ganciclovir inhibit lytic EBV infection through inhibition of EBV DNA polymerase but has no effect on latent infection, hence do not have role in prophylaxis of PTLD. While short-term suppression of viral shedding is seen, significant clinical benefit has not been noted.

In EBV-associated malignancies, there is no role of lytic infection, hence antivirals do not have much use. Management of PTLD include the following:

- Reduction of immunosuppression
- Immunotherapy with CD20 monoclonal antibody rituximab
- Chemo/radiation therapy or both

ANTIVIRALS FOR HEPATITIS VIRUSES[7]

Hepatitis B Virus

Oral antiviral agents can suppress viral replication leading to biochemical (normal aminotransferase activity), histologic (improvement of necroinflammation and fibrosis), serologic (seroconversion), and long-term improvements in natural history of disease.

Entecavir

Mechanism of action: Entecavir is intracellularly phosphorylated to GTP which inhibits hepatitis B virus (HBV) polymerase reducing viral DNA synthesis.

Resistance: Entecavir has a high barrier to resistance. Resistance develops due to emergence of YMDD mutation and in polymerase domain.

Pharmacokinetics and pharmacodynamics: Entecavir has 100% bioavailability and reaches peak plasma concentrations within 1.5 hours. Food delays absorption, hence ideally should be taken on an empty stomach. Excretion is primarily renal, hence dosage adjustment is necessary. For patients with liver disease, higher dose (1 mg) is recommended.

Route of administration and dosage:
- *Oral formulation*: 0.5 mg daily (1 mg in liver disease)
- Requires dosage modification in CrCl <50 mL/min

Toxicity:
- Food and Drug Administration (FDA) blackbox warning for lactic acidosis and steatosis
- Relatively well tolerated

Drug interactions: No drug interactions

Lamivudine

Mechanism of action: Lamivudine is a cytosine analog. The monophosphate form of lamivudine is incorporated into viral DNA by HBV polymerase, resulting in DNA chain termination.

Resistance: Point mutations in the YMDD motif of HBV DNA polymerase result in reduction in in vitro susceptibility and loss of viral fitness. Lamivudine also confers cross-resistance to emtricitabine and famciclovir. Lamivudine-resistant HBV retains susceptibility to tenofovir and entecavir.

Toxicity: Lamivudine is well tolerated and has been most widely used anti-HBV drug in pregnancy.

Dosage and administration: Oral—100 mg once daily

Drug interactions: No interactions

Tenofovir

Mechanism of action: Tenofovir disoproxil fumarate (TDF)/tenofovir alafenamide (TAF) is a prodrug of tenofovir, which is phosphorylated by cellular enzymes to form tenofovir diphosphate which competitively inhibits HBV polymerases and after incorporation into DNA, acts as a chain terminator.

Resistance: Tenofovir has a high genetic barrier to resistance against HBV. Very limited data on resistance has been noted in Africa.

Pharmacokinetics and pharmacodynamics: Tenofovir bioavailability increases with high-fat meal and is primarily excreted in urine via filtration and active secretion. It requires dose adjustment in renal function impairment.

Administration:
- *TDF oral*: 300 mg once a day
- *TAF oral*: 25 mg once a day

Toxicity:
- TDF has a higher risk of nephrotoxicity (Fanconi syndrome) as compared to TAF.
- Reduced bone mineral density
- Weight gain (TAF)

Drug interactions: Concomitant use of other nephrotoxic agents will increase risk of renal dysfunction.

Peg Interferon

Interferon induces specific genes that interfere with several steps in HBV lifecycle. They are also immunomodulatory, and augment cell-mediated immunity, thereby promoting clearance of HBV-infected hepatocytes.

Peg interferon can only be considered in treatment-naïve, immunocompetent patients, and is contraindicated in decompensated cirrhosis, patients with untreated psychiatric illness, autoimmune disease, untreated thyroid illness, severe leukopenia/thrombocytopenia, concurrent severe systemic disorders [heart failure, coronary artery disease, severe hypertension, uncontrolled diabetes mellitus (DM), and chronic obstructive pulmonary disease (COPD)], and immunocompromised patients (kidney, heart, and lung transplant).

Hence, its role as an antiviral in transplant recipients is not warranted.

Hepatitis C

Interferon

Interferons inhibit hepatitis C virus (HCV) internal ribosome entry site-dependent RNA translation in vitro.

Combination of PEG IFN and ribavirin has been used in acute hepatitis C, although its use in post-transplant setting is limited as acute rejection and graft failure is a common adverse effect. Other contraindications have been mentioned in HBV section.

Ribavirin

Oral ribavirin weakly inhibits NS5B-encoded RNA-dependent RNA polymerase.

It has good oral bioavailability and has a prolonged volume of distribution in erythrocytes. Clearance is primarily renal.

Ribavirin has been used in treatment of chronic HCV, but has been largely replaced by direct antiviral agents (DAAs).

Toxicity: Oral ribavirin produces dose-related extravascular anemia. Renal failure increases risk for hemolysis. It is contraindicated in pregnancy, and used with caution in patients with hemoglobinopathies, coronary artery disease, and renal insufficiency.

Direct-acting Antivirals

There are four classes of DAAs defined by mechanism of action: Nonstructural proteins NS 3/4A protease inhibitors (PIs), NS5B nucleoside polymerase inhibitors (NPIs), NS5B non-nucleoside polymerase inhibitors (NNPIs), and NS5A inhibitors.

Direct antiviral agents are administered as fixed-dose combinations (FDCs) based on HCV genotype. Most commonly used FDCs available in India are as follows:

- Velpatasvir–sofosbuvir
- Ledipasvir–sofosbuvir
- Daclatasvir–sofosbuvir

Toxicity: Overall DAAs are well tolerated. Rare adverse effects are as follows:

- HBV reactivation
- Hepatic decompensation with use of PIs

Drug interactions

- Velpatasvir, ledipasvir, and sofosbuvir are substrates of P-gp drug transporter, hence have significant interactions with P-gp-inducing drugs (rifamycin, carbamazepine, phenytoin, and ritonavir).
- Daclatasvir is a substrate of CYP3A4 enzyme and P-gp, hence has potential for significant drug interactions.
- Increased gastric pH levels decrease absorption of Ledipasvir, Velpatasvir, hence coadministration of proton pump inhibitors (PPIs) is avoided.

ANTIVIRALS FOR HUMAN IMMUNODEFICIENCY VIRUS[8]

Antiretroviral therapies (ARTs) are differentiated by their mechanism of action:

- *Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)*: Abacavir (ABC), tenofovir, lamivudine, and zidovudine (AZT)
- *NNRTI*: Efavirenz (EFV), nevirapine (NVP), and rilpivirine
- *PIs*: Atazanavir, darunavir, ritonavir, and lopinavir
- *Integrase strand transfer inhibitors (INSTI)*: Raltegravir (RAL), dolutegravir (DTG), and bictegravir (BIC)
- *Fusion inhibitor*: Enfuvirtide
- *CCR5 antagonist*: Maraviroc
- *Attachment inhibitor*: Fostemsavir
- *Postattachment inhibitor*: Ibalizumab

The latter four are used in drug-resistant human immunodeficiency virus (HIV) therapy.

Each ART class is associated with its own set of adverse effects and drug interactions

- NRTI:
  - *S/e*: Mitochondrial toxicity, coronary artery disease (ABC), nephrotoxicity (TDF) and bone loss (tenofovir), weight gain, dyslipidemia (TAF), and anemia (AZT)
  - *Interactions*: Rifamycin reduces level of TAF but not TDF.
  - ABC is contraindicated in persons who test positive for human leukocyte antigen (HLA)-B5701 mutation due to risk of ABC hypersensitivity reaction.
- *NNRTIs:* Only active against HIV-1:
  - QTc prolongation, neurologic and psychiatric side effects (EFV and rilpivirine), and hepatotoxicity (NVP)
  - *Interactions*: No significant interactions
  - *PIs*: Are administered with a pharmacological boosting agent such as ritonavir or cobicistat.
  - Insulin resistance, hyperlipidemia, lipodystrophy, and PR interval prolongation
  - *Interactions*: Necessary to check for interactions due to inhibition of hepatic CYP3A4 enzyme by ritonavir
- INSTIs:
  - Relatively well tolerated, apart from weight gain
  - *Interactions*: Decrease in INSTI concentrations when coadministered with polyvalent cation-containing antacids and supplements
  - *RAL, DTG*: Primarily metabolized by glucuronidation, hence few interactions
  - *BIC:* Cleared by glucuronidation and hepatic CYP450, hence is associated with more drug interactions.

VIRUSES WITH NO SPECIFIC ANTIVIRAL TREATMENT FOR PROPHYLACTIC REGIMEN: BK VIRUS, JOHN CUNNINGHAM VIRUS,[9] PARVOVIRUS B19,[10] HUMAN HERPESVIRUS-6, HUMAN HERPESVIRUS-7[11]

- *ParvoB19*: Usually needs symptomatic treatment with reduction in immunosuppression. In chronic infection, intravenous immunoglobulin (IVIg) has been used.
- *Human herpesvirus-6 (HHV-6)*: On in vitro data, foscarnet, ganciclovir-first line, or cidofovir-second line have been used for treatment of HHV-6B encephalitis.
- *HHV-7*: In vitro, foscarnet, cidofovir has shown anti-HHV7 action, but mainstay of treatment is reduction of immunosuppression.
- *John Cunningham (JC) and BK virus*: Reduction of immunosuppression and restoration of cellular immunity is mainstay of treatment (BK: reduction in immunosuppressant drug levels and JC: early initiation of ART for HIV).

CASE 1

NM 58 F had deceased kidney transplantation (DDKT) in January 2019 and received ATG + triple immunosuppression.

In January 2020, she developed diarrhea and mild fever continued off and on. The creatinine rose to 2.9 and WBC declined to 2,500. Multiplex polymerase chain

reaction (PCR) GI panel showed norovirus infection. This can produce prolonged illness and shedding in SOT patients causing graft failure and malnutrition but could not explain fever and leukopenia. Hence, it was thought that another cause like CMV disease could be present. Colonoscopy showed normal mucosa, but CMV DNAemia was 928 c/mL. In localized GI disease, DNAemia is present in 50% only, with lower sensitivity in R^+ and so this level of DNAemia is likely significant. Ideally a rising viral load has greater importance as there is ambiguity of thresholds for predicting disease across clinical settings and disease types. PO vGCV 450 alternate day was used for treatment in this case. GCV is used if certainty of adequate exposure needed as for serious disease, difficult oral intake, severe diarrhea, need for very low doses as in renal failure, and in children.

CASE 2

RJ 37 M had immunoglobulin A (IgA) nephropathy and was on maintenance hemodialysis (MHD). In March 2021, he developed COVID-19 followed by Bell's palsy and received steroids for 1 month. In May 2021, ABO compatible living-related kidney transplantation (LRKT) was done. The patient received basiliximab, TAC, prednisolone, and mycophenolate mofetil (MMF). He had a stormy course with rejection, wound dehiscence, episodes of urinary tract infection (UTI), and received methylprednisolone, meropenem, fosfomycin, and vGCV prophylaxis. Fever recurred along with an unexplained drop in hemoglobin (Hb) from 11 to 7 g. Bone marrow examination showed giant pronormoblasts as shown in **Figure 1**.

Parvo B19 VL in marrow was 84 billion c/mL and in blood was 44 billion c/mL. He was started with IVIg 400 mg/kg which could only be given at weekly intervals due to cost constraints. His clinical condition and anemia improved over 1 month. However, 2 months later, he had an influenza-like illness (ILI) and his father and daughter were similarly affected. The common diagnostic possibilities at that time were COVID-19 and RSV infection. Therefore, nasopharyngeal (NP) swab for multiplex PCR upper respiratory tract infection (URTI) panel was done. SARS-CoV-2 was positive and RSV was negative. Although he had COVID-19 earlier, the antispike Ab was negative, probably due to his immunocompromised state. There was mildly declining oxygen saturation and so he was given casirivimab/imdevimab (CAS-IMD) which resulted in a rapid recovery of symptoms and oxygenation.

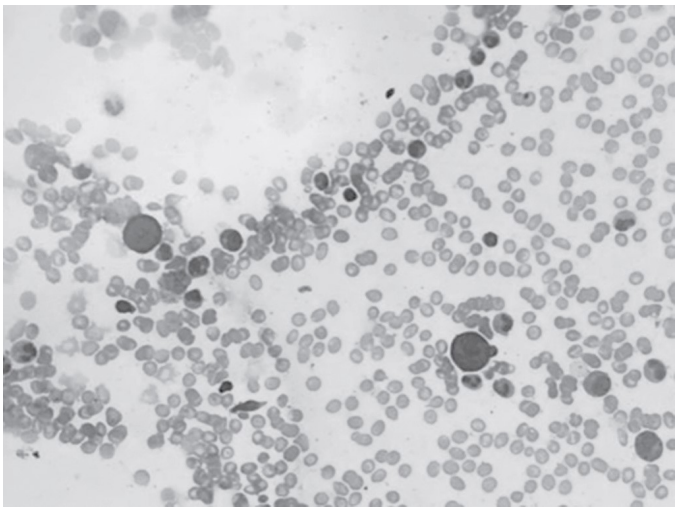


Fig. 1: Bone marrow examination showing giant pronormoblasts.

CONCLUSION

Transplant recipients are prey to a large number of pathogens including viruses which could either be new infections and activation of latent infections. The diagnostic approach is difficult and tests are often unavailable, expensive, and difficult to interpret. Some infections do not have specific antiviral treatment. Others do have specific treatment but with significant toxicities and drug interactions. Management of these patients is challenging and requires a team approach by the transplant physician, infectious diseases physician, intensivist, microbiologist, pharmacologist, and almost all specialties available in the hospital.

REFERENCES

1. Taplitz RA, Kennedy EB, Bow EJ, Crews J, Gleason C, Hawley DK, et al. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update. J Clin Oncol. 2018;36(30):3043-54.
2. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Prevention and treatment of cancer-related infections. Version 2.2020. [online] Available from: http://www.nccn.org. [Last accessed February 2022].
3. Aoki FY. Antivirals against herpesviruses. In: Mandell GL, Douglas RG, Bennett JE. Mandell, Douglas and Bennett's Principles and Practice of Infectious diseases, 9th edition. Philadelphia: Elsevier Inc.; 2020.
4. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients—Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13512.
5. Aoki FY. Antivirals for influenza and other respiratory virus infections. In: Mandell GL, Douglas RG, Bennett JE. Mandell, Douglas and Bennett's principles and practice of infectious diseases, 9th edition. Philadelphia: Elsevier Inc.; 2020.
6. Buxeda A, Arias-Cabrales C, Pérez-Sáez MJ, Cacho J, Arana C, Taurizano N, et al. Use and safety of remdesivir in kidney transplant recipients with COVID-19. Kidney Int. 2021;6(9):2305-15.
7. Dienstag JL. Antiviral drugs against hepatitis viruses. In: Mandell GL, Douglas RG, Bennett JE. Mandell, Douglas and Bennett's principles and practice of infectious diseases, 9th edition. Philadelphia: Elsevier Inc.; 2020.

8. Blumberg EA, Rogers CC; American Society of Transplantation Infectious Diseases Community of Practice. Solid organ transplantation in the HIV-infected patient: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13499.
9. Hirsch HH, Randhawa PS; AST Infectious Diseases Community of Practice. BK polyomavirus in solid organ transplantation—Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13528.
10. Eid AJ, Ardura MI; AST Infectious Diseases Community of Practice. Human parvovirus B19 in solid organ transplantation: Guidelines from the American Society of transplantation infectious diseases community of practice. Clin Transplant. 2019; 33(9):e13535.
11. Pellett Madan R, Hand J; AST Infectious Diseases Community of Practice. Human herpesvirus 6, 7, and 8 in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13518.

SECTION

15

Autoimmune Diseases

CHAPTER 80

Autoimmune Crisis Management: Drugs—Which One and When?

Arun Dewan, Bikram Kumar Gupta, Ritesh Aggarwal

INTRODUCTION

Management of systemic vasculitis in intensive care unit (ICU) is challenging. These patients are usually admitted to ICU with life- or organ-threatening manifestations (e.g., alveolar hemorrhage, glomerulonephritis, central nervous system vasculitis, mononeuritis multiplex, cardiac involvement, mesenteric ischemia, or limb/digit ischemia). Early and aggressive treatment strategy is essential to optimize outcomes while avoiding unnecessary harms of immunosuppression.

The management principles of common primary vasculitis conditions [granulomatosis with polyangiitis (GPA) microscopic polyangiitis (MPA), eosinophilic GPA, giant cell arteritis, Takayasu arteritis, and polyarteritis nodosa (PAN)] is discussed below. This is followed by a discussion on common secondary vasculitis requiring intensive care management.

MANAGEMENT OF PRIMARY VASCULITIS

Treatment regimens consist of an initial remission phase with aggressive immunosuppressive drugs (such as high-dose steroids), followed by a prolonged maintenance phase where less intense drugs and dosing are used.

Commonly used drugs and treatment strategies include the following:

- *Corticosteroids*: Corticosteroids are the mainstay of treatment in almost all vasculitis patients with severe disease or relapse. Steroids (methylprednisolone) are usually given in very high doses for 3–5 days (pulse steroid therapy) followed by a lower maintenance dose.
- *Immunosuppressants*: Cyclophosphamide and rituximab are commonly used immunosuppressive agents used during the induction phase. The preference of one over the other is determined by the nature of vasculitis and underlying patient factors (kidney dysfunction, pulmonary hemorrhage, risk of malignancy, etc.). Rituximab has shown to be equally effective as cyclophosphamide.[1,2] Although the currently used doses of cyclophosphamide are less toxic than previous regimens, rituximab is still preferred in GPA or MPA as it is less toxic than cyclophosphamide.[3] In case of severe PAN, cyclophosphamide is preferred because some recent studies have raised questions on the efficacy of rituximab in PAN.[4]

  Cyclophosphamide or rituximab are given along with pulse steroids. Some clinicians use steroids along with the combination of cyclophosphamide and rituximab. However, no trials have shown that a combination of both is superior to either rituximab or cyclophosphamide alone.

  During the maintenance phase, the recommended immunosuppressants include rituximab, azathioprine, methotrexate, and mycophenolate mofetil. The choice is influenced by disease severity and patient factors.

  Induction and maintenance therapies in severe vasculitis are shown in **Table 1**. Currently recommended doses of various immunosuppressants have been given in **Table 2**. These are based on recent (2021) American College of Rheumatology/Vasculitis Foundation guidelines for the management of vasculitis.[5-7]
- *Plasma exchange*: In general, plasmapheresis has a role in severe vasculitis in some circumstances:
  - Patients with GPA or MPA who are also positive for anti-glomerular basement membrane (GBM) autoantibody.
  - Patients with GPA or MPA with pulmonary hemorrhage, not responding to other therapies.[8]
  - Patients with GPA or MPA with severe and worsening kidney disease (serum creatinine >4.0 mg/dL or requirement of hemodialysis).

  When plasma exchange is done, usually a total of seven sessions are recommended over 2 weeks (60 mL/kg at each session).

  The rationale for limited use of plasma exchange is based upon data from the PEXIVAS trial of 704 patients with severe GPA or MPA [defined by an estimated glomerular

TABLE 1: Recommended induction and remission maintenance therapies in severe primary vasculitis diseases.

Vasculitis	*Induction therapies in severe disease*	*Remission maintenance therapies*
Granulomatosis with polyangiitis (GPA)/microscopic polyangiitis (MPA)	Pulse steroids and rituximab (preferred), or cyclophosphamide	• Rituximab, or • Methotrexate, or • Azathioprine, or • Mycophenolate
Eosinophilic granulomatosis with polyangiitis (EGPA)	Pulse steroids and cyclophosphamide or rituximab	• Methotrexate, or • Azathioprine, or • Mycophenolate
Giant cell arteritis	• Pulse steroids • Followed by high-dose oral steroids + tocilizumab	Taper oral steroids
Takayasu arteritis	High-dose oral steroids and methotrexate/azathioprine/TNF inhibitor	• Taper oral steroids • Continue methotrexate/azathioprine/TNF inhibitor
Polyarteritis nodosa	Pulse steroids and cyclophosphamide	• Taper oral steroids • Add methotrexate/azathioprine

(TNF: tumor necrosis factor)

TABLE 2: Induction and maintenance dosing recommendations for commonly used immunosuppressants.

Drug	*Induction dosing*	*Remission maintenance dosing*
Glucocorticoids	IV methylprednisolone 500–1,000 mg/day for 3–5 days (pulse steroids), followed by prednisolone 1 mg/kg/day × 7 days	• *High-dose oral steroids:* Prednisone 1 mg/kg/day (Maximum 80 mg/day) • *Low-dose oral steroids:* Prednisone <10 mg/day
Cyclophosphamide	*IV*: 15 mg/kg every 2 weeks for three doses, followed by 15 mg/kg every 3 weeks for at least three doses *Oral:* 1.5–2 mg/kg/day for 3–6 months	–
Rituximab	375 mg/m^2 IV weekly for four doses, or 1,000 mg IV on days 1 and 15	500 mg IV every 6 months
Methotrexate	15–25 mg/week (SC or oral)	Same as induction
Azathioprine	• Start at 50 mg/day (oral) • Gradually increased up to 2 mg/kg/day	Same as induction
Mycophenolate mofetil	1.5–3 g/day (oral) in two divided doses	Same as induction

(IV: intravenous; SC: subcutaneous)

filtration rate (eGFR) <50 mL/min/1.73 m^2 or diffuse pulmonary hemorrhage], in which the use of plasma exchange did not reduce the incidence of death or end-stage renal disease at 1 year or during the follow-up period of up to 7 years.[9]

- *Intravenous immunoglobulins (IVIg)*: IVIg should not be used routinely for severe GPA/MPA patients. It can be considered as adjunctive therapy in patients with refractory severe disease, not responding to steroids and rituximab/cyclophosphamide.[10]

MANAGEMENT OF SECONDARY VASCULITIS

Common complications of secondary vasculitis presenting to ICU include severe systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), and scleroderma renal crisis (SRC). The key management principles of each of these are discussed here.

Severe Systemic Lupus Erythematosus

Patients with severe manifestations due to major organ involvement [e.g., renal or central nervous system (CNS)] are generally treated with pulse steroid therapy either alone or in combination with other immunosuppressive agents such as mycophenolate, cyclophosphamide, azathioprine, or rituximab.[11] Role of rituximab in SLE remains unclear. Some observational studies have shown the efficacy of rituximab in severe SLE patients who failed to respond to standard treatment. In comparison, two randomized trials, EXPLORER and LUNAR, found that rituximab did not provide any significant benefit.[12,13] However, there were limitations in the study design of these trials.

Catastrophic Antiphospholipid Syndrome

Antiphospholipid syndrome can occur as a primary condition or in the setting of an underlying SLE. A small group of APS patients can develop severe thrombotic complications with multiorgan failure, called catastrophic antiphospholipid syndrome (cAPS).

Catastrophic antiphospholipid syndrome is associated with high mortality (30%)[14] and needs aggressive management with anticoagulation and immunosuppression. Anticoagulation is usually initiated with unfractionated heparin (UFH) with close activated partial thromboplastin time (aPTT) monitoring, or low molecular weight heparin (LMWH). In patients who are hemodynamically stable, transition to oral anticoagulants (warfarin) can be done, targeting an international normalized ratio (INR) of 3–4.5. Along with systemic anticoagulation, immunosuppression is given using pulse steroids for 3–5 days followed by high-dose oral steroids. If the patient fails to respond to pulse steroids, plasma exchange (for 3–5 consecutive days) and/or IVIg (400 mg/kg/day × 5 days) is given. IVIg and plasma exchange are not given together to prevent the removal of IVIg by plasma exchange.

A systemic review of 342 patients with cAPS found that a combination of anticoagulation, steroids, and either plasmapheresis/IVIg/both was associated with significantly lower mortality compared to strategies that did not use IVIg or plasmapheresis.[15]

Since IVIg is associated with a small risk of thrombosis, it should be discontinued when anticoagulation is interrupted (e.g., for bleeding).

In cAPS resistant to the above therapies, rituximab or eculizumab (monoclonal antibody against complement) have shown to be effective.[16,17]

Scleroderma Renal Crisis

Scleroderma renal crisis occurs in 5–20% of patients with diffuse cutaneous systemic sclerosis. It is characterized by acute onset renal failure and abrupt onset of moderate-to-severe hypertension.[18] If untreated, SRC can progress to end-stage kidney disease.[19] The mainstay of therapy is effective and prompt blood pressure (BP) control before irreversible kidney damage has occurred. The optimal antihypertensive agent is an angiotensin-converting enzyme (ACE) inhibitor.[20] Angiotensin receptor blockers (ARBs) have not been adequately studied in this setting; hence, their role is unclear. If BP control is not achieved with maximum recommended doses of ACE-I, a calcium channel blocker such as amlodipine can be added.

GENERAL CRITICAL CARE MANAGEMENT

Besides immunosuppression, there are other aspects of intensive care management which deserve special attention in vasculitis patients which are as follows:

- *Prevention of opportunistic infections*: *Pneumocystis jirovecii* pneumonia prophylaxis should be given in all patients receiving cyclophosphamide or rituximab in combination with prednisone at a dose ≥20 mg/day. Prophylaxis can be discontinued when the dose of prednisolone is reduced to <10 mg/day.
- *Glycemic control*: Uncontrolled sugars are common in these patients as they are on high doses of intravenous steroids. Blood glucose levels should be tightly controlled using insulin infusions where necessary.
- *Deep vein thrombosis (DVT) prophylaxis*: Potential risks of pulmonary and gastrointestinal (GI) hemorrhage should be kept in mind while deciding DVT prophylaxis.
- *Infection control measures*: Strict infection control measures should be in place while managing these patients, as they are immunocompromised and at a high risk of acquiring nosocomial infections. There is no role of prophylactic antibiotics routinely.
- *Sepsis*: Sepsis can be underdiagnosed or overdiagnosed in these patients because of the use of immunosuppressants, presence of an active vasculitis process with/without fever, or steroids-induced leukocytosis. It is very important to distinguish between vasculitis and sepsis in ICU, as the treatment of two entities (immunosuppression vs antibiotics) is in opposite directions.
- *Complications of treatment*: Glucocorticoids and other immunosuppressant drugs are associated with important side effects which need close observation and management. Common toxicities and their ICU implications are listed in **Table 3**.

TABLE 3: Side effects of commonly used immunosuppressants.

Drug	*Side effects*	*Comments*
Glucocorticoids	• Infections • Bones and muscles (osteoporosis, avascular necrosis, and myopathy) • Hyperglycemia • Fluid retention, hypertension • Cataract • Gastritis	• Increased risk of critical illness myopathy • Increased risk of delirium and psychosis in ICU • Leukocytosis may occur, mimicking sepsis • Cataract occurs with long-term use

Contd…

Contd…

Drug	*Side effects*	*Comments*
Cyclophosphamide	• Bone marrow suppression (leukopenia and lymphopenia) • Infections (bacterial, opportunistic, and viral) • Hemorrhagic cystitis • Infertility • Malignancy (especially lymphoma)	• Toxicity mainly depends on cumulative dose and duration. Intermittent IV regimens are associated with less toxicity compared to daily oral therapy • WBC count of <4,000/mm^3 is associated with substantial immunosuppression
Rituximab	• Infusion reactions • Progressive multifocal leukoencephalopathy • Hypogammaglobulinemia (infections)	• Premedication with antihistamines and acetaminophen reduces the risk of infusion-related reactions • Monitor IgG levels every 6–12 months, stop rituximab if IgG <5 g/L
Methotrexate	• Hepatotoxicity • Leukopenia • GI upset • Fatigue/headache/malaise • Stomatitis • Pulmonary toxicity	Use of daily folic acid or weekly leucovorin supplementation reduces the incidence of side effects

(GI: gastrointestinal; ICU: intensive care unit; IgG: immunoglobulin G; IV: intravenous; WBC: white blood cells)

CONCLUSION

The natural course of vasculitis may be interspersed by acute and life-threatening "flares" of disease or secondary complications (such as infections), requiring management in the ICU. A high level of suspicion, timely and accurate diagnosis, and appropriate treatment are essential to improve outcomes. Treatment strategies have evolved over time, and newer regimens have significantly improved the outcomes even in those presenting to ICU.

REFERENCES

1. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010;363(3):211-20.
2. Jones RB, Furuta S, Tervaert JW, Hauser T, Luqmani R, Morgan MD, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial. Ann Rheum Dis. 2015;74(6):1178-82.
3. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010;363(3):221-32.
4. Ribeiro E, Cressend T, Duffau P, Grenouillet-Delacre M, Rouanet-Larivière M, Vital A, et al. Rituximab efficacy during a refractory polyarteritis nodosa flare. Case Rep Med. 2009;2009:738293.
5. Chung SA, Langford CA, Maz M, Abril A, Gorelik M, Guyatt G, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the management of antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheumatol. 2021;73(8):1366-83.
6. Chung SA, Gorelik M, Langford CA, Maz M, Abril A, Guyatt G, et al. 2021 American College of Rheumatology/Vasculitis Foundation guideline for the management of polyarteritis nodosa. Arthritis Rheumatol. 2021;73(8):1384-93.
7. Maz M, Chung SA, Abril A, Langford CA, Gorelik M, Guyatt G, et al. 2021 American College of Rheumatology/Vasculitis Foundation guideline for the management of giant cell arteritis and Takayasu arteritis. Arthritis Rheumatol. 2021;73(8):1349-65.
8. Klemmer PJ, Chalermskulrat W, Reif MS, Hogan SL, Henke DC, Falk RJ. Plasmapheresis therapy for diffuse alveolar hemorrhage in patients with small-vessel vasculitis. Am J Kidney Dis. 2003;42(6):1149-53.
9. Walsh M, Merkel PA, Peh CA, Szpirt WM, Puéchal X, Fujimoto S, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. N Engl J Med. 2020;382(7):622-31.
10. Crickx E, Machelart I, Lazaro E, Kahn JE, Cohen-Aubart F, Martin T, et al. Intravenous immunoglobulin as an immunomodulating agent in antineutrophil cytoplasmic antibody-associated vasculitides: A French Nationwide Study of ninety-two patients. Arthritis Rheumatol. 2016;68(3):702-12.
11. Fanouriakis A, Kostopoulou M, Alunno A, Aringer M, Bajema I, Boletis JN, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. 2021.
12. Merrill JT, Neuwelt CM, Wallace DJ, Shanahan JC, Latinis KM, Oates JC, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum. 2010;62(1):222-33.
13. Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum. 2012;64(4):1215-26.
14. Bucciarelli S, Espinosa G, Cervera R, Erkan D, Gómez-Puerta JA, Ramos-Casals M, et al. Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients. Arthritis Rheum. 2006;54(8):2568-76.

15. Cervera R, Rodríguez-Pintó I, Colafrancesco S, Conti F, Valesini G, Rosário C, et al. 14th International Congress on Antiphospholipid Antibodies Task Force Report on Catastrophic Antiphospholipid Syndrome. Autoimmun Rev. 2014;13(7):699-707.
16. Berman H, Rodríguez-Pintó I, Cervera R, Morel N, Costedoat-Chalumeau N, Erkan D, et al. Rituximab use in the catastrophic antiphospholipid syndrome: descriptive analysis of the CAPS registry patients receiving rituximab. Autoimmun Rev. 2013;12(11):1085-90.
17. Strakhan M, Hurtado-Sbordoni M, Galeas N, Bakirhan K, Alexis K, Elrafei T. 36-year-old female with catastrophic antiphospholipid syndrome treated with eculizumab: a case report and review of literature. Case Rep Hematol. 2014;2014:704371.
18. Gutiérrez-González LA. Rheumatologic emergencies. Clin Rheumatol. 2015;34(12):2011-9.
19. Penn H, Howie AJ, Kingdon EJ, Bunn CC, Stratton RJ, Black CM, et al. Scleroderma renal crisis: patient characteristics and long-term outcomes. QJM. 2007;100(8):485-94.
20. Steen VD, Costantino JP, Shapiro AP, Medsger TA Jr. Outcome of renal crisis in systemic sclerosis: relation to availability of angiotensin converting enzyme (ACE) inhibitors. Ann Intern Med. 1990;113(5):352-7.

CHAPTER 81

Identifying Autoimmune Crisis in Intensive Care Unit

Kapil Borawake, Reena Sharma

INTRODUCTION

Autoimmune diseases are relatively rare (approximately 3%) of general population. However, 25% of these patients present to emergency room (ER) and among them one-third require intensive care.[1] Majority of these patients comprise rheumatoid arthritis, systemic lupus erythematosus (SLE), scleroderma while other rare entities include anti-phospholipid syndrome, vasculitis. Since rheumatic diseases are associated with multiorgan failure, mortality ranges from 17 to 33% among these intensive care unit (ICU) stays **(Box 1)**.[2]

A significant proportion of these patients are undiagnosed. Discussing every rheumatic condition and how it may present to critical care specialist is beyond the scope of this chapter. Instead, it is more prudent to discuss the important clinical presentations that should not be missed.

BOX 1: Why rheumatic diseases are important to an intensivist?

- Predominantly young patients are affected
- Multisystem involvement and multiorgan failure
- Effective treatment available, if administered in time, can be lifesaving/prevent lifelong morbidity
- High mortality in intensive care unit
- Complicated drugs with extensive side effects

MACROPHAGE ACTIVATION SYNDROME

Macrophage activation syndrome (MAS) or secondary hemophagocytic lymphangiohistiocytosis (HLH) is a life-threatening complication of systemic rheumatic diseases. Initial studies described around 50% mortality however, with increasing awareness of this condition and prompt treatment, recent studies show 15–20% mortality.[3] Initially described in systemic juvenile idiopathic arthritis (sJIA), it has been reported in SLE, vasculitis, and coronavirus disease (COVID). Apparently nonrheumatic conditions including sepsis, tuberculosis, and cytomegalovirus (CMV) infection can develop MAS during the course of their disease.

Clinical and Laboratory Features

- High-grade fever
- Worsening cytopenias
- Hyperferritinemia
- Transaminitis, triglyceridemia
- Decreasing or normal erythrocyte sedimentation rate
- Disseminated intravascular coagulation and multiorgan failure.

Treatment

High-dose steroid make the cornerstone of the treatment of MAS. Simultaneously, aggressive supportive management and treatment of the underlying cause are needed. Cyclosporine, intravenous (IV) immunoglobulin, and tocilizumab especially in the setting of COVID-19 are needed for a prolonged period depending on the primary condition.

VASCULITIS

Vasculitis is a group of disorders caused due to destruction of blood vessels. Patients admitted with fulminant pulmonary vasculitis in the ICU have 25–30% mortality.[4] It is a life-threatening/organ-threatening condition where prompt diagnosis and treatment may be lifesaving. In a series of 26 patients admitted to ICU, vasculitis was initially diagnosed in 42%. Vasculitis should be kept in differential in patients of unexplained renal and lung failure **(Table 1)**.[5]

Clinically, it is useful to classify vasculitis according to the size of the blood vessel involved **(Fig. 1)**.[6]

Diagnosis

Key bedside points help to diagnose vasculitis. Past history of sinusitis, upper respiratory involvement can guide to Wegener's granulomatosis. Asthma can precede up to 10 years in a patient of eosinophilic granulomatosis with polyangiitis (Churg-Strauss disease). Hepatitis B and C are associated with polyarteritis nodosa and cryoglobulinemic vasculitis, respectively.

Normocytic anemia, neutrophilic leukocytosis, and thrombocytosis, although nonspecific can be important pointers. Urine examination showing proteinuria and microscopic hematuria in the absence of leukocytes suggest an inflammatory process over infection.

Antineutrophilic cytoplasmic antibodies (ANCA): Although serology is useful in the diagnosis of ANCA associated vasculitis, it can be negative in 20–30% of patients. A combination of clinical, histopathologic, radiologic, and serologic findings is necessary for diagnosis of these diseases.

Treatment of vasculitis depends on the severity of the condition. On one hand leukocytoclastic vasculitis may not require treatment at all while fulminant ANCA-associated vasculitis with pulmonary renal involvement may need IV steroids, cyclophosphamide, rituximab, and plasmapheresis.

TABLE 1: Types of vessels and their clinical features.

Type of vessel	*Clinical feature*
Large	Limb claudication, asymmetric blood pressure, absence of pulse, bruits, aortic dilation, and renovascular hypertension
Medium vessel	Nonhealing ulcers, digital gangrene, cutaneous nodules, mononeuritis multiplex, microaneurysms, renovascular hypertension, and scleritis
Small	Purpura, urticaria, glomerulonephritis, alveolar hemorrhage, splinter hemorrhage, uveitis, and episcleritis

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus is a heterogeneous, multisystem disease with numerous critical complications that may present to the intensivist. In the last 15 years, SLE has surpassed rheumatoid arthritis as the leading cause of admission to ICU among autoimmune conditions.[8] Patients with SLE need intensive care for hematologic, neuropsychiatric, and cardiovascular complications.

Diagnosis

It is a disease commonly seen in females of reproductive age group. Past or recurrent history of malar rash, although pathognomic, is seen in one-third of patients. It is more prudent to look for photosensitivity on face, sun exposed part of limbs, and neck. Recurrent palatal ulcers, recent onset alopecia, recurrent leukopenia, and unexplained thrombocytopenia are important bedside pointers. Urine examination suggestive of proteinuria, hematuria with no leukocytes and no obvious foci of infection are more likely to suggest glomerulonephritis than infection. Antinuclear antibodies (ANAs) by immunofluorescence are an excellent screening test with >99% negative predictive value. However, false positive cases are common with increasing age, comorbidities, and systemic infections such as tuberculosis, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), and infective endocarditis. ANA profile is a relatively costly test which often does not add to the clinical decision making. Another important aspect is to differentiate disease activity from infection. Hypocomplementemia favor disease activity.

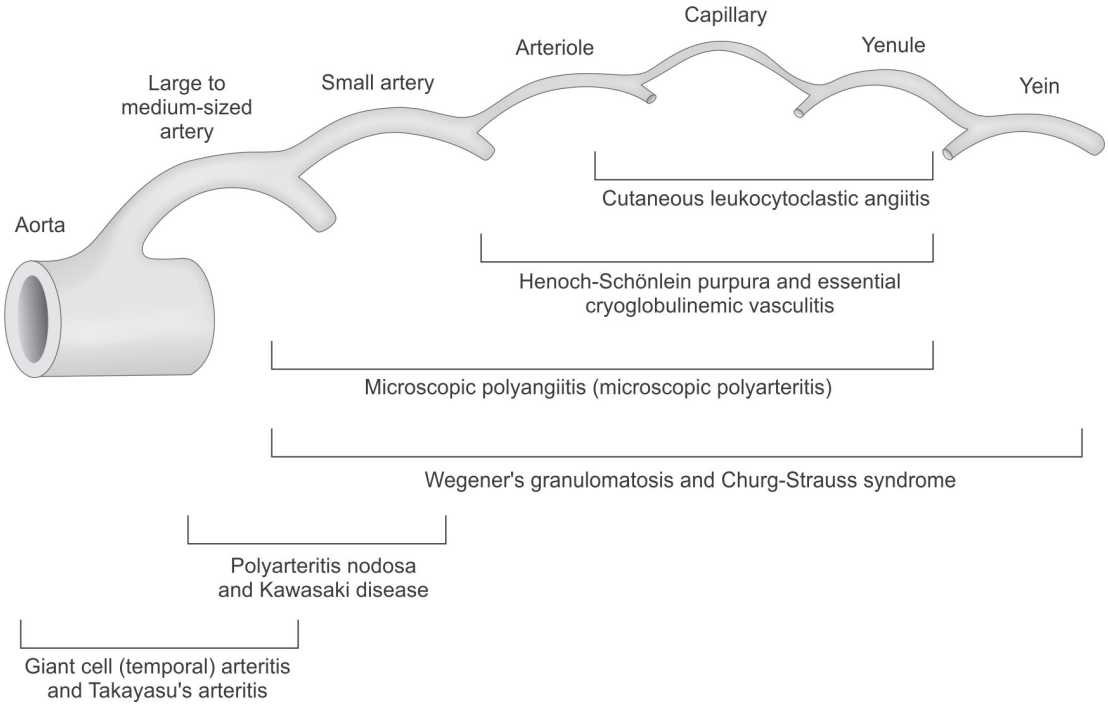


Fig. 1: Classification of vasculitis according to vessel size.[7]

C reactive protein (CRP) is normal in lupus and high CRP favors infection. However, there are caveats such as pleuritis, arthritis in lupus where CRP may be high.

Steroids form the cornerstone of treatment with lupus. Azathioprine, mycophenolate mofetil, cyclophosphamide, and rituximab are also required in majority of patients depending on the clinical scenario. Detailed insight in the treatment strategies is beyond the scope of this review.

CATASTROPHIC ANTIPHOSPHOLIPID ANTIBODY SYNDROME

It is a rare multisystem disease with fulminant course, if not diagnosed on time, associated with significant mortality. Antiphospholipid antibody syndrome (APS) is a procoagulant state with recurrent arterial or venous thrombosis, pregnancy loss, and presence of antiphospholipid antibodies. Catastrophic antiphospholipid antibody syndrome (CAPS) is characterized by disseminated thrombosis and multiorgan failure. Definition of CAPS comprise development of thrombosis in three organs within a week, histologic evidence of intravascular thrombosis, and serologic evidence of antiphospholipid antibodies.[9]

Diagnosis

Antiphospholipid antibody syndrome is predominantly seen in females of childbearing age. Less than 1% of patients of APS develop CAPS. A precipitating factor, infection (22%), surgery (10%), discontinuation of anticoagulation (8%), medicines (7%), obstetric complication (7%), and neoplasia (5%) can be identified.[10] Kidney (71%), lung (64%), central nervous system (62%), and skin (50%) are the major organs involved. Thrombocytopenia is seen in half of the patients; however, severe thrombocytopenia (below 50,000/microliter) is rare. ANA is seen in two-thirds of the patients.

High-dose steroids, anticoagulation with heparin, IV immunoglobulin, and cyclophosphamide comprise the treatment strategy. Recent evidence suggests reduction of mortality from >50% to 20–33% due to the awareness leading to early diagnosis and evolution of treatment strategies.[11]

SCLERODERMA RENAL CRISIS

Scleroderma is an inflammatory condition characterized by fibrosis of skin and internal organs. Scleroderma renal crisis (SRC) is a rare complication of scleroderma seen with increasing blood pressure, renal failure, and microangiopathic hemolytic anemia. Recent worsening of creatinine should raise the suspicion of SRC. It is commonly seen in diffuse scleroderma patients who are treated with high dose corticosteroid therapy. Angiotensin converting enzyme inhibitors (ACEI) form the cornerstone of the treatment of SRC. Prompt diagnosis and treatment can help to save life and prevent chronic renal damage in most patients of SRC.

PHARMACOTHERAPIES

Patients of rheumatic conditions present to ICUs due to complications and infections after prolonged immunosuppression. A basic knowledge of immunosuppressive agents commonly used is imperative for an intensivist for the management of such patients.

Methotrexate

It is an antifolate drug with immunosuppressive and anti-inflammatory properties. It is administered once in a week as oral tablet or subcutaneous injection. It is most commonly used drug in the treatment of rheumatoid arthritis.

Bone marrow toxicity: Pancytopenia is uncommon with methotrexate at the doses used in the treatment of rheumatic conditions. However, bone marrow suppression can be seen in patients with:

- Inadvertent daily dosing as compared to taking it weekly
- Renal insufficiency leading to reduced clearance
- Elderly patients with reduced bone marrow reserve
- Reduced albumin levels.[12]

Treatment begins with cessation of the offending drug, folinic acid, and supportive management. Neutropenia care, granulocyte-colony stimulating factor, and broad-spectrum antibiotics are required in patients of febrile neutropenia.

Methotrexate pneumonitis: Lung toxicity most often occurs after weeks to months of low-dose oral methotrexate therapy but can occur following relatively short-term use of IV or intrathecal administration of higher doses. The precise frequency with which methotrexate pulmonary toxicity occurs is difficult to assess since rheumatoid arthritis can involve the lungs and pleura. In a study of 3,463 patients with rheumatoid arthritis receiving methotrexate, 84 patients (2%) had some type of lung toxicity, but only 15 were felt to be definitive cases of pneumonitis attributable to methotrexate (0.43%).[13] Management includes discontinuation of methotrexate, supportive care, and glucocorticoids in patients with rapid worsening.

BIOLOGIC AGENTS

It comprises targeted monoclonal antibodies against various cytokines and immune cells. These are strong immunosuppressive agents requiring special insight in immunology for their understanding. A rheumatologist should be involved for the care of patients admitted to ICU taking these medications.

Antitumor Necrosis Factor Agents (Infliximab, Adalimumab, Golimumab, and Etanercept)

Owing to their powerful inhibitory action on tumor necrosis factor-alpha (TNF-α), they suppress the immune system significantly leading to risk of infection. Patients on these agents are specifically at higher risk of tuberculosis.

Anti-interleukin-6 Agents (Tocilizumab)

Tocilizumab is a monoclonal antibody used for treatment of juvenile idiopathic arthritis, rheumatoid arthritis, and giant cell arteritis/Takayasu arteritis. Recently, it has shown mortality benefit in COVID.

B-cell Depleting Agents (Rituximab)

Rituximab is a monoclonal antibody against CD20, a B cell protein. It is given every 6 months. There is higher risk of bacterial pneumonia, gram-negative septicemia, and reactivation of hepatitis B with rituximab.

CONCLUSION

Although these conditions are rare, low threshold of suspicion, early diagnosis, and prompt treatment of rheumatic disease and hyperinflammatory conditions can be lifesaving in an ICU. With the recent advances in the pharmacotherapy of rheumatic diseases, it is likely that every intensivist comes across patients taking these medicines. Although management of patients with these conditions require special immunology insight of a specialist, basic awareness of these medicines in an intensivist is necessary for efficient management of these conditions.

REFERENCES

1. Camargo JF, Tobón GJ, Fonseca N, Diaz JL, Uribe M, Molina F, et al. Autoimmune rheumatic diseases in the intensive care unit: experience from a tertiary referral hospital and review of the literature. Lupus. 2005;14(4):315-20.
2. Parperis K, Al-Charakh M, Nzuonkwelle S, McPherson M, Al-Marzooq A, Bhattarai B. Characteristics and Outcomes Among Patients With Autoimmune Rheumatic Diseases Requiring a Higher Level of Care. J Clin Rheumatol. 2021;27(7):286-91.
3. Weitzman S. Approach to hemophagocytic syndromes. Hematology Am Soc Hematol Educ Program. 2011;2011:178-83.
4. Griffith M, Brett S. The pulmonary physician in critical care* illustrative case 3: pulmonary vasculitis. Thorax. 2003;58(6):543-6.
5. Semple D, Keogh J, Forni L, Ven R. Clinical review: Vasculitis on the intensive care unit--part 1: diagnosis. Crit Care. 2005;9(1):92-7.
6. Firestein G, Budd R, Gabriel S, McInnes I. Kelley and Firestein's Textbook of Rheumatology, 10th edition. Philadelphia: Elsevier; 2017.
7. Vasculitis UK. Reproduced. [online] Available from https://www.vasculitis.org.uk/about-vasculitis/types-of-vasculitis [Last accessed March, 2022].
8. Bernal-Macías S, Reyes-Beltrán B, Molano-González N, Augusto Vega D, Bichernall C, Díaz LA, et al. Outcome of patients with autoimmune diseases in the intensive care unit: a mixed cluster analysis. Lupus Sci Med. 2015;2(1):e000122.
9. Asherson RA, Cervera R, Piette JC, Font J, Lie JT, Burcoglu A, et al. Catastrophic antiphospholipid syndrome. Clinical and laboratory features of 50 patients. Medicine (Baltimore). 1998;77(3):195-207.
10. Nayer A, Ortega LM. Catastrophic antiphospholipid syndrome: a clinical review. J Nephropathol. 2014;3(1):9-17.
11. Espinosa G, Bucciarelli S, Asherson RA, Cervera R. Morbidity and mortality in the catastrophic antiphospholipid syndrome: pathophysiology, causes of death, and prognostic factors. Semin Thromb Hemost. 2008;34(3):290-4.
12. Bell A, Tattersall R, Wenham T. Rheumatological conditions in critical care. BJA Education. 2016;16(12):427-33.
13. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. Ann Rheum Dis. 2009;68(7):1100-4.

SECTION

16

Medicolegal and Ethics

CHAPTER 82

Humanization of Healthcare in the Intensive Care Unit

Deven Juneja, Suneel Kumar Garg, Siddharth Verma

INTRODUCTION

Critical care has expanded over the years in terms of resources, availability of intensivists, critical care nurses, and application of artificial intelligence. However, in the midst of trying to treat the patient with full enthusiasm, we have forgotten the art of humanization, as we never try to read the patient's mindset about what they actually need. We all know that patients in intensive care unit (ICU) can have multiple tubes or catheters in situ, may be unable to speak or communicate, are sometimes even stripped naked and restrained, and have strangers all around doing multiple procedures with no relatives around. This experience may be very traumatizing and may lead to a feeling of helplessness, humiliation, and isolation. In fact, patients even lose their identity and are called by their room or bed number. In other words, patient gets treated in the ICU as an "object" rather than a "person" causing dehumanization of ICUs.[1]

WHAT IS HUMANIZATION?

As stated in the Oxford handbook of emergency medicine "Treat your patient, the way you wanted to be treated."

Humanization means adapting a patient-centric approach and treat them as humans, and not as objects. A "human-centered" ICU is not only restricted to promoting and protecting health, and treating diseases but is also concerned with emotional, social, and even spiritual well-being of the patients. It respects the basic rights of the patients and ensures their respect and dignity. Humanizing also encompasses the needs and wishes of the patient's family members and ensures that they are not only informed but are included in the care of their patients. Healthcare workers (HCWs) are an integral part of the ICUs and hence, a "human-centered" ICU provides a healthy and friendly environment to safeguard their interests and promote their growth.

WHY DOES DEHUMANIZATION OF INTENSIVE CARE UNIT PATIENTS OCCUR?

Several factors may contribute to dehumanization of ICUs. ICU patients are sick and are unable to speak for themselves. They are dependent on help of others, especially the HCWs. Traditionally, ICU visitation had been restricted, limiting the number of visitors and the time spent in ICU. Family members are considered to be outsiders and limited information is shared with them on "need-to-know" basis. Long working hours, high workload, and stressful working environment for HCWs may lead them to become desensitized to the humanization aspects of critical illness.[2] In addition, the concept of humanization of medical care is not taught as a part of medical curriculum and hence is not understood and given importance to by the HCWs.

STEPS TO HUMANIZE INTENSIVE CARE

In our zest to provide aggressive intensive care, we sometimes tend to ignore the compassionate care which is required by the critically ill patients. These patients are often dependent on the ICU staff not only for their medical needs but also for social, emotional, and functional support. A multipronged approach is proposed to help them provide this support and humanize the ICUs **(Box 1)**.[3]

BOX 1: Proposed steps to humanization of intensive care.

- Liberal ICU visitation policy
- Communication
- Well-being of patient
- Participation of relatives in intensive care
- Care for the healthcare worker
- Prevention, management, and monitoring of PICS
- Humanized infrastructure
- End-of-life care

(ICU: intensive care unit; PICS: postintensive care syndrome)

Liberal ICU Visitation Policy

Even the most modern ICUs continue to have a restrictive visitation policy, even though there is mounting evidence against such policies. "Open-door" ICUs have been shown to be technically feasible and may be advantageous to patients, family members, and even the HCWs.[4-6] Increasing family presence in the ICU may reduce feeling of isolation in the patients, help in building trust and confidence among the family members, increase their understanding of the care process, and also increase their satisfaction and acceptance.[7] Involvement of family members during morning rounds can improve communication and make them feel that they are a part of care of their patient.[8] This in-turn aids in reducing stress, anxiety, and distrust in the patients and their families and may also help in reducing the incidence of postintensive care syndrome (PICS) and improve patient outcomes.[9]

Communication

Communication is an essential component of care of any patient and has been recognized as a primary need of patients and their family members.[10] It encompasses exchange of information among different doctors, between patient and doctors, and relatives and doctors. It is a vital tool to build and enhance trust, understanding, respect and help in facilitating decision-making, and improving patient care. Communication failure may lead to conflicts, disagreements, and may even affect patient outcomes.[11] After entering the patient's room, the physician or nurse should greet and introduce him/herself to the patient and family members. Patients should be addressed with names rather than bed numbers. HCWs should take permission from patient or family members to examine the patient.

Several factors influence effective communication **(Table 1)**. ICU patients may not be in a condition to effectively communicate with the doctors or their family members. Obstacles should be identified and all remedial measures should be instituted to ensure their effective communication. Conscious patients on ventilators may be given pen/paper, or tablets and they should be encouraged to write and express their feelings and thoughts. ICUs should adopt their own policies to ensure effective and timely communication with the families. All the family meetings should be recorded in the doctor's notes. If required, in special circumstances, family meetings may be recorded in audio-visual room. ICU care is all about teamwork, because many different teams of doctors are involved, chances of miscommunication or noncommunication increase. Hence, multidisciplinary rounds and multidisciplinary meetings should be encouraged to ensure that all the teams are informed and involved in the patient care. To ensure continuity of care, handovers between different shifts should be written to avoid any miscommunication.

TABLE 1: Factors influencing effective communication.

Patient-related	*Medical factors*: Drugs or sedatives, on invasive or noninvasive ventilation *Disease-related*: Altered mental status, inability to speak
Family-related	Limited ICU access, working status/hours
Healthcare worker-related	Lack of time, lack of initiative, and communication skills

(ICU: intensive care unit)

Well-being of Patient

Many nonmedical reasons may contribute to patient's well-being. Apart from pain, patient may feel distressed because of several other reasons such as anxiety, depression, uncomfortable positioning, inability to pass motion or urine, or simply because of feeling heat, cold, or thirst.[12] In addition to having policies on pain, agitation, and sedation, all these aspects should also be kept in mind and addressed accordingly. Observe "quiet hours" at night keeping noise in ICU to a minimum, reducing alarm volumes, and ensuring no routine pricks or procedures to the patients, can help them get a few hours of undisturbed sleep. The psychological and emotional stress of ICU patients may be very high because of the feeling of inadequacy, dependence, loneliness, and loss of privacy, dignity, and family support. Recognition and alleviation of these factors should be an important component of patient care. These factors may need to be individualized as per the needs of the patient and family.

Participation of Relatives in Intensive Care

Management of critically ill requires active support and participation of their family members. The support they provide should not be limited to financial and psychological support, but their active participation in day-to-day patient care may increase their understanding, trust, and may also improve the patient care. Empowering them to be actively involved in patient care, be a part of multidisciplinary meetings, and involving them in active decision-making may reduce their level of stress and anxiety and improve their satisfaction levels.[8,13] They should be allowed to groom, feed, and even give rehabilitative exercises, to keep them actively involved in patient care. The emotional and psychological needs of the family members must also be assessed and addressed appropriately.

Care for the Healthcare Worker

Healthcare professionals are an integral part of the ICU and ICUs cannot be humanized until their physical, emotional, and mental well-being is not taken care of. Because of high workload, stressful work environment, and high patient morbidity and mortality, ICU HCWs are more prone to

TABLE 2: Effects of postintensive care syndrome.

Physical	Persistent pain, breathing difficulties, ICU-acquired neuromuscular weakness, sexual dysfunction, malnutrition, pressure ulcers, sleep disturbances, and pulmonary dysfunction
Cognitive	Cognitive deficits, delirium, memory disorders, inability to concentrate, speech deficits, attention deficits, inability to organize the thoughts, and reduced mental processing speed
Mental	Depression, anxiety, and post-traumatic stress disorder (PTSD)

TABLE 3: Bundle approach to prevention of postintensive care syndrome (PICS).

A	Assessment, management, and prevention of pain
B	Breathing and spontaneous awakening trials
C	Choice of sedation and analgesia (light sedation, avoiding benzodiazepines, and paralytics)
D	*Delirium*: Assessment, prevention, and management
E	Early mobility and exercise
F	Family engagement and empowerment

develop anxiety, depression, and even burn-out syndrome. This in-turn may reduce their professional efficacy and affect patient care. All measures to recognize, evaluate, prevent, and alleviate professional burn-out syndrome should be an integral component of a humanized ICU. Ensuring a friendly work environment, flexible working hours, social support, and improving financial compensation can help in improving job satisfaction, work engagement, and reducing burn-out syndrome. Further, behavioral therapies, stress reduction training, and support groups may also be helpful in reducing the burn-out syndrome in the HCWs.[14]

Prevention, Management, and Monitoring of Postintensive Care Syndrome

Postintensive care syndrome has been defined as new and persistent decline in health impairments, affecting physical, cognitive, and mental health functioning, in ICU survivors **(Table 2)**. These impairments cannot be explained by other causes, such as traumatic brain injury (TBI) or cerebrovascular accident (CVA). This can have prolonged and lasting effect on the well-being of the patients and their family members, who are caring for them. When family members are affected, it is called PICS-F. Up to 30–80% of ICU survivors develop PICS.[15]

Certain factors increase the risk of developing PICS. These include prolonged bed rest, need for invasive mechanical ventilation, electrolyte abnormalities, use of paralytic agents, and hypo/hyperglycemic episodes. In addition, pain, discomfort, and feeling of confusion and disorientation may all contribute to the development of PICS. The effect of establishing post-ICU clinics is limited.[16] Hence, the best option is to prevent development of PICS while the patient is still admitted in the ICU. A bundled approach has been advocated for prevention of PICS **(Table 3)**.[17]

Humanized Infrastructure

Intensive care units should be designed to provide technical effectiveness while ensuring quality of care and comfort for the patients as well as healthcare workers. The design should incorporate open spaces but allowing for patient's privacy. There should be adequate natural light and outside view for the patients to feel connected to the surroundings and maintain day–night rhythm. Temperature, noise, and humidity control are of paramount importance to ensure patient comfort. Use of nonpharmacological interventions such as music therapy, and meditation may also reduce pain, anxiety, and improve sleep quality. Use of books, magazines, radio, tablets, or even laptops may be allowed as per the patient's need and condition.[18] Care should also be given to the family waiting rooms and staff resting places to ensure their comfort.

End-of-life Care

In spite of recent advances in the field of critical care, sometimes the only treatment we can offer is palliative care. The aim of palliative care is to provide comprehensive care to a patient with terminal illness to reduce discomfort and suffering at the end-of-life (EOL). The protocols for EOL care should be in accordance to the regional guidelines and recommendations, but should also take in to account the religious and ethnical beliefs and the wishes of the family and the patient.[19,20] Emotional and spiritual needs should also be addressed. In addition to all the physicians caring for the patient, the patient's family should also be involved in EOL-related decision-making.

OBSTACLES TO HUMANIZATION

Many factors hinder adoption of a humanized ICU **(Table 4)**. However, most of these factors are changeable with a positive mindset and commitment from all the stakeholders. The concept of humanization of ICU should be kept in mind while designing an ICU and at each following steps, especially while designing the ICU policies. Sensitization and training of the HCWs to the nonmedical needs of the patients and their family members may help in making the ICU environment more humane.

HUMANIZATION OF COVID INTENSIVE CARE UNITS

COVID-19 ICUs are unique in many ways. At many places, these ICUs are makeshift ICUs, or ICUs converted from other

TABLE 4: Obstacles in humanizing the intensive care units (ICUs).	
Infrastructural factors	ICU design, lack of space or facilities
Managerial factors	Lack of funds, lack of initiative
Workforce related factors	Lack of initiative, limited manpower, high workload, inadequate working conditions, lack of sensitization
Factors related to family members	Lack of finances, lack of time, and social/cultural factors

existing hospital space. This may compromise ICU space and infrastructure. In most of the hospitals, the attendants are also not allowed in these ICUs to contain the spread of infection. Hence, the patients are dependent on HCWs for not only medical care but also for social, mental, and physical support.

COVID-19 patients are also prone to anxiety because of being left alone in the ICUs, suffering and loss in their family, and uncertainty regarding their own treatment and outcomes. Even for conscious patients, the only way to communicate with their loved ones is through mobile phones, which is also possible only with some assistance. This makes the suffering of the patient even worse due to absence of face-to-face contact with their relatives.[21] Personal protective equipment (PPE) prevents spread of COVID-19 but it remains an obstacle for communication which may further aggravate patient's agony. It also makes difficult for people to recognize each other and especially the patients are unable to recognize who is caring for them. The touch of a hand, protected by double gloves, is often the only and sometimes the last human contact.

It is important to take care of physical and emotional well-being of these patients. Visits to COVID-19 ICUs, if properly conducted, may not pose any additional safety risk to patients or visitors. In fact it reduces their anxiety which in turn helps in better cooperation.[22] It is equally important to care for the families who have limited access to their patients. Frequent and detailed discussion, along with video calls to their patients, may reduce their apprehension and enhance trust. Even after the death of patients, counseling and emotional support may be required to facilitate postloss adjustment as rituals that normally provide comfort after death are not readily available to bereaved individuals to prevent spread of infection.[23]

The staff working in COVID-19 ICUs also face difficult work conditions, increased working load, and have to work wearing PPE in constant fear of getting infected or taking infection home to their families. In addition to making working conditions hot and humid, wearing PPE makes performing procedures difficult, and it becomes impossible to take any nature breaks or eat or drink anything. PPE also make communicating with patients and other fellow HCWs challenging. In addition, they have to cope-up with limited resources and shortages of drugs and medical resources. This puts them at risk of emotional disturbance and burnout syndrome. Hence, it becomes imperative to provide them with psychological, social, emotional, and financial support in these challenging conditions.

Specific measures have to be adopted for helping the ICU teams to process and grieve the loss of patients and colleagues, to alleviate stress and to prevent burn out syndrome. This may include behavioral therapies, establishment of support groups, and stress reduction training. They should be encouraged to work in COVID-19 areas, and their work should be appreciated and well compensated. ICU temperature should be properly regulated and the staff should be given shorter shifts with regular breaks to make the working environment more friendly. A strategy to reduce the fear of unrecognized faces is to have a PPE portrait, in which the attending staff and doctors can have a good smiling face portraits of a postcard size so that patient can have an idea of the HCW who is taking care of them.

CONCLUSION

Intensive care in recent years has shown dramatical improvement due to mechanical and technical developments which in turn has resulted in much better patient survival rates but at the cost of dehumanization of ICUs. Multiple stepwise interventions may be required to ensure a more humanized ICU environment ensuring a holistic approach to patient care. This should not only include medical care and therapeutics but also empathy, sympathy, and loving care for the patients. Patient's families should also be given equal importance and they should be actively involved in day-to-day care of their patients. No ICU is complete without the HCWs, hence, their comfort and well-being should also be prioritized to ensure a healthy work environment and better patient care. Even though COVID-19 pandemic has proven to be a major set-back in our quest to humanizing ICU care, but with better understanding of the disease, worldwide vaccination and availability of better healthcare resources, we can overcome this hurdle and make humanized COVID-19 ICUs a reality.

REFERENCES

1. Brown SM, Azoulay E, Benoit D, Butler TP, Folcarelli P, Geller G, et al. The practice of respect in the ICU. Am J Respir Crit Care Med. 2018;197(11):1389-95.
2. Embriaco N, Papazian L, Kentish-Barnes N, Pochard F, Azoulay E. Burnout syndrome among critical care healthcare workers. Curr Opin Crit Care. 2007;13(5):482-8.
3. Vaeza NN, Delgado MCM, La Calle GH. Humanizing intensive care: Toward a human-centered care ICU model. Crit Care Med. 2020;48(3):385-90.
4. Escudero D, Martín L, Viña L, Quindós B, Espina MJ, Forcelledo L, et al. Visitation policy, design and comfort in Spanish intensive care units. Rev Calid Asist. 2015;30:243-50.

5. Liu V, Read JL, Scruth E, Cheng E. Visitation policies and practices in US ICUs. Crit Care. 2013;17(2):R71.
6. Nassar Junior AP, Besen BAMP, Robinson CC, Falavigna M, Teixeira C, Rosa RG. Flexible versus restrictive visiting policies in ICUs: A systematic review and meta-analysis. Crit Care Med. 2018;46(7):1175–80.
7. Jabre P, Belpomme V, Azoulay E, Jacob L, Bertrand L, Lapostolle F, et al. Family presence during cardiopulmonary resuscitation. N Engl J Med. 2013;368(11):1008-18.
8. Au SS, Roze des Ordons A, Soo A, Guienguere S, Stelfox HT. Family participation in intensive care unit rounds: Comparing family and provider perspectives. J Crit Care. 2017;38:132-6.
9. Beesley SJ, Hopkins RO, Francis L, Chapman D, Johnson J, Johnson N, et al. Let them in: Family presence during intensive care unit procedures. Ann Am Thorac Soc. 2016;13(7):1155-9.
10. Alonso-Ovies A, Álvarez J, Velayos C, García MM, Luengo MJ. Expectations of relatives of critically ill patients regarding medical information. Qualitative research study. Rev Calid Asist. 2014;29(6):325-33.
11. Azoulay E, Timsit JF, Sprung CL, Soares M, Rusinová K, Lafabrie A, et al; Conflicus Study Investigators and for the Ethics Section of the European Society of Intensive Care Medicine. Prevalence and factors of intensive care unit conflicts: The conflicus study. Am J Respir Crit Care Med. 2009;180(9):853-60.
12. Alonso-Ovies Á, Heras La Calle G. ICU: A branch of hell? Intensive Care Med. 2016;42(4):591-2.
13. Beesley SJ, Hopkins RO, Francis L, Chapman D, Johnson J, Johnson N, et al. Let them in: Family presence during intensive care unit procedures. Ann Am Thorac Soc. 2016;13(7):1155-9.
14. Moss M, Good VS, Gozal D, Kleinpell R, Sessler CN. An official critical care societies collaborative statement-burnout syndrome in critical care health-care professionals: A call for action. Chest. 2016;150(1):17-26.
15. Colbenson GA, Johnson A, Wilson ME. Post-intensive care syndrome: impact, prevention, and management. Breathe. 2019;15(2):98-101.
16. Schofield-Robinson OJ, Lewis SR, Smith AF, McPeake J, Alderson P. Follow-up services for improving long-term outcomes in intensive care unit (ICU) survivors. Cochrane Database Syst Rev. 2018;11:CD012701.
17. Ely EW. The ABCDEF Bundle: Science and Philosophy of How ICU Liberation Serves Patients and Families. Crit Care Med. 2017;45(2):321-330.
18. Liu K, Chen Y, Wu D, Lin R, Wang Z, Pan L. Effects of progressive muscle relaxation on anxiety and sleep quality in patients with COVID-19. Complement Ther Clin Pract. 2020;39:101132.
19. Truog RD, Campbell ML, Curtis JR, Haas CE, Luce JM, Rubenfeld GD, et al; American Academy of Critical Care Medicine. Recommendations for end-of-life care in the intensive care unit: A consensus statement by the American College [corrected] of Critical Care Medicine. Crit Care Med. 2008;36(3):953-63.
20. Myatra SN, Salins N, Iyer S, Macaden SC, Divatia JV, Muckaden M, et al. End-of-life care policy: An integrated care plan for the dying: A Joint Position Statement of the Indian Society of Critical Care Medicine (ISCCM) and the Indian Association of Palliative Care (IAPC). Indian J Crit Care Med. 2014;18(9):615-35.
21. Kentish-Barnes N, Degos P, Viau C, Pochard F, Azoulay E. It was a nightmare until I saw my wife: the importance of family presence for patients with COVID-19 hospitalized in the ICU. Intensive Care Med. 2021;1-3.
22. Liu M, Cheng SZ, Xu KW, Yang Y, Zhu QT, Zhang H, et al. Use of personal protective equipment against coronavirus disease 2019 by healthcare professionals in Wuhan, China: cross sectional study. BMJ. 2020;369:m2195.
23. Morris SE, Moment A, Thomas JD. Caring for bereaved family members during the COVID-19 pandemic: before and after the death of a patient. J Pain Symptom Manage. 2020;60(2):e70-4.

CHAPTER

83

Public Health Concerns in Pandemic Related to Critical Care Medicine

JV Peter

INTRODUCTION

The coronavirus disease (COVID-19) pandemic has caused major disruption to life and has made quarantine, isolation, masking, and social distancing as the new norm. During the last 2 years, >243 million people have been infected globally and over 4.9 million people have died.[1] Although we witnessed advances in the understanding of the disease and its treatment, including the rapid development of COVID vaccines, the emergence of variants of concern (VOC) with increased transmissibility and higher virulence posed challenges in overcoming the pandemic.

The pandemic has unmasked several public health concerns and exposed lacunae in the health system in many countries. It is important to take stock of these lacunae and address them so that we are better prepared to deal with future pandemics.

WHAT IS PUBLIC HEALTH AND ITS ROLE?

The Centre for Disease Control and Prevention (CDC) defines public health as the "science of protecting and improving the health of people and their communities."[2] The goal of public health is to "improve health outcomes for populations through the achievement of the objectives of preventing disease and the health consequences of environmental hazards and natural or man-made disasters; promoting behaviors that reduce the risk of communicable and noncommunicable diseases and injuries; and ensuring the public's access to quality health services."[3]

World Health Organization (WHO) in its recent update in its website has reiterated its commitment to help countries strengthen preparedness for pandemics and other emergencies and build strong health systems and healthy populations.[4] They outlined 10 global health issues to track in 2021 which included (1) building global solidarity for worldwide health security, (2) speeding up access to COVID-19 tests, medicines, and vaccines, (3) advancing health for all, (4) tackling health inequalities, (5) providing global leadership on science and data, (6) revitalizing efforts to tackle communicable diseases, (7) combating drug resistance, (8) preventing and treating noncommunicable diseases (NCDs) and mental health conditions, (9) building back better and (10) acting in solidarity.[4] Many of these domains tend to get neglected in the setting of a pandemic, given that there is prioritizing of resources to tackle the pandemic and mitigate the risk to the population.

BROAD AREAS OF CONCERN DURING PANDEMICS

This can be addressed in several levels, namely population level, institutional level, and individual level.

Population Level

At the population level, public health concerns that arise include infection control, the ethics of approach to the pandemic, economic concerns, and the balance between pandemic-related health care versus other illnesses.

Infection Control

Mitigating the risk of spread of the virus assumes huge importance in the setting of the pandemic. One of the widely used methods of reducing the spread and "flattening the curve" of the pandemic, so that the health system does not get overwhelmed, is to initiate lockdown. Three aspects of lockdown merit discussion—the timing, severity, and duration. The question of *timing of lockdown* has been the subject of much debate—does it need to be early, late, or just right (and what is the just right time!). To understand this dilemma and how it might influence decision-making by the government, we need to go back to history to see if potential threats evolved into pandemics. In 2003, the severe acute respiratory syndrome (SARS) epidemic affected 29 countries but it did not become a pandemic.[5] The Middle Eastern respiratory syndrome (MERS), which was also caused by a corona virus, affected 27 countries; it did not become a pandemic.[6,7] Thus it was difficult to predict as to how SARS-CoV2 would pan out at the beginning of the epidemic in China.

The *severity of lockdown* was also variable across the globe; intense pan-country lockdown posed several public health problems such as difficultly in accessing emergency care and care of chronic illnesses. In hindsight, it is now evident that at least in the initial phase, the distribution of cases was patchy and restricted to some areas and zones and a pan-country lockdown was probably not necessary and counterproductive. However at that time, limited understanding of the disease necessitated more global lockdowns. It is now clear that "one size did not fit all." During the subsequent waves of the pandemic, the lockdown was restricted to regions and districts with high case-loads. The concept of "dynamic lock-unlock" was introduced in the state of Tamil Nadu where the locking and unlocking of districts/regions took into consideration the number of new cases and active cases.

The duration of lockdown was also difficult to ascertain at the beginning of the pandemic. Although the initial lockdown enabled institutions and states to build capacity to deal with the pandemic, protracted lockdown led to the neglect of chronic diseases, economic hardship, and psychological impact, particularly among students.

In the initial phase of the pandemic, restriction of testing to a few centers contributed to concerns on infection control. However this policy was quickly reversed and permission was given to many private laboratories to also perform testing.

Lockdown with a view to infection control at the population level has significant implications for intensive care. Two aspects merit discussion: (1) Enhancing capacity of intensive care and (2) reducing the burden of severe illness. The lockdown prior to the first wave of the pandemic provided the opportunity for institutions to ramp up and enhance critical care services. Although some institutions were able to do that, the timeframe to create additional beds was short and the need for significant capital expenditure was a limiting factor. The lockdown also helped flatten the curve thereby reducing the number of infected patients at any time which translated to less number of critically ill COVID-19 patients. However, once lockdown was slowly released, there was a surge of cases that engulfed the healthcare system and the demand-supply mismatch was stark in many regions of the country, particularly during the second wave of the pandemic.

Ethical Considerations

There are ethical considerations that have implications in a pandemic. There is danger that some core ethical principles may be compromised. These principles are elegantly described in an ethical framework article[2] and include (1) *minimizing harm* (includes physical, psychological, social, and economic), (2) *proportionality* (which requires that restrictions to individual liberty and measures taken to protect the public from serious harm should not exceed what is necessary), (3) *solidarity* (which requires working together), (4) *fairness* (which requires that resource allocation is done in a fair manner and not arbitrarily), (5) *duty to provide care,* (6) *reciprocity* (requires that society supports those who face a disproportionate burden in protecting the public good, e.g., healthcare workers, and takes steps to minimize risks as much as possible), and (7) *privacy*.

In pandemics, from a public health perspective, the fairness of resource allocation assumes importance. In this context, the principles of utility and equity are widely discussed. It is generally agreed that *equity* implies equality. From an individual's perspective, the expectations are the maximum life expectancy with the best quality of life and with the best chance to achieve it. Although this is ideally pursued in any healthcare setup, at a population level this may not be possible or achievable during pandemics. In pandemics, the *utilitarian principle* may need to be applied. The utilitarian principle attempts to maximize good to the maximum number of people. The definition of "good" is challenging since it may range from probability of survival to length of life or quality of life. The utility principle will maximize the number of lives saved, but may not provide an equal chance to everyone, nor will it maximize the good of the outcome in terms of years of life saved, adjusted for their quality.[8] The aspect of equity and utility assumes significance in the critical care setting since these resources are finite, particularly in countries such as India which was already stretched prior to the pandemic in terms of intensive care unit beds. The lack of sufficient number of beds forced the application of the utilitarian principle over equity.

Economic Concerns

There is a clear relationship between health and socioeconomic status. Pandemics affect the economy in many ways—lives lost, days of work lost due to illness of individual and that of families that need to care for the individual, reduced economic activity due to lockdown, reduced demand for goods as well as financial loss due to job loss or illness. Thus, pandemics have a strong link to economy and health. In the context of pandemics, the economic losses suffered by families limit the ability of patients to source and pay for critical care services.

Balance of Healthcare

It is unclear as to what was the cost of lockdown on the health of the population? This is a difficult question to answer and would require the work of epidemiologists and public health experts. Broadly, there is evidence that road traffic accidents reduced dramatically during lockdown leading to reduced death rate.[9] However, routine healthcare was also affected due to lockdown. It is unclear if there was excess mortality due to this because of delayed presentations or

severe disease for non-COVID illnesses. Added to this was the additional mortality due to the pandemic. So on the one hand, lives were saved by lockdown but on the other hand, there was possibly additional lives lost during the period of the lockdown and the pandemic and it needs to be ascertained as to which side the balance tilted.

From the intensive care perspective, the balance of critical provision was also altered significantly in that elective and essential surgeries had to be postponed in order to create capacity for COVID patients. Although medical and surgical emergencies were attended to during the pandemic, the diversion of manpower affected non-COVID critical care work.

Institutional Level

At the institutional level, the public health concerns include infection control, resource allocation, and healthcare worker protection.

Infection Control

Infection control in healthcare organizations is crucial in a pandemic setting. This is because there is a possibility of nosocomial transmission of infection, either from an infected patient to other noninfected patients or healthcare workers or from an asymptomatic-infected healthcare work to patients under their care. In this context, the practice of screening, isolation, cohorting, and infection prevention control (IPC) measures are important.

Screening entails asking symptomatic or asymptomatic individuals presenting to a healthcare setup, a series of questions to determine a person's risk for COVID-19. This may include questions on symptoms (fever, cough, and breathlessness), travel history (to high prevalence areas), exposure to someone who has been confirmed to have infection as well as checking temperature prior to entry. Those deemed to be at risk based on the above assessment may then be subject to testing.

The concept of isolation, an important public health measure during pandemics, is not new. Isolation in infectious diseases is the possibility to separate infected (or suspected to be infected) people from other subjects not affected by the disease. Its origins in recent history can be traced to mass isolation in the mid-14th century due to Black Death (Bubonic plague) that killed nearly one-third of Western Europeans.[10] The practical challenge on how to isolate is put to the test during pandemics since large numbers of patients would need isolation and this can overwhelm health systems. In this context, it is an important public health perspective to ascertain if the policy should be that of institutional isolation with direct supervision or home isolation with remote monitoring for those with mild disease or asymptomatic positive contacts. While the former may be a better measure to mitigate the spread of COVID, healthcare institutions may get filled and blocked with milder patients, at the expense of those who really need hospitalization. This was evident during the first wave of the pandemic. In general, China adopted institutional monitored programs, while many Western countries adopted home isolation programs.[11,12] The advantage of home isolation programs is lower cost and patient comfort but it comes with the potential risk of spread of infection to other family members.

As pandemics evolve and the numbers increase, it may not be possible to practice isolation of patients given the limitations of number of single rooms and those with negative pressure. In this context, cohorting of individuals can be practiced, whereby individuals affected by common disease, environmental, or temporal treatments may be managed in the same area. These cohorts are based on clinical diagnosis, microbiological confirmation, epidemiology, and mode of transmission. In the case of COVID-19, patients were isolated prior to testing and once they were confirmed to have COVID-19, they were cohorted in designated areas.

At the institutional level, infection control in the intensive care assumes significance in the setting of a pandemic given that intensive care units are closed areas and there is greater chance of nosocomial COVID-19 infection of the healthcare worker given the confined space, the potential for aerosol generation, and the long periods of contact between the patient and the healthcare worker. There is also the challenge to create separate intensive care areas for screening, positive patients, and negative patients resulting in the need to triplicate services.

Ethics of Resource Allocation

The ethics of resource allocation can be difficult for any institution in the setting of a pandemic. The demand–supply mismatch places stress on the system. This was particularly important in the context of the COVID-19 pandemic where there were scare ICU resources in terms of beds, oxygen, ventilators, monitoring equipment, and trained manpower. Intensivists not only had to deal with the pressure of managing critically ill COVID patients but also the challenges of responding to the additional demands that arose during the peak of the pandemic as well as the pressure of determining how to allocate beds to the ones needing them the most.

Healthcare Worker Protection

Healthcare worker protection is important during pandemics since they are in the frontline of care of patients. This involves protection from infection, physical safety, and mental well-being. It is estimated that around 115,000 healthcare workers succumbed due to the COVID pandemic till May 2021.[13] During the first wave of the pandemic, the priority was to ensure that healthcare workers were able to get sufficient personal protective equipment (PPE), which was difficult during the initial stages in many countries.

Subsequently, the priority shifted to ensuring that frontline workers received the vaccine early. Healthcare workers also faced difficulties due to physical abuse and violence when patients died; this has received much attention in India. Finally, there was mental exhaustion and fatigue and burnout. One study reported that 12.3% experienced burnout.[14] Another study reported that healthcare workers who were in direct contact with COVID-19 patients reported more sleep problems and were more exhausted physically when compared with those who were not managing COVID-19 patients.[15] Institutions struggled to meet the emotional and mental needs of healthcare workers. These problems are more likely to be experienced by frontline workers in the emergency department and intensive care.

Individual Level

At the individual level, treatment policies and doctor-patient relationship are important.

Treatments

Treatments can be categorized as (1) *recommended for routine use:* Where there are available treatments with proven scientific evidence, (2) *rescue therapy:* Where there are treatments with limited or no evidence of benefit but plausible scientific basis such that it can be tried for patients with severe illness and low probability of survival, and (3) *research drugs:* Situations where newer therapies, repurposed drugs, or drugs with limited evidence are used on a research mode.

Unfortunately, during the COVID pandemic, many therapies were promoted without evidence, pushing up the cost of healthcare. In one report, over 52,000 patients received convalescent plasma in the US outside clinical trial settings prior to evidence becoming available of lack of benefit. The same was true for treatments such as hydroxychloroquine and remdesivir. On the other hand, good quality clinical trials demonstrated the benefit of low-dose corticosteroids in COVID and this impacted outcomes.

Vaccination

Vaccination is an important public health measure to mitigate the risk of the pandemic and reduce the severity of illness. The urgency to develop vaccines led to some compromise initially in generating evidence for benefit. Once vaccines became available, at the time of roll out, supply issues resulted in ethical dilemma on whom to vaccinate first? The question as to whom among the population should be prioritized for vaccination and who should be compromised when there is only limited supply of vaccine are difficult questions in the setting of a pandemic. Although ethical principles mandate priority vaccination for the most vulnerable, the definition of who was most vulnerable was challenging (healthcare worker, other frontline workers such as police or sanitary workers or elderly patients with comorbidities). Among healthcare workers, it was also important to prioritize vaccination to those most likely to be exposed for longer periods of time (nursing staff, emergency department staff, and intensive care unit staff).

Doctor–Patient Relationship

The doctor–patient relationship which is vital for the process of treatment and healing as well as doctor–family relationship took a hit during the pandemic. Communication with patients was difficult with PPE; communication with families was challenging due to lockdowns and restrictions on visiting. Intensive care units provided teleconsultation and video consultation updates and also facilitated visits of family in situations where patients were very sick and unlikely to survive.

CONCLUSION

Pandemics pose several public health concerns. The challenges are at a population level, institutional level, and individual level. Many of these impact delivery of healthcare. Ethical management principles should guide the approach to the pandemic. It is important that we are well prepared to face pandemics in the future.

REFERENCES

1. Worldometer. [online] Available from: https://www.worldometers.info/coronavirus/. [Last accessed February 2022].
2. CDC Foundation. What is public health? [online] Available from: https://www.cdcfoundation.org/what-public-health. [Last accessed February 2022].
3. US Department of Health and Human Services. Public Health in America. Washington (DC): US Department of Health and Human Services; 1994.
4. World Health Organization. 10 Global health issues to track in 2021. [online] Available from: https://www.who.int/news-room/spotlight/10-global-health-issues-to-track-in-2021. [Last accessed February 2022].
5. World Health Organization. Consensus document on the epidemiology of severe acute respiratory syndrome (SARS). [online] Available from: https://www.who.int/csr/sars/en/WHOconsensus.pdf. [Last accessed February 2022].
6. World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV). [online] Available from: https://www.who.int/health-topics/middle-east-respiratory-syndrome-coronavirus-mers#tab=tab_1. [Last accessed February 2022].
7. Slainte AN. Department of Health. Ethical framework for decision making in a pandemic. [online] Available from: https://www.gov.ie/en/publication/dbf3fb-ethical-framework-for-decision-making-in-a-pandemic/[Last accessed February 2022].
8. Savulescu J, Cameron J, Wilkinson D. Equality or utility? Ethics and law of rationing ventilators. British J Anaesth. 2020;125(1):10-5.

9. Abhilash KPP, Paul AJ, Das S, Hazra D, Jain S, Arelly SPD. Changing pattern of trauma during the COVID-19 pandemic. Med J Armed Forces India. 2021;77(Suppl 2):S338-44.
10. Rosenberger LH, Riccio LM, Campbell KT, Politano AD, Sawyer RG. Quarantine, isolation and cohorting: From cholera to *Klebsiella*. Surg Infect. 2012:13(2):69-73.
11. Dickens BL, Koo JR, Wilder-Smith A, Cook AR. Institutional, not home-based, isolation could contain the COVID-19 outbreak. Lancet. 2020;395(10236):1541-2.
12. Ya Zhu, Chun Wang, Li Dong MX. Home quarantine or centralized quarantine, which is more conducive to fighting COVID-19 T pandemic? Brain Behav Immun. 2020;87: 142-3.
13. India News. (2021). 115,000 healthcare workers died due to COVID: WHO chief. [online] Available from: https://www.indiatvnews.com/news/india/1-15-000-healthcare-workers-died-due-to-covid-who-chief-706771. [Last accessed February 2022].
14. Kapetanos K, Mazeri S, Constantinou D, Vavlitou A, Karaiskakis M, Kourouzidou D, et al. Exploring the factors associated with the mental health of frontline healthcare workers during the COVID-19 pandemic in Cyprus. PLoS One. 2021;14(16): e0258475.
15. Van Roekel HV, Van der Fels IMJ, Bakker AB, Tummers LG. Healthcare workers who work with COVID-19 patients are more physically exhausted and have more sleep problems. Front Psychol. 2021;11:625626.

CHAPTER 84

Indemnity Insurance for Intensivist

Anirban Hom Choudhuri, Sudhir Khunteta, Manish Munjal

INTRODUCTION

There are no two opinions that medical practice is becoming increasingly competitive with a steep rise in the patients' expectations about the deliverables. One of the common culminations of an undesirable outcome is the filing of a legal suit claiming compensation. In a study published using data from National Practitioner Data Bank, the paid malpractice claim rate in US was 0.76 per 1,000 resident years among resident physicians between the periods 2001 to 2015.[1] Although this figure may seem as apparently low, it is well known that the resident physicians pay substantially lesser claim rates in comparison to senior physicians and that the median inflation adjusted claim rates are much higher in cases of delayed verdict.

In India, a survey conducted by National Law School, Bangalore in 2016 found a rise in the medical negligence cases by 400%.[2] Despite the fact that only a fraction of such cases are usually found to be genuine, a felt need for financial and legal protection is experienced by most doctors during the period of crisis. In critical care, the risk of death and disability is much higher than other branches with an increased risk of legal claims.[3] Therefore, professional indemnity not only serves as a financial safeguard against claims during legal row but also reduces psychological stress during unexpected judgments.

DIFFERENCE BETWEEN INDEMNITY AND INSURANCE

From insurance perspective, indemnification refers to the obligation owed by one of the parties to another in providing compensation for losses incurred as per the provisions of the contract. The actual contract stipulating the terms and conditions of the policy provider and is accepted by the policy holder. This is called indemnity. Thus, indemnity facilitates the transfer of the onus of losses from the insurance holder to the insurance provider. The extent of coverage in the insurance policy is purely determined by the indemnity clauses encrypted in the policy.

Certain parlance used in the insurance indemnity needs understanding:

- *Indemnitee*: The insurance holder who is free from the liability for compensation related losses.
- *Indemnitor*: The insurance provider who is legally liable for losses and has agreed to bear the burden of losses.
- *Hold harmless*: A provision that typically exists within an indemnity clause—and is sometimes confused with the meaning of indemnity. Hold harmless necessarily releases an indemnitee from the liability for losses. It therefore absolves the indemnitee from liability while being responsible for costs and vice versa.

Regardless of which term is used to describe the indemnification process, the key thing to recognize from a risk management perspective is the laid out clauses for specific financial responsibilities in case of specific occurrences. Where one is an indemnitor, it is vital to ensure the terms of the clause are not overly broad, to limit the risk exposure. Conversely for an indemnitee, it is advantageous to ensure that the clause covers every eventuality, to guarantee maximum coverage.

How to choose an indemnity plan?

- *Check for coverage*: The professional indemnity insurance for doctors differs from policy to policy. One should thoroughly understand the coverage and features delivered by the policy. For example, a basic indemnity which covers damage to the third party and legal expenses is less useful. A more proficient policy that will deliver comprehensive coverage as well can be more useful. It is important to pay attention to the coverage to be sure that the policy caters to the risks actually faced. While a basic policy may not cover beyond the damages for the third party, an advanced indemnity policy can also deliver coverage for negligence of employees and subordinates and host of other subjects **(Box 1)**.

BOX 1: Extensive coverage for indemnity insurance.

- Defense costs
- Third party damages
- Breach of confidentiality
- Libel and slander
- Loss of documents
- Claims arising out of professional services

BOX 2: Subjects not covered under indemnity insurance.

- Criminal acts, penalties, fines, punitive, exemplary damages
- Acts committed under influence of intoxicants and narcotics
- Treatment given for weight loss, plastic surgery, genetic damages, etc.
- HIV
- Noncompliance with statutory provisions
- Radioactivity
- Losses arising out of insolvency/bankruptcy
- Intentional noncompliance, willful neglect, deliberate act
- Loss of goodwill
- Loss due to act of war, terrorism, etc.

- *Cost analysis*: Professional indemnity insurance for doctors is costlier in comparison to any average insurance policy. But it is also true that the coverage is of a much higher value than others. So one must always check and ascertain that the insurance policy is delivering value beyond the premium that is paid. Therefore choosing a policy which is worth investment and cost-effective is very important.
- *Checking credentials of past claims*: It is worth taking time to check the cases that the insurers have handled in the past which judges their capability to handle the crisis and understand their response time. Ideally, select the policy that offers services of a specialized claims team for intensive care. If an insurance provider is willing to take us through the procedures and protocol well in advance, it assures that they know what they are doing and have the ability to handle emergency situations.
- *Inspect flexibility*: It is necessary to check whether the insurance provider permits the decrease or increase of the sum of insurance during the middle of the tenor. The claims procedure should be hassle-free. There should not be any need for lengthy documentation. One should choose a provider who has the ability to provide maximum convenience and flexibility.

Opting for the Sum Assured Value

Sum assured value is the limit of Indemnity. This limit is fixed as per accident and per policy period which is called Any One Accident (AOA) limit and Any One Year (AOY) limit respectively. The ratio of limit can be chosen as desired. For example, for a sum assured value of 5,000,000, one can choose 1:1 (per event limit should be between INR 100,000 and 5,000,000), 1:2 (per event limit should be between INR 100,000 and 2,500,000), 1:3 (per event limit should be between INR 100,000 and 1,650,000), 1:4 (per event limit should be between INR 100,000 and 1,250,000) etc.

Items not Covered Under Professional Indemnity Insurance

Some items are not covered under indemnity **(Box 2)** although they may not be relevant for ICU.

PROCEDURE TO CLAIM INDEMNITY INSURANCE

"Liability" applies to onus and "legal liability" entails responsibilities which are remediable under legal provisions. They can either due to criminal or civil liability. Only civil liability claims are payable as per law.

The claim for civil liability arise when there is prima facie evidence of negligence by the insured leading to any injury or death to any party or resulting in any form of damage to the property of any person other than insured.

Negligence is established subject to the fulfillment of the following factors:

- An existence of duty of care
- A breach of this duty
- An injury inflicted upon that person as a consequence of that breach.

If such an event happens and the question of compensation is raised, the insurance company should be immediately communicated. If any legal notice or summons is received, this should be forwarded to the insurance company. The company is within its right to defend the case if it chooses to. To claim indemnity insurance once must submit written notice to the insurance provider with full details (e.g., Form 1). The nature of requirements may vary slightly from provider to provider. Once the claim is assessed for its genuineness and scrutinized for exact claim amount, the settlement amount is confirmed. The entire process is completed within the period specified in the terms and conditions of the policy.

ORGANIZATIONS PROVIDING PROFESSIONAL INDEMNITY INSURANCE

Some societies like Indian Medical Association (IMA), Indian Society of Anesthesiologist, etc. provide professional indemnity insurance for its life members upon application. The claims and administrative tasks are taken care of by the organization.

The highlights of the IMA National Professional Protection Scheme are given here.[4]

- One pays a nonrefundable membership fee during joining. The membership fee is INR 3,000 for the first year. If no claims are made in the year, the subsequent membership fee diminishes at a defined proportion—the second year membership fee reduces to INR 2,900, third year membership fee to INR 2,800, fourth year membership fee to INR 2,700, fifth year membership fee becomes INR 2,600, and sixth year membership fee to INR 2,500. Once the minimum fee of INR 2,500 is reached, no further reduction takes place even if there is no claim. If claim is raised and settled, the membership fee moves back to INR 3,000 from the next year.
- If any incident leading to the insurance claim arises, the member informs the Honorary Secretary and State Representative of the Scheme at the earliest after the incident but not later than the period specified as per policy. Such communication applies even to the receipt of legal notice from lawyer, any legal forum, individual patients or their relatives or any intimation to the effect that a case has been registered with the police. If the member fails to inform the concerned office bearers of the scheme about such an incident with the stipulated time frame, he or she forfeits the right to enjoy the benefits of the scheme for that particular case. After informing the Honorary Secretary and State Representative of the scheme the affected member must abide by the instructions conveyed by the management of the scheme pertaining to his or her conduct.
- If a case is filed, the scheme cannot be made a party because the scheme is not insurance company, per se. When the member is instructed by the representative of the scheme to file a counter petition or suit against the party concerned for damages and defamation, the member should abide by. In the event of any compensation being ordered, 50% of the amount should be remitted to the scheme after deducting all the expenses.
- The maximum liability to be paid to any member for damages is INR 500,000 in a single case and INR 1,000,000 for more than one case in a year as per the scheme.
- The legal aid is chosen as far as possible in consultation with the member. But the Chairman/Honorary Secretary reserves the right to appoint a different advocate if they so desire.
- The scheme does not protect the institution or the management of the institution where the affected member is employed for its lapses even if the institution is headed by the affected member. The scheme only admits alleged professional lapses against individual members enrolled in the scheme.

The Indian Society of Anaesthesiologists (ISA) has launched ISA Professional Indemnity Scheme and constituted the ISA Legal Cell. CoverYou (https://www.coveryou.in) is authorized to provide doctor's professional indemnity for ISA members (anesthesiologists, ISA members working in intensive care, chronic pain, obstetric anesthesia, pediatric anesthesia, cardiac anesthesia, neuroanesthesia, etc.) with special benefits and 75% savings on premium through ICICI Lombard General Insurance Co. Ltd. One can register themselves for ISA Professional Indemnity Scheme after taking life membership. Those already possessing prior indemnity policies are entitled to transfer from old to the new policy provided by this scheme from the retrospective date of their old policy.

CONCLUSION

Doctors are humans and are fallible to errors and mistakes. With the evolution of legal and societal norms, these mistakes are often considered as negligence. Although rationally an intensivist makes his best efforts to save lives, situations do arise when intensivists are made liable for unintended errors. Professional indemnity insurance provides protection during such setbacks and ensures that one or two of such failures do not affect the professional career of the intensivist.

REFERENCES

1. Glover M, McGee GW, Wilkinson DS, Singh H, Bolick A, Betensky RA, et al. Characteristics of Paid Malpractice Claims Among Resident Physicians From 2001 to 2015 in the United States. Acad Med. 2020;95(2):255-62.
2. IndiaMedicalTimes.com. (2016). 98,000 people lose their lives because of medical negligence. [online]. Available from http://www.indiamedicaltimes.com/2016/05/25/98000-people-lose-their-lives-because-of-medical-negligence [Last accessed December, 2021].
3. Szalados JE. Legal issues in the practice of critical care medicine: a practical approach. Crit Care. Med. 2007;35 (2 Suppl):S44-58.
4. IMA National Professional Protection Scheme. [online]. Available from http://www.nimapps.com/ [Last accessed December, 2021].

CHAPTER 85

Ethical Concern in Economically Restricted Package Patients

Ashish Bhalla, Bikram Kumar Gupta, Deepak Malviya

INTRODUCTION

- Ethics is concerned with moral principles, values, and standards of conduct [World Health Organization (WHO)]
- Dictionary meaning—"System of moral principle, rules, and conduct."
- The origin of this word is ETHOS, which means "Character."
- Ethics is defined as "the ability to distinguish between right and wrong and to act accordingly."
- The ethics of medicine must balance the healthcare professional's responsibility to each patient and the professional, collective obligation to all who need medical care.

All graduating medical students take the Hippocratic Oath at the time of their commencement. It states, "*I will come for the benefit of the sick, remaining free of intentional injustice, free of all mischief.*" Thus, the message—First, do no harm.

The World Medical Association developed the Declaration of Helsinki to deal with medical research ethics (1964). There were revisions in 1975, 1983, 1989, 1996, and 2000. The fifth revision in 2,000 remains controversial. The reason for this is that the revision discourages placebos and mandates that researchers provide the best-proven therapy to participant's in a trial. This makes it a complicated order to determine its efficacy. In the Nicomachean Ethics, Book I, Aristotle said, "every investigation, and likewise every action and decision, seem to aim at good; hence, the good has been well described as that at which everything aims." Medical practice has evolved from the kind physician to the near-absolute right of patients to control the means and manner.

- In intensive care unit (ICU), there are many ethical problems. The ICU patient is often wired, ventilated, irrigated, restrained, sedated, and has many tubes.
- Principles of ethics in ICU, both medical and surgical, are:
  - Importance of the individual
  - Privacy of the patient
  - Dignity of the patient
  - The right to die peacefully
- The question has been asked, who monitors in the ICU? Who oversees the patient's privacy and dignity? The primary decision-makers are the patient's relative and the doctor. Helpful secondary agents in the process can be the ICU staff, nurses, chaplains, relevant religious traditions, and an ethics committee of the hospital.

There are two ethical danger points in ICU; (1) what is experimentation versus treatment? (Sometimes they seem very similar); and (2) what are hopeless versus heroic measures? Although heroic efforts may be suitable for the patient and even help them, they should not be done in a desperate situation.

The status of DNR (do-not-resuscitate) is essential to consider, and many patients want that to be honored if their situation is hopeless. Some families wish to it, DNR status is used to prevent unwarranted intervention. The question is why is not this done on admission to the ICU? That surgery could treat. The surgery is carried out, and immediately afterward, the family gives a DNR order. Why perform a major operation on an older person who the family does not think should survive anyway?

There is a difference between euthanasia or assisted suicide and letting a patient go or die in the ICU when they have a terminal illness and deteriorate. For example, in a patient with a severe stroke who is brain dead, there is no issue with the family and stopping ventilator support at an appointed time with the family around.

Healthcare costs vary in different part of world and may vary within the country in different healthcare setups. In an environment with resource constraints, it is crucial to have fair allocation of resources for better results and efficiency.[1] Healthcare providers and public need accurate information about "cost-effectiveness," of different options in order to make informed decisions to maximize the impact of funds allocated for healthcare

spending.[2] This leads to more effective utilization of meager resources. For any developing country with a huge and diverse population base, optimal allocation of resources is the first crucial step in healthcare provision.

India has a "double whammy" of continued struggle with communicable diseases, especially tropical infections (established and emerging) along with ever increasing burden of noncommunicable (lifestyle-related) diseases. Although India has invested a lot of money in a "tiered" health care system with primary/basic health care (village level), secondary health care at district level, and tertiary health care (medical colleges/institutes/corporate hospitals)[3] **(Fig. 1)**. Establishment of newer AIIMS (All India Institute of Medical Sciences) and peripheral centers of institutes like PGIMER (Postgraduate Institute of Medical Education and Research), Chandigarh, are a few steps to bring quality care at reasonable price to the general public; however, the ever increasing cost of newer medication, newer investigative modalities, and lack of insurance cover continues to burden the patients financially.[4] Coupled with it, the accessibility of knowledge regarding newer treatment options on social media platforms encourages patients to demand "the best treatment" for their loved ones. Sometimes they forget that the newer treatment options are not always the best and the "economic viability/cost-effectiveness" of therapies have to be taken into consideration by the doctors while taking treatment decisions.

Hospital costs can be classified in two broad categories, fixed and variable costs. The fixed costs remain constant and are independent of change in the number of patients being cared for at the healthcare facility. They reflect the operational costs required to provide care in the hospital.[5] Fixed costs include staff salaries, equipment cost, and the maintenance required on the building and the equipment. Variable cost is actually the hospital costs associated with the care of individual patients. This usually fluctuates with patient volumes. Variable costs tend to differ from patient to patient. They include the costs of specific medications the patient receives, interventions done, or the cost of an additional equipment/drugs used.[6] The main costs associated with care in the hospital are fixed costs, often estimated to account for over 80% of total costs.[5] Irrespective of bed occupancy, the hospital has to pay therefore most cost reductions are due to changes in variable costs only. The hospitals can make care bundles which are economically feasible based on fixed costs, but the variable cost may change the economics of these bundles.

Treatment of critically ill patients requires highly skilled personnel, dedicated nearly sterile environment, monitoring, and life-saving procedures which may be

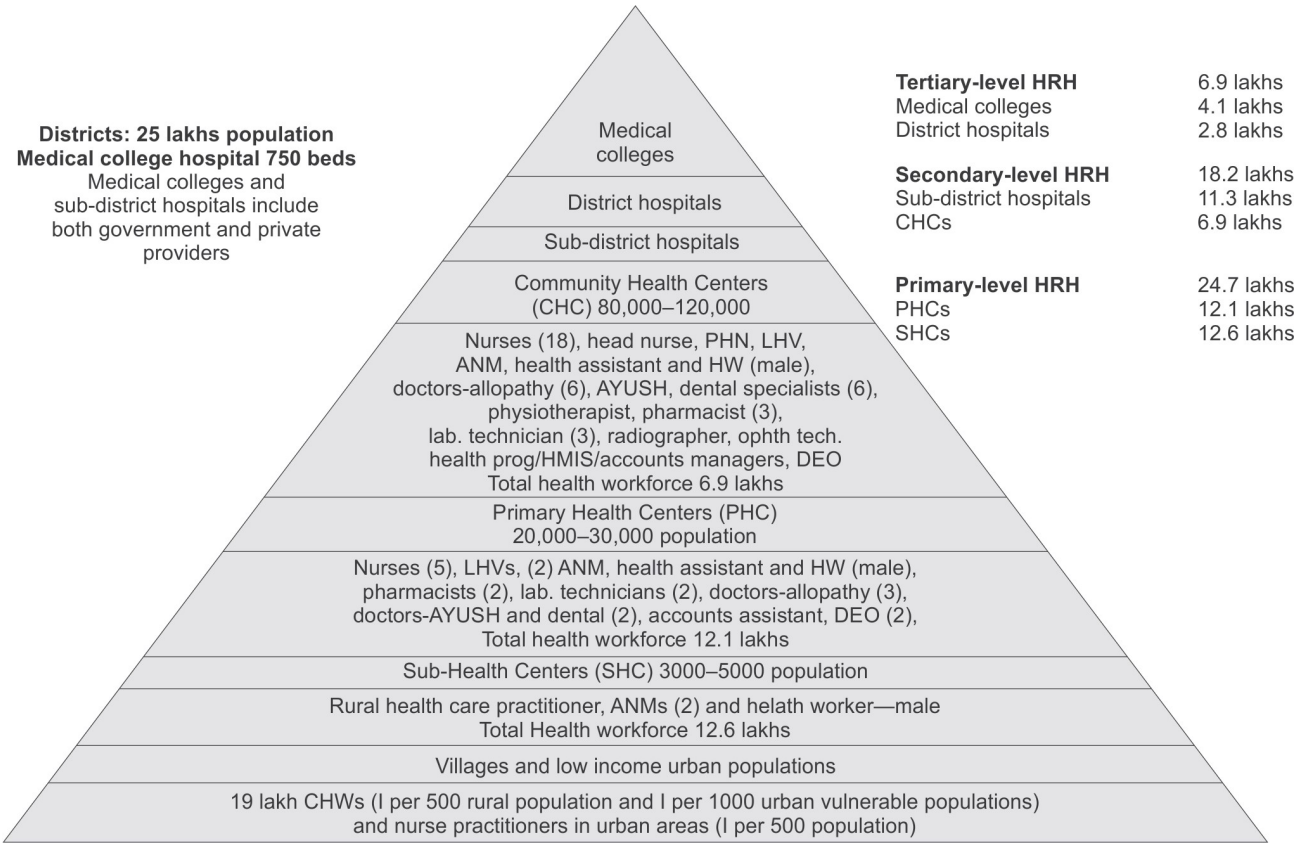


Fig. 1: Indian Public Health System.
Source: National Rural Health Mission, Ministry of Health and Family Welfare, Government of India.

expensive. Mortality in critically ill patients varies between 8 and 33%. This variation is affected by the skill of the treating intensivist, life support systems, and state of the art treatment units. In addition, 11–64% patients may die after ICU treatment in the general hospital wards, further emphasizing the fact that altered physiology in a critically ill patient may take a longer time to limp back to normal.[7,8] Intensive care becomes an expensive specialty due the heavy cost involved to hire highly trained personnel and equally important modern technology for monitoring critical parameters.[9]

The high mortality of critically ill patients, high cost of care, and a certain yet limited possibility of survival of patients without ICU care raise a question of whether the treatment in an ICU provides morale value for invested resources, especially in a resource limited country. The economics of ICU from the perspective of the hospital also depend on how a hospital is reimbursed by a health system.[10] Government hospitals receive a fixed budget irrespective of the number of patients it treats, whereas the private hospitals will receive the money from the patients and the profits are based on the footfall a hospital receives.

The government and health expert continuously try to make efforts to make health care more accessible and "affordable." Various government schemes which aim at providing subsidized treatment to economically deprived or extend these schemes to elderly and special disease conditions such as "cancer" are aimed at making care affordable but it comes at a huge burden on the government exchequer. Some of these welfare schemes for ex-servicemen and employees of government offices have been further extended by including certain corporate hospitals to provide quality care at affordable price to these groups.

One such effort is to make economically affordable bundles for certain common conditions under various schemes in government hospitals as well as making an economic package for affording population in corporate hospitals. These bundles or economic packages work on the premise of calculating average cost of procedures and average duration of the stay in the hospitals to make "economic packages" and they work on the principle of cost cutting by procuring material/drugs used in bulk, thus reducing the cost to the hospitals and making the hospital stay as limited as possible to cut down the running expenditure. Making surgical interventions/radiological interventions as "day care procedures" is one such effort on the part of hospital administrators to reduce the hospital stay thereby reducing the daily bed running cost. In intensive care settings reducing use of technology and equipment that have not been linked to improved patient outcomes will likely decrease costs.[11] Coupled with standardization of treatment approaches and the use of protocols in ICU can help reduce the use of unproven and expensive treatments (or at least ensure that they are used only in situations that are supported by strong levels of evidence) thus reducing the variable cost. In addition, this will also lead to increased use of evidence-based therapies and improved patient outcomes.

These "economic bundles" work on the premise that a day care package procedure will draw more people and this increased footfall would help the revenues. This is a very important component of hospital economics. These are very smart strategies and may work for relatively routine ailments/conditions but their success will depend on the "footfall," number of procedures, capability of the interventionist, and the complication rate. If the complication rate in a particular procedure or in the hands of a particular provider is high, the length of hospital stay will increase, increasing the cost and defeating the whole purpose of economic bundles.

World Health Organization gives a general interpretation of cost-effectiveness of health interventions in the scenario of a country's geographical position and economic development.[12] Cost-effectiveness of some medical interventions, such as coronary artery bypass graft (CABG) surgery, mitral valve replacement (MVR) for rheumatic disease, medical treatment for hypertension, and tertiary management for lung, liver, esophageal, and stomach cancer, was classified by the World Bank as so high that was recommended that public policy should discourage their use in settings where resources are severely constrained.[13] In spite of those recommendations, some of these interventions are being supported by public health authorities in developing countries including India, as they can be economically beneficial.

According to the WHO, values of ICER (incremental cost-effectiveness ratio) less than gross domestic product (GDP) per capita are highly cost-effective, between one to three times GDP per capita are effective in terms of cost, while the value of ICER over three times GDP are not cost-effective. One has to be careful in recommending interventions for economic packaging. Interventions which are more cost-effective are based on many economic parameters.[12] With increasing GDP, the priorities and the approach may change, as is happening in India with increased emphasis now on screening and management of noncommunicable diseases.

These "economically restrictive bundles" are likely to be more successful in certain situation which brings high volumes to a particular healthcare facility such as routine coronary angiography, normal deliveries, dialysis sessions, and routine surgeries such as cataract, joint replacement, and cancer radiotherapy. In certain situations where the physiologic condition of the patient may change rapidly and the risk of developing complications is higher such as

COVID-19 pneumonia, septicemia, and tropical illnesses, it is nearly impossible to make economic bundles for patient care.

At times drastic measures are needed to make treatment "economically viable." During COVID-19 pandemic, the government took a decision to make care for COVID-19 patients in government hospital "free" thus making intensive care available to every citizen of India. An effort to make an economically restrictive bundle to rationalize intensive care in private/corporate sector was made by putting in a "cap" over the ICU charges during COVID-19 pandemic. This was largely successful but led to a huge burden on government exchequer. This effort by policy makers has put "Cost of productive life" over and above "the cost of treatment."

This fact is amply supported by a study from resource constraint setting where the authors concluded that authorities should support the development of critical care services and their availability to general public, in low and middle income countries because the ICU treatment of critically ill patients is fruitful and cost-effective in terms of quality and longevity of life attained.[1]

Further rationalizing of treatment cost in any hospital and especially ICU can be done by careful patient selection (acutely ill patients preferred over patients with chronic illness and multiple comorbidities) and expediting discharge to facilities where nursing care or supportive care can be provided. During COVID-19 pandemic developing step down COVID care centers where observation and supportive care could be provided, help reduce the patient load and financial burden on the hospitals. These small changes in patient care policies can further strengthen the government initiatives of "economic health acre bundles" for certain illnesses.

ADVANTAGES OF ECONOMICALLY RESTRICTED TREATMENT PACKAGE (ESPECIALLY IN INTENSIVE CARE UNIT)

Easy Accessibility

With more and more healthcare facilities opting to be a part of government initiated programs, the number of patients, especially in defense services and government institutions, employees have easy access to care at big corporate hospitals and tertiary care institutions. The easy accessibility may increase the "footfall" making the hospitals economically viable.

Moral Approach

For a country such as India where the aim of government has always been to treat even the poorest of the poor; "concessional treatment" to economically challenged population provides a ray of hope to them. Bringing them back to productive life and economic stream strengthens the economics of the country.

Improvement of Intensive Care Unit Service Provider's Skills

More number of patients coming to institutions, especially critically ill patients, gives the students opportunity to pick up patient management skill sets at bedside first hand. It also gives the opportunity to the teachers/trainers to hone their skills as well.

Each Individual's Life shall be Valued

The Constitution of India grants right to equality to all its individuals, in front of law all the individuals stand equal, but inability of a few to receive emergency medical help, especially in case of critical care medicine, has created a negative impact amongst the public, of the medical fraternity, being money centric, and a feeling for no health services for poor. Stabilizing economically restricted ICU package shall help the poor to believe in the fact that each individual's life matter.

The Snowball Effect

More hospital beds/ICU for treating patients has an economic "snowball effect" on country's economy. As the demand for equipment, drugs, and procedures increases, more and more trained, tax paying, health care workers get employed. This may lead to economic stimulus to growth, provide gainful employment opportunities, and generate taxes for the country. This may also stimulate the country's industrial growth and encourage the population to become self-reliant.

DISADVANTAGES

Quality Compromise

Just in the name of providing ICU services at equitable cost, the quality cannot be compromised. If adequate facilities, trained personal and quality care is not available, the results are likely to be dismal.

Financial Burden on Service Providers

Economic bundles may result in making a hospital/the ICU facility to be largely a nonprofitable business hence making private sector hospitals, refraining from creating these facilities.

Disinterest Among Young Doctors to Peruse it as a Career Option

A compulsory bar on the ICU charges shall create a sense of reluctance in the young doctors to peruse it as a career option, thus bringing down development in this field of critical care.

Compromise with the Team Layout

An ICU setup needs a team having well-trained doctors, nurses, ward attendants, and then very well-sterilized, autoclaved equipment, emergency drugs, etc. Putting economical restriction shall lead to bringing down the number of each of them, this shall lead to shortage of staff and equipment which may land up in medical negligence.

Compromised Quality of Drug and Equipment

Economic restrictions will bring down the revenues, forcing service providers to compromise with the quality of drugs, life-saving equipment, infection control practices, etc. This setup may have long-term adverse effects as the patient care and ultimately outcomes will suffer.

Fairness in Allocation of Intensive Care Unit Resources

Economically restricted package for ICU/hospital beds may lead to unfair allocation of ICU resources. This may actually defeat the very purpose of creating economically restricted bundles.

ETHICAL CONCERNS

For the Physicians

The concerns of treating a patient in the hospital or in ICU when the patient has an "economically restricted care package" are many fold.

The "variable cost" cutting compromises the quality of medication and equipment, which may be locally produced but may have not been rigorously tested as is far as the safety, purity, and quality is concerned. This is probably the biggest concern for the physician. At the end of the day, if the patients have a favorable/successful outcome, nothing matters but if there is any unfortunate outcome, the physicians get all the blame. This is one of the strongest reasons for the physicians to not like/not go for treating these patients.

The healthcare workers want to provide the best care to everyone, when the perceived "best" is compromised, the healthcare workers lose motivation to work. The "malpractice/negligent care" cases or complaints against the healthcare facilities and healthcare workers make them vary of "these patients" as both the parties perceive that in an economically restricted package, the chances of compromised care leading to negligence are high.

The "pressure" of decreasing the length of stay in the hospital or the ICU makes the physician take decisions to discharge/shift the patients out of the ICU to the wards/stepdown areas which may compromise the quality of monitoring and care.

For the Hospital

When the hospitals receive a certain amount or reimbursement for the cost incurred, the "fixed cost," i.e., infrastructure, salaries of the healthcare workers, electricity, and equipment cost remain the same. The only way a hospital will compromise in caring for the patients with "economically restricted care package" is by compromising on the "variable costs," i.e., drugs and other consumables. Another approach is to compromise on the healthcare workers' remunerations. The first step may compromise the quality of care (drugs/equipment) and the safety of the healthcare workers (personal protective equipment).

When quality comes down, the footfall suffers, when safety is compromised, the healthcare workers lose motivation. When the remuneration is affected, the healthcare workers lose interest in caring for the patient. These factors ultimately affect the faith of the patients/society in that healthcare facility.

The fear of litigations/audits of case records for the "best quality treatment" within the economic restrictions sometimes discourages the healthcare facilities to take these patients up for admissions or interventions. This actually defeats the very purpose of the "packaged care."

CONCLUSION

Economically restricted bundles are likely to be the way forward for many common conditions and in much resource constrained countries, including India. The government is morally bound to provide quality health care at affordable price to every citizen of the country. Rationalizing the prices of consumable, equipment by making them locally instead of importing is one way of going about it. Cutting down on the hospital admission duration/ICU admission duration by having dedicated step down units for continued care, rapid turnaround time of the investigations, using information technology in an intelligent way may go a long way to make health care more affordable in coming future.

REFERENCES

1. Cubro H, Somun-Kapetanovic R, Thiery G, Talmor D, Gajic O. Cost effectiveness of intensive care in a low resource setting: A prospective cohort of medical critically ill patients. World J Crit Care Med. 2016;5(2):150-64.
2. Sukcharoen N. Basic principles of health economics for obstetricians and gynecologists. Thai J Obstet Gynaecol. 2003;15(1):3-7.
3. Government of India. (2012). MOHFW Indian Public Health Standards. Revised guidelines New Delhi Directorate General of Health Services, Ministry of Health and Family Welfare.

4. Chokshi M, Patil B, Khanna R, Neogi SB, Sharma J, Paul VK, et al. Health systems in India. J Perinatol. 2016;36(s3): S9-12.
5. Roberts RR, Frutos PW, Ciavarella GG, Gussow LM, Mensah EK, Kampe LM, et al. Distribution of variable vs fixed costs of hospital care. JAMA. 1999;281(7):644-9.
6. Rossi C, Simini B, Brazzi L, Rossi G, Radrizzani D, Iapichino G, et al. Variable costs of ICU patients: a multicenter prospective study. Intensive Care Med. 2006;32(4):545-52.
7. Cuthbertson BH, Rattray J, Campbell MK, Gager M, Roughton S, Smith A, et al. The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomized controlled trial. BMJ. 2009;339:b3723.
8. Williams TA, Dobb GJ, Finn JC, Webb SA. Long-term survival from intensive care: a review. Intensive Care Med. 2005; 31(10):1306-15.
9. Ridley S, Morris S. Cost effectiveness of adult intensive care in the UK. Anaesthesia. 2007;62(6):547-54.
10. Kahn JM. Understanding economic outcomes in critical care. Curr Opin Crit Care. 2006;12(5):399-404.
11. Scales DC, Laupacis A. Health technology assessment in critical care. Intensive Care Med. 2007;33(12):2183-91.
12. World Health Organization. WHO-CHOICE. WHO. [online] Available from: URL: http//www.who.int/choice/en/. [Last accessed February 2022].
13. Jamison DT, Mosley WH. Disease control priorities in developing countries: health policy responses to epidemiological change. Am J Public Health. 1991;81(1):15-22.

SECTION

17

Quality/ICU Organization

CHAPTER

86

Effective Communication Skills and Tools in Intensive Care Unit

Monika Gulati

INTRODUCTION

An intensive care unit (ICU) is an overwhelming place for the family due to the critical condition of the patient and the wide range of unfamiliar equipment, monitors, and ventilators. Coupled with this and the emotional stress the family faces, one of the features of a good successful ICU is how patient and family centric it is. Family-centered care has been associated with better satisfaction, lesser family–physician conflict, and potentially lesser litigations **(Fig. 1)**.[1]

Communication is an art as much as a science and a lot has been written about its importance in terms of good quality care delivery to the critically ill. Rupert Gauntlett et al. in an excellent educational article described the various areas of communication in ICU as listed in **Table 1**.[2]

A doctor working in the ICU needs to be able to communicate well to the nurses, interdepartmental colleagues, to the patients, and to the families. Clear, honest, and timely information to the families can potentially decrease the development of post-traumatic stress disorder and depression in the closest members of the critically ill patient. Studies indicate that early, inclusive, and proactive communication with family members was associated with shorter ICU stays, fewer conflicts, and less futile care.[3-5]

Patients in the ICU are also more prone to experiencing a medical error as compared to the general ward because of the complex medical issues and multiorgan involvement with dynamic changes in the clinical condition. Medication errors are commonly due to poor communication. Donchin and colleagues found that nurse and doctor communication was associated with one-third of detected errors in one of the most extensive studies on human factors investigations of errors in ICU.[6]

In this article, we will focus on the communication between doctors and families.

Fig. 1: Family-Physician conflict.

TABLE 1: Areas of communication.

Skill	*Example*
Communication during crisis	Team leadership, role allocation, etc., in a code blue, cardiac arrest, and intubation
Interprofessional discussion	Engagement with other specialties, dealing with conflict due to difference in opinion about management of patients
Communication with nurses, allied health	Clarity and simplicity, respectful orders
Communication with a sick patient and intubated patient	Ensuring patient rights, dignity, and communication aids (writing boards/pictures)
Meetings with families	First update, modifying expectations, pacing with family. Explanation of poor prognosis, establishing treatment goals with family involvement without creating a burden, i.e., shared decision-making

WHAT SKILLS ARE REQUIRED TO BE AN EFFECTIVE COMMUNICATOR?

Perceptual Skills

Perceptual skills refer to the ability to understand and manage one's own emotions and feelings that arise during a family meeting, this requires a high level of self-awareness and the understanding of one's own judgments, values, and bias.[2] Curtis and colleagues showed that intensivists not only need to deliver information but also need to learn how to listen with genuine intense attention. The proportion of time spent by the family talking was a major determination of their satisfaction in this study.[7] One may ask can these be taught or are they a personality trait? Fallowfield et al. found that perceptual skills can be improved with training.[8] Acknowledging emotions of the family and alleviating guilt can turn a difficult conversation into an amicable one.

Let's understand this with a clinical vignette.

Mr Sugar is a poorly controlled diabetic, who has been admitted in ICU in septic shock after being in the hospital for 2 weeks for treatment of his diabetic ulcer. Multiple debridements have been done and the surgeon is now recommending an above knee amputation for source control. The nurse makes the doctor in the ICU (Dr Marathon) aware of the angry relatives as they are blaming the surgical team as a reason for the amputation. Dr Marathon himself is a diabetic; he is a strong believer of exercise, maintenance of one's own health, and he maintains his diabetes by strict eating habits and regular jogging. In his 30 minutes conversation with the family, he displays a body language of irritation toward the family members and expresses his anger to Mr Sugar's family of them not supporting and guiding Mr Sugar in managing his weight or diabetes (as below).

Dr Marathon: Hello Mrs Sugar, I believe Mr Sugar has had poor control of diabetes for years, has had multiple admissions for the same, I am not sure why he would stop taking insulin at home? Did you not tell him to eat healthy and exercise? Unfortunately, Mr Sugar is going to need to lose his leg to control the infection all because of his bad healthy habits and no amount of wound care and debridement could have prevented this from happening.

Mrs Sugar: You are putting the blame on me!!!!, hmm he never listened to us anyways. All of you did not take care of him properly, that's why this is happening.

Dr Marathon stares at her and says, "let me know your decision about the operation" and walks away in anger.

Mrs Sugar (in frustration and despair): Oh!! he won't be able to live without the leg so we shouldn't go for the amputation, I wanted to tell this to the doctor, but Dr Marathon seems to have no time!!!

TABLE 2: Key points of perceptual skills.

Ability to introspect one's own expressions, body language, bias, and content and modify according to the situation	• For example, in the above scenario saying to the family, "I understand your concerns but let me explain why debridement of the wound did not prevent infection spread and so and so forth • Accepting their frustrations • Not being judgmental
Observation of the body language and mood of the family	• Like the anger of the family members may be evident in their body language—sitting with arms folded across, looking away from the doctor, shaking head • Poor coping with depression/grief—may be evident with the family member's head bowed down, persistent crying • These observations may change your plan of lets say treatment limitations so that you may pace it with the family's acceptance of the prognosis
Empathy	• Using words like *unfortunately* while breaking bad news, deteriorating clinical condition • Offering support—by asking *if they would want more family members to be around?*

Experience of a clinician alone may not be a good marker of his communication skills.[9] Many a times the above scenario is what plays internally in a doctor's mind, which affects his body language and may affect his relationship with the family in a negative way **(Table 2)**.

Content Skills

This refers to the information which is given to the relatives. It consists of what is being said, the language being used, simplicity of information versus complexity.[2]

Commonly what happens in many meetings is information overload, which is imposed on the relatives to be comfortable with oneself that nothing was hidden.

Lots of doctor's struggle with this and this leads to an ineffective conversation as research shows that only 20% of the information conveyed is retained by the families.

Let's look at content issues in the following conversation in the clinical vignette stated above.

Dr Marathon: Mrs Sugar, your husband has worsening sepsis and he has developed low blood pressure, kidney dysfunction, and abnormal liver function. He has been put on noradrenaline and we are titrating it to his mean pressure measured through the arterial line. We also inserted a central line in his right neck vein. He is also needing noninvasive ventilation through a mask and his lungs are getting injured as well. The wound had grown resistant organisms in the

TABLE 3: Key points of content skills.

Nontechnical vocabulary examples	Brain damage (instead of poor neurological outcome), medicines to keep blood pressure up (noradrenaline and vasopressors), low oxygen (hypoxia), breathing machine (ventilator), big line in a big vein (central line), etc.
Avoiding complexity	One big main message—for example, brain damage with multiple organ failure instead of *"on vasopressors, liver dysfunction, kidney failure, clotting failure and ileus, and also poor neurological outcome"*
Check retention of information	Opportunity to ask questions—the kind of questions the family asks will help you know what they have understood
Language as per the comfort level and the mother tongue of the family	Always ask if Hindi/English/a regional language is preferred. Availability of a professional interpreter may be needed.

culture, so we have changed his antibiotic today. He may need a breathing tube put in soon. To control the infection, the surgeon is saying that his legs need to be amputated.

Mrs Sugar: Oh I don't understand that doctor, his kidney does it have an infection too? Do you think he will be better tomorrow? What is amputation?

This is a perfect example of information overload, also showing how doctors tend to use their technical language either unconsciously as a reflex to decrease their anxiety early in their career or sometimes later as well if there has been no feedback given for improvement ***(Table 3)***.

Process Skills

Process skill refers to how a meeting is structured, e.g., if you are meeting up with a family for the first time, it is important to do the following steps:

Introduction—of oneself, what role you play in the care of the patient

Telling upfront the purpose of the meeting—update, discussion about goals of care, treatment options (surgery, dialysis, plasma exchange), etc.

Summarizing the conclusions drawn at the meeting **(Table 4)**.

TABLE 4: Key points of process skills.

Introduction of oneself, role in the ICU	Never assume everyone knows you!! Clarify how many days you will be looking after if you are in a shift system, how the next meeting can be organized?
Confirm that you are talking to the right family	For example, *"May I confirm that you are Mr Sugar's family and also how all of you are related to him?"*
Purpose of the meeting	For example, *"We are meeting today to tell you how Mr Sugar's condition is and discuss the various options of treatment"*
Explore family's understanding of situation, ask if they have any questions upfront and be ready to pace with the family	For example, *"May I know Mrs Sugar what you have been told by the doctors so that I can explain better"*
Do not leave loose ends in the meeting	Not having the time to clarify and address family members' questions, *for example, does the kidney have an infection!* was left unanswered in the above clinical vignette which will affect the understanding of family of patient's illness
Examples of conclusions drawn at the meeting	(In the clinical vignette) *"So as I understand Mr Sugar would not want to undergo amputation and therefore we would like to respect his wishes"* so and so forth...
Appropriate closure and planning for next meeting	Time and day as well as the purpose of the next meeting should be mutually decided as per convenience of both the parties and the hospital visitation policies

(ICU: intensive care unit)

WHAT ARE THE TOOLS WHICH ARE USEFUL FOR EFFECTIVE COMMUNICATION?

Information Booklet

An information booklet about the ICU which gives information about the functioning of ICU, visitation policies, explanation of common equipment—ventilator, monitor, nasogastric (NG) feeding with explanatory images should be given to the family member identified as the closest next of kin. This should be available in at least two to three common languages spoken in that area and a verbal explanation of the same may be carried out by the bedside nurse. In a multicenter randomized trial by Azoulay et al. in France, it was shown that the family information booklet reduced the proportion of patients with poor comprehension and was also associated with more family satisfaction.[10]

Physical Space

Family meeting room, a family-centered ICU must have a dedicated room/corner where meetings can be conducted with at least five people and information of the patient's clinical status may be discussed along with end-of-life care planning. The privacy of the space ensures patient

confidentiality and also allows families to open up, vent out, and express their emotions—sadness, shock, and grief, all of which if left pent up may affect the family's ability to do appropriate decision-making about further interventions in ICU.

Infectious High-risk Zones—Teleconference Equipment

Video conferencing devices must be available to allow family to see their near and dear one if visitation is prohibited in the form of dedicated ICU iPad, mobile phone, etc. during times such as a pandemic and in nonpandemic times for patients who need isolation, e.g., sputum positive tuberculosis (TB).

Time

Adequate manpower, that is doctor and nursing to patient ratio to take care of patients, will ensure that the clinician has enough time for an effective and compassionate family meeting. Fassier et al. in their 1-day quantitative cross-sectional study of family information time in 90 ICUs in France found that the median family information time was 16 (8–30 minutes) minutes per patient with 60% of the time spent in explaining the prognosis. A median of 3 hours in a day may be spent by intensivists informing families in a 12-bed ICU. Communication is a skill therefore which takes time as much as many other ICU procedures.[11]

Involvement of Nurses and Social Workers

A medical social worker may not be available in many resources constrained ICUs in the developing countries, however the nurse looking after the patient must always accompany the doctor in the family meeting. The nurse before the meeting may be able to guide the doctor in the family dynamics, especially in larger families, help in relaying the informational needs of the family, and these will assist the clinician in adjusting the style and the content of the information better suited to that particular family. Contradictory information provided by nurses and doctors can also be prevented by this information sharing.

Training and Simulation Sessions

Senior clinician versus junior, who is ideal to lead the family meeting? Curtis and coworkers showed that ICU physicians even with considerable ICU experience need to improve their communication skills,[7] so each ICU must have a communication policy according to the manpower available. It is recommended that training sessions with actors and simulation as well as real-time feedback after a family meeting will improve this core skill.

Dr Marathon: Hello Mrs Sugar, I am the specialist in ICU looking after your husband now, I would like to tell you about his condition and discuss the treatment options with you and your family. Before I do that, I would like to know what is your understanding of his condition?

Mrs Sugar: I feel he has gotten sicker, and the doctor told me that he is being shifted to ICU as his blood pressure was low.

Dr Marathon: Yes unfortunately, he has become very sick due to the infection in his foot. His organs have started failing as he has what we call as blood poisoning due to very strong bugs coming from the foot. We are doing all we can to support him but to get the infection under control unfortunately antibiotics are not enough, and the foot is full of pus so that needs to be removed. He is in a very critical condition, and he is fighting for his life, with lots of medicines being used to keep his heart strong and BP up. He pauses....as he can see Mrs. Sugar is crying.

Mrs Sugar: Do you think he will be ok if the foot is not removed? Maybe you can support him with medicines only and dressings on the wound. He told me once that he would never want any part of his body to be removed even if it meant he could die!

Mr Marathon: Unfortunately Mrs Sugar, Mr Sugar has very advanced diabetes and his blood sugars are always high even when he is well and this has made his body so weak that he has been unable to clear the infection with the strong antibiotics being given to him for the last 7 days. His wound has been cleaned by the surgeons' multiple times, but the pus keeps on forming again. I would have to say that without the foot being removed that is the amputation he has very chances of dying due to blood poisoning.

Mrs Sugar: Ok I will need time to think about this, I will get back to you after talking to my family in an hour.

Mr Marathon: Sure, let me know if you have any more questions. We are all here to help him get better. I will meet you again here itself in an hour.

Compare and contrast the conversation before to the one above and notice some key points of a good conversation.

In a diverse country such as India (with multiple regional differences, urban rural divide, different paying capabilities, poor patient doctor nurse ratio), effective communication is a much-neglected part of clinical care. There is a huge scope of improvement with communication skill development workshops and its recognition as a core skill requiring it to be examined in licensing examinations of intensive care in the future.

REFERENCES

1. Dhar S. I'll see you in ICU. Times of India. TNN; 2016. [online] Available from: https://timesofindia.indiatimes.com/india/ill-see-you-in-icu/articleshow/52851629.cms. [Last accessed February 2022].
2. Gauntlett R, Laws D. Communication skills in critical care. Contin Educ Anaesth Crit Care Pain. 2008;8(4):121-4.
3. Way J, Back AL, Curtis JR. Withdrawing life support and resolution of conflict with families. BMJ. 2002;325(7376):1342-5.
4. Lilly CM, De Meo DL, Sonna LA, Haley KJ, Massaro AF, Wallace RF, et al. An intensive communication intervention for the critically ill. Am J Med. 2000;109(6):469-75.
5. Campbell ML, Guzman JA. Impact of a proactive approach to improve end-of-life care in a medical ICU. Chest. 2003;123(1):266-71.
6. Donchin y, Gopher D, Olin M, Badihi Y, Biesky M, Sprung CL, et al. A look into the nature and causes of human errors in the intensive care unit. Crit Care Med. 1995;23(2):294-300.
7. Curtis JR, Engelberg RA, Wenrich MD, Shannon SE, Treece PD, Rubenfeld GD. Missed opportunities during family conferences about end-of-life care in the intensive care unit. Am J Respir Crit Care Med. 2005;171(8):844-9.
8. Fallowfield L, Jenkins V, Farewell V, Saul J, Duffy A, Eves R. Efficacy of a Cancer Research UK communication skills training model for oncologists: a randomized controlled trial. Lancet. 2002;359(9307):650-6.
9. Aspegren K, Lonberg-Madsen P. Which basic communication skills in medicine are learnt spontaneously and which need to be taught and trained? Med Teach. 2005;27(6):539-43.
10. Azoulay E, Pochard F, Chevret S, Jourdain M, Bornstain C, Wernet A, et al. Impact of a family information leaflet on effectiveness of information provided to family members of intensive care unit patients. A multicenter, prospective, randomized, controlled trial. Am J Respir Crit Care Med. 2002;165(4):438-42.
11. Fassier T, Darmon M, Laplace C, Chevret S, Schlemmer B, Pochard F, et al. One day quantitative cross-sectional study of family Information time in 90 intensive care units in France. Crit Care Med 2007;35(1):177-83.

CHAPTER 87

Critical Care in Discrete Locations

Rohit Aravindakshan Kooloth, Suresh Kumar Sundaramurthy, Nagarajan Ramakrishnan

INTRODUCTION

Critical care, dealing with the management of seriously ill patients with life-threatening illnesses, remains a resource-limited domain in India, thus compromising the timely delivery of essential services. A critically ill patient in a remote area is often left with poignant choices of either making a costly trip to the urban health sector or delay in the care. In a nation which already lacks over 60,000 doctors to reach the World Health Organization's (WHO) recommended doctor-to-patient ratio of 1:1,000, the availability and accessibility of appropriately staffed intensive care services for rural population remain a distant dream.[1,2]

India has just 2.3 intensive care unit (ICU) beds (29,997 beds) for every 100,000 people in comparison with many developed countries such as Germany and Canada which have 29.2 and 12.9 such beds, respectively.[3] More than three quarters of these beds are concentrated in metropolitan cities, while almost three-fourth of the population reside in rural areas. Lack of adequate healthcare infrastructure has always been a challenge, but COVID-19 (coronavirus disease) has exposed the inadequacies further.

The COVID-19 pandemic has unmasked many of the vulnerabilities in our healthcare system. We realized the need for ramping up the ICU beds several fold in a short period of time, but the lack of skilled manpower was a significant limiting factor to provide the services. These pressing times enabled us to understand not only the seriousness of these deficiencies in remote and rural areas, but also the limitations in resources for intrahospital and interhospital transfers for higher level of care. These scenarios emphasized the importance of services such as tele-ICU and extended intensive care services (EICSs) also referred as critical care outreach services (CCOSs) **(Flowchart 1)**.

EXTENDED INTENSIVE CARE SERVICES

Rapid Response Teams

The fundamental principle of EICS is to recognize and manage the at-risk patients before their deterioration. EICS is provided for hospitalized patients by a team which has different nomenclature in different countries—rapid response teams (RRTs) in the United States, medical emergency teams (METs) in Australia, critical care outreach teams (CCOTs), or patient at risk teams (PARTs) in the United Kingdom.

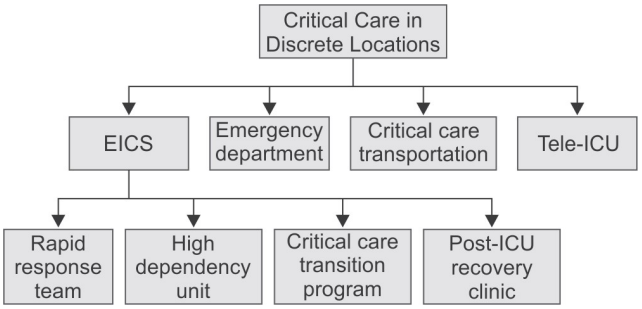
Though there might be minor differences in the structure of RRT as per institutional protocol, it conventionally includes critical care providers such as nurses and respiratory therapists with a physician back up. Even though RRTs respond to cardiac arrest scenario as well, they are different from cardiac arrest teams in that their prime function is to prevent cardiac arrest. This system has four arms as shown in **Figure 1**.[4]

Meta-analyses on effectiveness of RRTs have not consistently shown benefit. The studies that were included were mostly short-term studies from healthcare systems that have accepted RRT as standard of care.[5,6] Although irrefutable evidence is lacking, the concept of early care to prevent deterioration rather than managing later sounds intuitively right.

High Dependency Unit

High dependency units (HDUs) are dedicated areas that provide close monitoring and a level of care that is intermediated between that of the ICU and the ward or floor.

Flowchart 1: Critical care in discrete locations.



(EICS: extended intensive care service; ICU: intensive care unit)

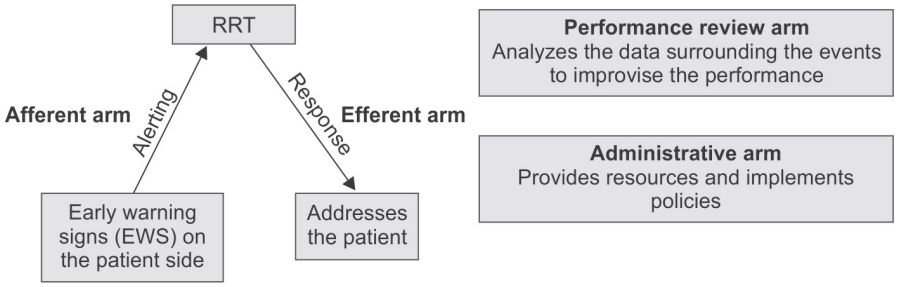


Fig. 1: Arms of rapid response team (RRT).

It may receive patients from the ICU who may no longer require intensive care (step down), from the ward or emergency department (ED) that may have increased requirements (step up) and patients from the postoperative recovery room that need extended monitoring. This unit, which usually has a minimum of four beds with appropriate monitors and equipment to manage any emergencies, is staffed with a nurse-to-patient ratio of 1:3 to 1:4 as compared to 1:1 to 1:2 in ICU and 1:6 to 1:10 in wards.[7] Although there are contradictory reports, there is evidence that the HDU provides a safe and economical transition from ICU to ward especially for severely ill patients.[8]

CRITICAL CARE TRANSITION PROGRAM

Despite recovery from critical illnesses, patients discharged from ICU remain at risk for clinical worsening during the hospital stay, which may result in ICU readmission or even death. Often the transition between ICU, HDU, and ward is fragmented, leading to loss of information and omissions in treatment which compromise patient and family experience. A critical care transition program could fill up these gaps by extending critical care services beyond the confines of the ICU. The outreach teams support the staff in general care areas by following up patients recently discharged from the ICU. They differ widely in composition, ranging from lone liaison nurse to multiprofessional teams, and in their working patterns and activity. Some outreach teams follow-up patients on a regular basis, whereas others attend once patients show early warning criteria. There are multiple studies with variable results on whether this decreases ICU readmission rate and mortality.[9,10]

Post-Intensive Care Unit (Post-ICU) Recovery Clinic

After discharge from ICU, patients can present with physical limitations (due to ICU acquired weakness), cognitive dysfunction, and other mental health problems such as depression, anxiety, and post-traumatic stress disorder (PTSD). These manifestations are being covered under the broad term "post-intensive care syndrome" (PICS). The common risk factors for PICS include older age, female sex, previous mental health problems, disease severity, negative ICU experience, and delirium. In some institutions, these issues are tackled by the post-ICU recovery clinic, where an interdisciplinary team consisting of physicians, nurses, psychologists, pharmacists, case managers, physiotherapists, occupational therapists, speech and language therapists, and nutritionists work together to address the lingering physical and psychological sequelae. In addition to general examination, laboratory investigations, and imaging, the post-ICU care visits include a 6-minute walk test and pulmonary function tests (PFTs). Multidisciplinary care in the post-ICU recovery clinics has been shown to reduce ED visits, hospital readmissions, improve continuity of care, and accelerate resolution of critical illness sequelae.[11] COVID-19 survivors, who have several of these risk factors, are at high risk of developing PICS.

CRITICAL CARE IN THE EMERGENCY DEPARTMENT

The ED operationally was designed around urgent diagnostic testing and medical stabilization of critically ill patients. Studies suggest that the ED presentation for evaluation of critically ill has almost doubled between 2006 and 2014.[12,13]

It is noted that about 8% of all patients presenting to the ED are critically ill. Interestingly, 25% of all patients who are hospitalized after evaluation in ED require admission to the ICU which has limited availability of beds in most hospitals.[14]

Emergency department-based boarding of critically ill patients is common, but no national representative numbers have been reported. There is no definition that is universally accepted of ED boarding which may be varied based on the total time spent in the department.[15] Both retrospective and prospective observational studies have demonstrated worse outcomes for critically ill patients after ED boarding[15] including higher hospital mortality,[16] and duration of mechanical ventilation. Simultaneously, it contributes to greater pressures on the critical care team (intensivists, outreach nurses, and critical care practitioners) caring for the patients in the ED to provide continued intensive care input. There is often a shortage of safe and effective multidisciplinary team including nurses, therapists, and

pharmacists and also a lack of standardized care pathways that minimize harm and promote recovery from critical illness (e.g., delirium prevention, early initiation of enteral nutrition, etc.).

Various mitigation strategies have been formulated by different societies to address the care of the critically ill patients in the ED by the health systems.

- Provide timely care in the ED and also emphasize on training the ED physicians to initiate evidence-based protocols keeping in mind the longitudinal management of critically ill patients.
- Hospital management teams must optimize the use of the critical care capacity at all times on a priority basis and have documented escalation plans to accommodate surge capacity.
- Some centers have proposed adding resources to ED beds to address boarding or even building full critical care units within or adjacent to EDs to manage boarding patients.[17] The ED-based ICUs provide short-term critical care trying to fill the unmet needs for timely resuscitation, stabilization, and advanced triage of patients across many conditions requiring high intensity and time-sensitive diagnostics and interventions.

TELEMEDICINE IN THE INTENSIVE CARE UNIT

The WHO defines telemedicine as "the delivery of healthcare services, where distance is a critical factor, by all healthcare professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of healthcare providers, all in the interests of advancing the health of individuals and their communities."[18]

In India, 80% of physicians work in urban areas, while 70% of the population resides in remote locations that suffer from a severe shortage of trained intensivists,[19] hence the imbalance in critical care availability that leads to high costs, mortality, and morbidity.[20]

There are different models of tele-intensive care unit (tele-ICU) that have been described which include centralized versus decentralized, continuous versus episodic (which could be scheduled or reactive) and open versus closed model.[21,22] In the centralized "hub and spoke" model **(Fig. 2)**, the hub represents the remote monitoring center (commonly referred to as "command center") consisting of physicians, nurses, and other allied staff connected to the spoke or remotely located ICUs and provide consultative care.[21] In the decentralized model, physicians and healthcare staff can be located anywhere and provide consultation through Internet via applications on smartphones or tablets. There is no defined command center or dedicated staffing in this model.

Benefits and Pitfalls of Tele-intensive Care Unit

Various studies have demonstrated that tele-ICU improved adherence to best practices, like care bundles for ventilator-associated pneumonia (VAP) prevention, for deep vein thrombosis (DVT) prophylaxis, sepsis management (antibiotic delivery, etc.), glycemic control, and strategy of lung protective ventilation.[23] The use of tele-ICU services has also translated to overall improved utilization of resources, shorter length of stay, reduction in prescription errors, and improved patient safety.[24,25]

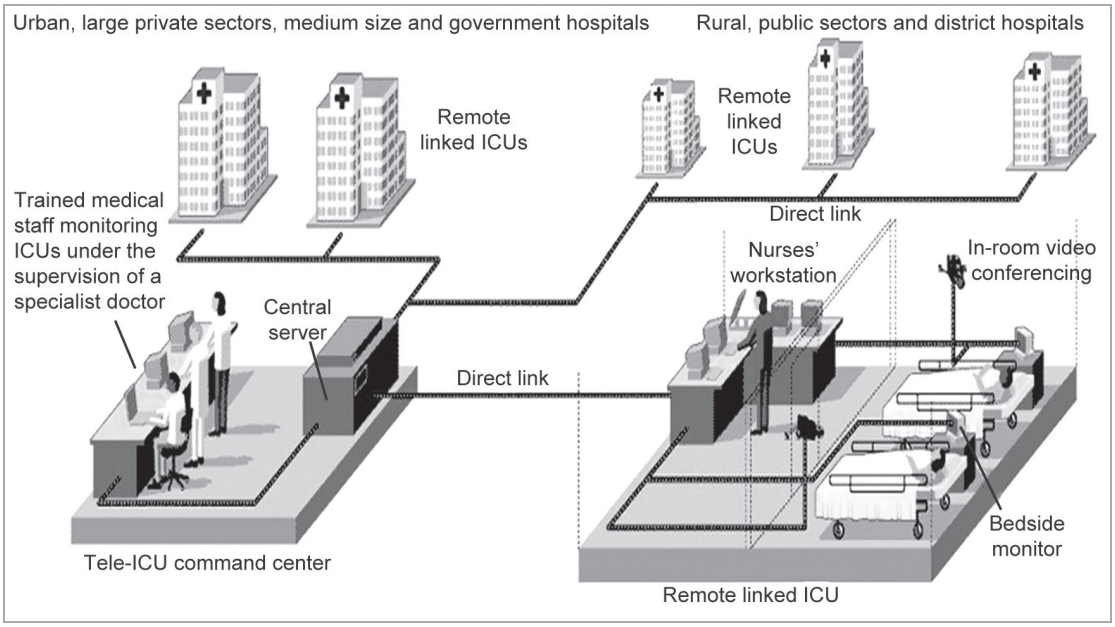


Fig. 2: Centralized "hub and spoke" model of tele-ICU.

The biggest pitfall to a hub and spoke model-based tele-ICU is the initial and operational cost. In a country such as India, barriers in widespread establishment of tele-ICU services include acceptance and attitude among patients and physicians, policy and regulatory challenges, training of healthcare professionals, and the lack of trained personnel on site who could effectively execute the suggestions of the tele-intensivists.[23]

CRITICAL CARE TRANSPORTATION

Transportation of critically ill patients is a high-risk process which might involve unpredictable events occurring in an uncontrolled environment. Some of the critical care societies including Society of Critical Care Medicine (SCCM) in USA and Australian and New Zealand Intensive Care Society (ANZICS) have developed their own guidelines. The ultimate goal of critical care transportation (CCT) is to provide a comparable or higher level of monitoring and care under which the patient was prior to the transport.

A formalized protocol for intra- and interhospital transport should address the following:

- *Pre-transport coordination and communication:* The referring physician has the responsibility to contact the receiving physician to ensure his acceptance of the patient and to convey a full description of patient's condition. The receiver may place his recommendations regarding stabilization and mode of transport.
- *Personnel:* While a critical care nurse and respiratory therapist/critical care technician can safely transfer a stable patient, a trained physician would be required during the transfer of unstable patients.
- *Equipment:* The availability of essential medications required for emergency resuscitation and equipment such as laryngoscope, defibrillator and those required for vascular access and emergency procedures.
- *Monitoring:* Cardiac monitoring, pulse oximetry, blood pressure (BP), pulse rate, and respiratory rate form the absolute essential during transport; capnography, intra-arterial BP, pulmonary artery pressure, intracranial pressure monitoring might be required based on the criticality of the patient.
- *Documentation:* Along with the general and clinical details of the patient, timeline of transport-related activities, documentation regarding informed consent from a competent patient or a legally authorized representative before the transfer is a prerequisite.

It is recommended to use a checklist such as COBRA (Consolidated Omnibus Budget Reconciliation Act)/ EMTALA (Emergency Medical Treatment and Labor Act) (checklist followed in the United States), which covers all the above-mentioned aspects and ensures that all the regulations are complied with during transfer.[26]

CONCLUSION

The care of critically ill patients has evolved and extends beyond the concept of treatment confined to the four walls of the ICU. With the help of EICSs (RRTs or CCOTs), it has been demonstrated that critical care intervention outside the physical limits of the ICU results in improved care and survival of the hospitalized seriously ill patients. PICS should be prevented and treated by a well-designed longitudinal care model including post-ICU recovery clinics providing multidisciplinary care. The COVID-19 pandemic has exposed the persistent increase in demand for ICU beds, and shortage of trained intensivists and support staff which has led to the implementation of tele-ICU and remote monitoring services. A pragmatic solution would be a combination of skill-based care at the bedside supported by cognitive/strategic decision making that can be delivered by trained intensivists remotely through tele-ICU services.

REFERENCES

1. India's shortage of specialist doctors is still staggering - Health Issues India. [online] Available from: https://www.healthissuesindia.com/2019/07/02/indias-shortage-of-specialist-doctors-is-still-staggering/. [Last accessed February 2022].
2. The Economic Times. India facing shortage of 600,000 doctors, 2 million nurses: Study. [online] Available from: https://economictimes.indiatimes.com/industry/healthcare/biotech/healthcare/india-facing-shortage-of-600000-doctors-2-million-nurses-study/articleshow/68875822.cms. [Last accessed February 2022].
3. Phua J, Faruq MO, Kulkarni AP, Redjeki IS, Detleuxay K, Mendsaikhan N, et al. Critical care bed capacity in Asian countries and regions. Crit Care Med. 2020;48(5):654-62.
4. DeVita MA, Bellomo R, Hillman K, Kellum J, Rotondi A, Teres D, et al. Findings of the first consensus conference on medical emergency teams. Crit Care Med. 2006;34(9):2463-78.
5. Maharaj R, Raffaele I, Wendon J. Rapid response systems: a systematic review and meta-analysis. Crit Care. 2015;19(1):254.
6. Hillman K, Chen J, Cretikos M, Bellomo R, Brown D, Doig G, et al. Introduction of the medical emergency team (MET) system: a cluster-randomised controlled trial. Lancet (London, England). 2005;365(9477):2091-7.
7. Sjoding MW, Valley TS, Prescott HC, Wunsch H, Iwashyna TJ, Cooke CR. Rising billing for intermediate intensive care among hospitalized medicare beneficiaries between 1996 and 2010. Am J Respir Crit Care Med. 2016;193(2):163-70.
8. Lekwijit S, Chan CW, Green LV, Liu VX, Escobar GJ. The impact of step-down unit care on patient outcomes after ICU discharge. Crit Care Explor. 2020;2(5):e0114.
9. Stelfox HT, Bastos J, Niven DJ, Bagshaw SM, Turin TC, Gao S. Critical care transition programs and the risk of readmission or death after discharge from ICU. Intensive Care Med. 2016;42(3):401-10.
10. So HM, Yan WW, Chair SY. A nurse-led critical care outreach program to reduce readmission to the intensive care unit: a quasi-experimental study with a historical control group. Aust Crit Care. 2019;32(6):494-501.

11. Jensen JF, Thomsen T, Overgaard D, Bestle MH, Christensen D, Egerod I. Impact of follow-up consultations for ICU survivors on post-ICU syndrome: a systematic review and meta-analysis. Intensive Care Med. 2015;41:763-75.
12. Healthcare Cost and Utilization Project-HCUP. A Federal-State-Industry Partnership The NEDS Contains A Full Year of International Classification of Diseases, Tenth Revision, Clinical Modification/Procedure Coding System (ICD-10-CM/PCS) Codes Beginning Wit.
13. Center for Health Statistics. National Hospital Ambulatory Medical Care Survey: 2015 Emergency Department Summary Tables. [online] Available from: https://www.cdc.gov/nchs/data/nhamcs/web_tables/2015_ed_web_tables.pdf. [Last accessed February 2022].
14. Nguyen HB, Rivers EP, Havstad S, Knoblich B, Ressler JA, Muzzin AM, et al. Critical care in the emergency department a physiologic assessment and outcome evaluation. Acad Emerg Med. 2000;7:1354-61.
15. Mathews KS, Durst MS, Vargas-Torres C, Olson AD, Mazumdar M, Richardson LD. Effect of emergency department and ICU occupancy on admission decisions and outcomes for critically ill patients. Crit Care Med. 2018;46(5):720-7.
16. Singer AJ, Thode Jr HC, Viccellio P, Pines JM. The association between length of emergency department boarding and mortality. Acad Emerg Med. 2011;18(12):1324-9.
17. Leibner E, Spiegel R, Hsu CH, Wright B, Bassin BS, Gunnerson K, et al. Anatomy of resuscitative care unit: expanding the borders of traditional intensive care units. Emerg Med J. 2019;36(6):364-8.
18. Ryu S. Telemedicine: Opportunities and Developments in Member States: Report on the Second Global Survey on eHealth 2009 (Global Observatory for eHealth Series, Volume 2). Healthc Inform Res. 2012;18:153.
19. Homeobook. (2014). India requires 1.4 million doctors, 2.8 million nurses. [online] Available from: https://www.homeobook.com/india-requires-1-4-million-doctors-2-8-million-nurses/. [Last accessed February 2022].
20. Jayaram R, Ramakrishnan N. Cost of intensive care in India. Indian J Crit Care Med. 2008;12:55-61.
21. Reynolds HN, Bander JJ. Options for tele-intensive care unit design: centralized versus decentralized and other considerations. Crit Care Clin. 2015;31:335-50.
22. Venkataraman R, Ramakrishnan N. Safety and Quality Metrics for ICU Telemedicine: Measuring Success. In: Telemed. ICU. New York: Springer International Publishing; 2019. pp. 145-54.
23. Ramakrishnan N, Tirupakuzhi Vijayaraghavan BK, Venkataraman R. Breaking barriers to reach farther: A call for urgent action on tele-ICU services. Indian J Crit Care Med. 2020;24(6):393-7.
24. Khunlertkit A, Carayon P. Contributions of tele–intensive care unit (Tele-ICU) technology to quality of care and patient safety. J Crit Care. 2013;28(3):315.e1-315.e12.
25. Venkataraman R, Ramakrishnan N. Outcomes related to telemedicine in the intensive care unit: What we know and would like to know. Crit Care Clin. 2015;31(2):225-37.
26. Warren J, Fromm RE, Orr RA, Rotello LC, Horst HM. Guidelines for the inter- and intrahospital transport of critically ill patients. Crit Care Med. 2004;32(1):256-62.

CHAPTER

88

Safety Tips for Critical Care Personnel

Mohan Maharaj, Shweta Chandankhede, Venkat Kola

INTRODUCTION

Critical care personnel are exposed to many risk in their lifetime due to the nature of our work. It is not only due to the exposure to various infections which can be contracted by direct contact or due to transmission of infections by various routes but also due to the psychological stress and strain. In the last 2 years, the amount of workload and risk of acquiring COVID-19 infection has caused lot of negative impact on physical and psychological health of the critical care personnel. There are many things which can help decrease this physical and psychological stress. In this chapter, we attempt to give some tips which can help safeguard the critical care personnel.

Infections in the intensive care unit (ICU) can be transmitted by:

- Airborne transmission
- Contaminated water
- Blood-borne transmission
- Contact with contaminated surfaces, feces, and body fluids

To ensure safety, standard and transmission-based precautions should be implemented and meticulously followed by critical personnel **(Table 1)**.

TABLE 1: Standard and transmission-based precautions to prevent infections.

Standard precautions	*Transmission-based precautions*
• Applied to all patients receiving care in health facilities • To minimize the risk of transmission of infectious agents • Used to avoid contact with: – Blood – Body fluids – Secretions – Excretions – Nonintact skin – Mucous membrane	• Precautions taken based on the route of transmission of organisms: – Contact precautions – Airborne precautions

BASIC TIPS FOR PREVENTION OF INFECTION[1]

- Hand hygiene with soap and water or an alcohol-based preparation
- Equipment for personal protection
- Respiratory mannerism
- Sharps injury prevention
- Patient-care equipment handling with safety
- Aseptic precautions
- Infection control of surrounding

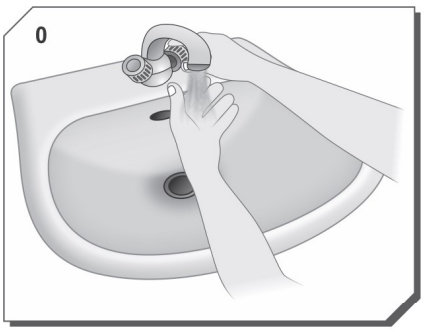
Hand wash and hand rub should be done in accordance to World Health Organization (WHO). For visibly soiled hand, hand wash should be done with soap and water for 40–60 seconds, otherwise hand rub should be done with alcohol-based hand rubs (ABHR) for 20–30 seconds.[1]

PERSONAL PROTECTIVE EQUIPMENT[1]

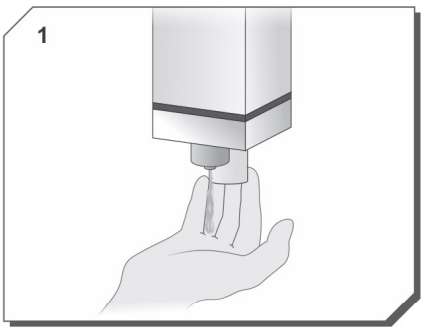
These are physical barriers such as various types of gowns and aprons, types of gloves, facial protective equipment such as shields and googles, hair and foot cover, which can be used alone or in combination to protect from mucous membranes, airways, skin, and clothing from contact with infectious agents.

Gloves

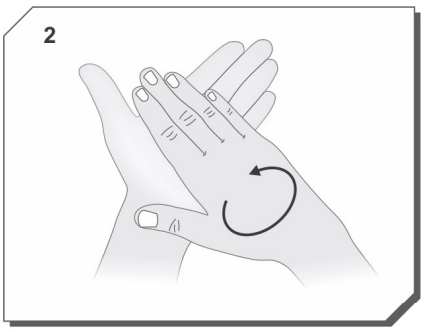
- Worn as an additional measure, not as a substitute for hand washing
- Not required for routine care but must while touching contagious body fluids, breached skin, and mucous membranes
- Need to change gloves after contact with potentially infectious material
- Change of contaminated gloves before touching noncontaminated items
- Immediate hand hygiene after removing gloves.



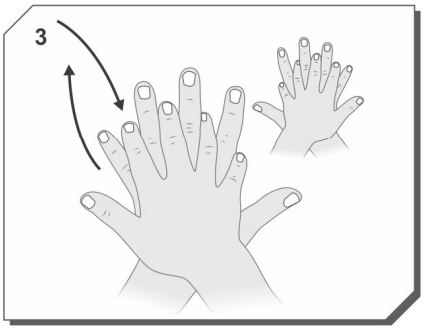
Wet hands with water



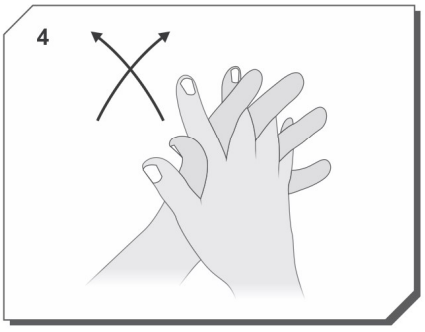
Apply enough soap to cover all hand surfaces



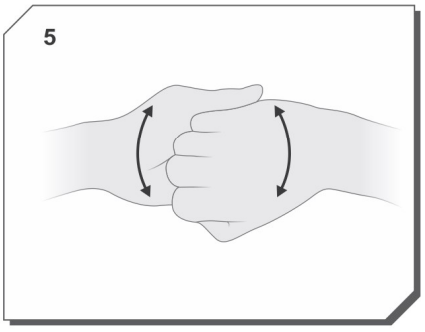
Rub hands palm to palm



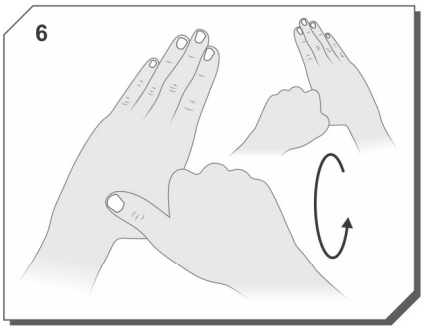
Right palm over left dorsum with interlaced fingers and vice versa



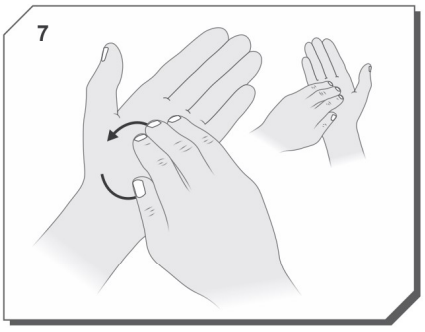
Palm to palm with fingers interlaced



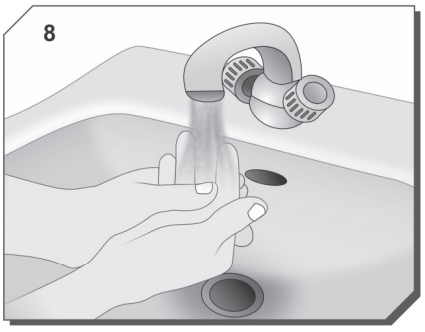
Backs of fingers to opposing palms with fingers interlocked



Rotational rubbing of left thumb clasped in right palm and vice versa

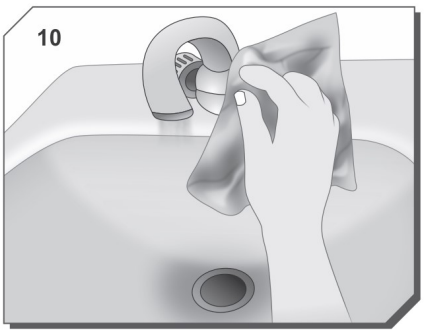


Rotational rubbing, backwards and forwards with clasped fingers of right hand in left palm and vice versa

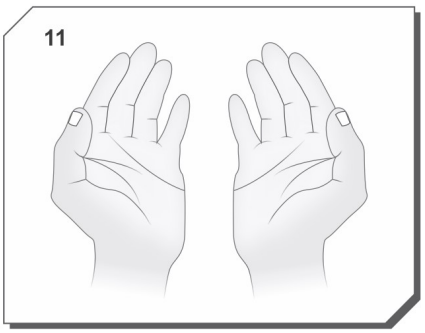


Rinse hands with water

Dry hands thoroughly with a single use towel



Use towel to turn off faucet



Your hands are now safe

Fig. 1A

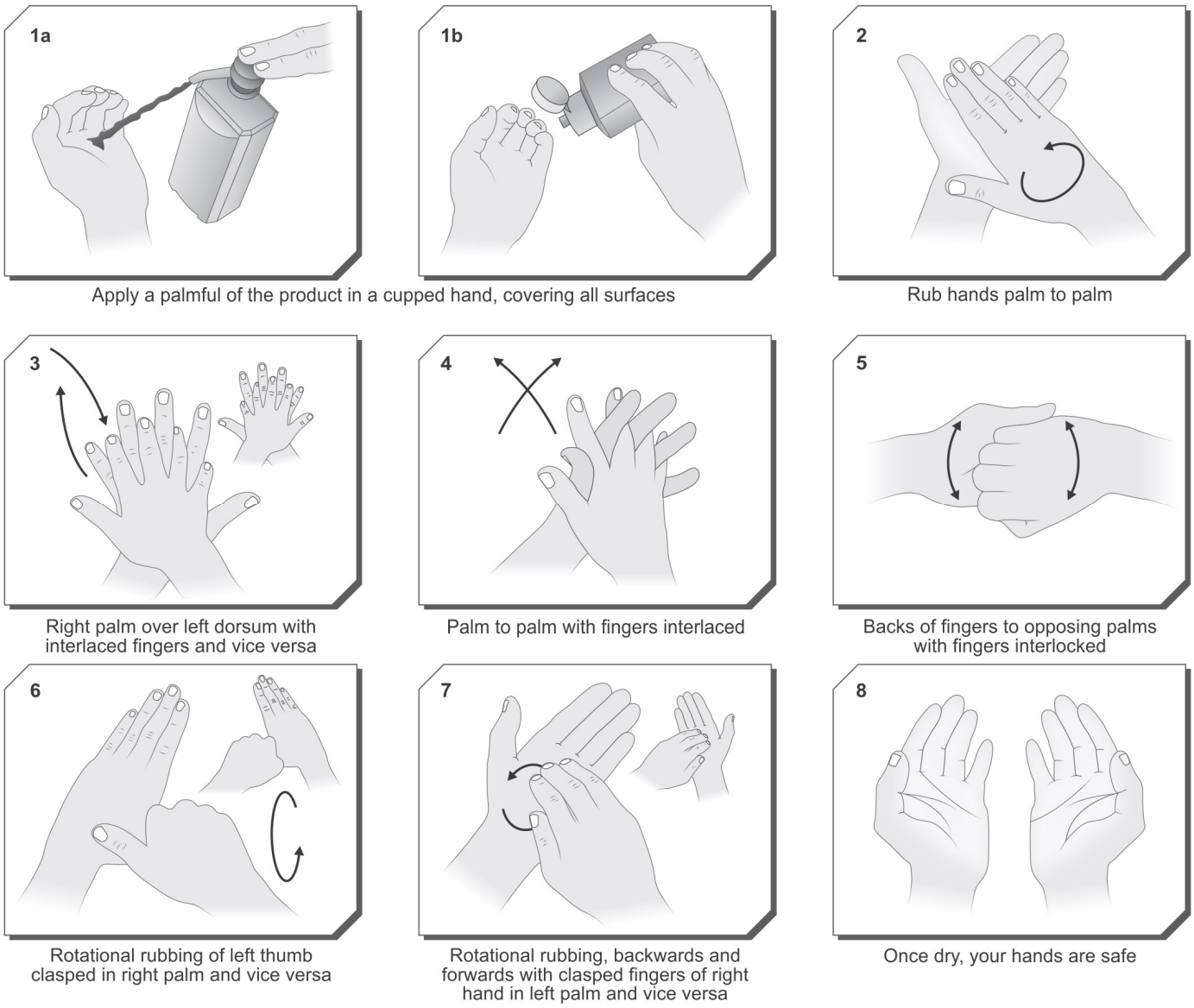
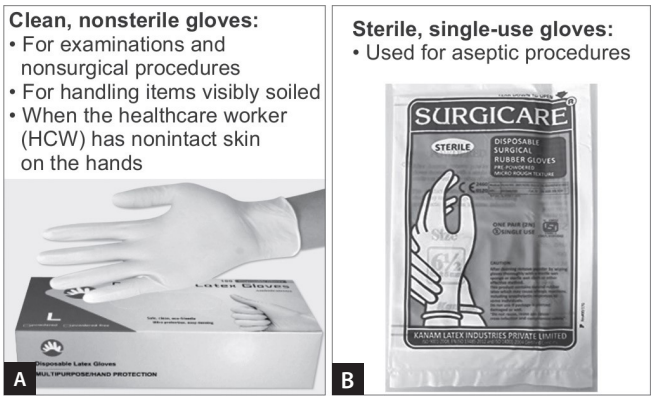


Fig. 1B

Figs. 1A and B: Steps of handwashing and hand rub.

Types and Indications for Wearing Gloves



Figs. 2A and B: Clean and sterile gloves.

Aprons and Gowns

According to international guidelines, protective clothing is must when there is high-risk contamination of skin, scrubs, or other clothing with infectious agents such as body fluids and secretions. Choosing the type of apron or gown depends on various factors: Type of procedure and potential of penetration of the body fluid through it.[1]

A clean nonsterile apron or gown during simple procedures to protect skin and soiling of cloths.

A fluid-resistant apron or gown during procedures producing spray or splash of contaminated body substances.

Facial protection with goggles snuggly fitting around eyes and face shield for mouth, nose, and facial skin protection.

Various types of mask fully covering nose and mouth.

Respirators: Various types of respirators which can filter particles >0.3 microns in diameter are used to prevent inhalation of infectious aerosols, while performing aerosol generating procedures such as bronchoscopy, nebulization, and bag masking. It is important to train the user how to properly wear the respirator and check the seal.

- Particulate respirators such as N95
- Half- or full-face elastomeric respirators
- Powered air-purifying respirators (PAPRs)

A closed footwear or shoe covers should be used to prevent foot injury or protect from spillage of blood or body fluids.

Hair cover is must with caps or bandana.

Selection and safe use of personnel protective equipment (PPE) depends on the route of transmission of infection and risk of contamination. Donning and doffing of PPE must be done meticulously to prevent hazards **(Table 2)**. Respiratory hygiene and cough etiquette also play a very vital role to prevent spread and acquisition of infections.

Safe Handling of Patient-care Equipment

- Hospital disinfection policy
- Dedicated team for decontamination

TABLE 2: Donning and doffing of personal protective equipment (PPE).

Before donning of PPE	*While doffing of PPE*	*After doffing of PPE*
Training to put on PPE	Training to put off PPE	Proper disposal of PPE
Written protocols and picture charts for donning	Written protocols and picture charts for doffing	Management of potentially contaminated PPE
Buddy to assess the competency of donning	Buddy to assess the competency of doffing	Hand and body hygiene
Proper place for donning	Proper place for doffing	
Resource and stock management		

TABLE 3: Tips for prevention of blood-borne infections.

Do	*Don't*
Use single hand scoop method	No recapping of used needles
Immediate disposal of used sharps	No bending or breaking of used needles
Use of puncture proof containers for sharp disposal	No reuse of sharps
Proper handling of sharp ends of instruments	
Contact superior in case of injury	

- Availability of resources for decontamination, cleaning, and disinfection of instruments
- Biomedical waste management

TIPS FOR PREVENTION OF BLOOD-BORNE INFECTIONS

Blood-borne infections not only limited to hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) are always a risk in ICU environment due to as many invasive procedures involve needle stick and sharp-related injuries. The risk is more in critical care personnel as they are mostly the first responders to the critical cases and many times breach the universal protocol with an intention to save the deteriorating condition of the patient as well as inadequate supply of resources. Strategies have to be implemented to prevent or minimize the risk of exposure to blood-borne pathogens and management of the exposure to avoid dreadful outcomes **(Table 3)**.

To implement the prevention strategies, it is crucial to know the mode of transmission of blood-borne pathogen through percutaneous or mucous route, the percentage of risk involved with every procedure, risk of infection with single exposure, and possibility of the pathogen to penetrate the intact skin. Assessment of the risk of blood-borne pathogen can be done with the help of surveillance data, risk of exposure, and seroconversion postexposure.[2]

- HIV and HCV are susceptible to several hours of drying, whereas HBV is unaffected by room temperatures, drying, alcohol, or simple detergents.
- HIV and HCV are not transmitted by environmental surfaces, whereas HBV indirect inoculation can occur via inanimate objects.

Various Preventive Strategies

- Exposure control plan
- Work practice controls
- Personnel protective barriers—such as gloves, masks, gowns, and goggles
- *Use of safer medical devices*:
  - Needleless devices
  - Shielded needle devices
  - Resheathable and blunt-able needles
  - Plastic capillary tubes
- Use of safe techniques, e.g., use of instrument than finger for knotting
- Employee training
- Medical surveillance
- Hepatitis B vaccinations—provides both pre-exposure and postexposure protection
- Sterilization, disinfection, and environmental concerns:
  - Cleaning before disinfection is important.
  - Adequate temperature and duration of exposure to temperature

  - Proper solution concentration
  - Proper duration of exposure to disinfectant
- Detection and diagnosis of HIV, HBV, and HCV infections

Enzyme immunoassay (EIA) and the Western blot are often used to detect HIV. The median time for development of detectable antibody postexposure is 2.4 months and maximum 6 months in 95% of people.[3] An HIV test is flagged as positive when the EIA result is repeatedly reactive and confirmatory test, such as the Western blot, is also positive.

The average incubation period for acute hepatitis B is 120 days. There are various serological markers for detection of HBV at different stages of infection and convalescence. Anti-HBs (hepatitis B surface antigen) is elicited in persons who respond to the hepatitis B vaccine. The appearance of immunoglobulin M (IgM) anti-HBc (hepatitis B core antigen) indicates HBV infection within the prior 4–6 months.[2]

The average incubation period for acute HCV infection is 6–7 weeks. Screening EIA and supplemental immunoblot assays are used to detect antibodies to HCV (anti-HCV).

MANAGEMENT OF OCCUPATIONAL EXPOSURE

Written Protocols

- Prompt reporting
- Evaluation of exposed and source patient for evidence of blood-borne infections
- *Emergency management*:
  - First aid
  - Soap and water wash for injured cutaneous sites
  - Flushing of oral and nasal mucosa with water
  - Eye irrigation with water or saline
  - No evidence of antiseptics, bleach, or caustic agents for wound care
- Counseling
- *Treatment*:
  - *Postexposure chemoprophylaxis for HIV*:[4] Reverse transcriptase inhibitor lamivudine and protease inhibitors such as saquinavir and indinavir combined with zidovudine remarkably decrease plasma HIV level. Postexposure prophylaxis (PEP) should be started immediately within hours of the exposure.
  - *PEP for HBV*: Hepatitis B vaccine and hepatitis B immunoglobulin is remarkably efficacious in preventing infection after an exposure.
  - *Postexposure management of HCV*: No data to support postexposure management of HCV
- Follow-up of occupational exposures
- Maintenance of confidentiality

VACCINATION OF CRITICAL CARE PERSONNEL

Though vaccination cannot be imposed on critical care personnel but contact with patients involves risk, which can be deadly. Additionally, unvaccinated professionals can cause harm to other colleagues by spreading flu. Vaccination should be voluntary as it cannot be mandatory due to legal concerns.[5]

Despite of recommendation, vaccination rate is less which may be due to various factors such as concerns of its effectiveness, adverse effects, and older age. Centers for Disease Control and Prevention (CDC) has recommended some vaccines for the healthcare workers to minimize the risk of vaccine preventable infections. Critical care personnel should take voluntary decision to safeguard themselves from vaccine-preventable diseases after gauging their personal situation. Following facilities should be provided by organization to increase the percentage of vaccination:[6]

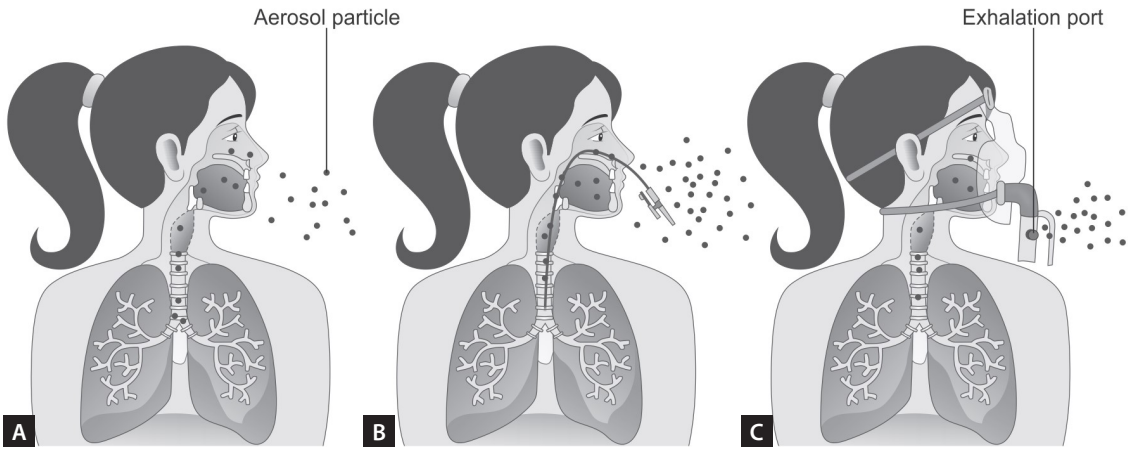
- Free vaccines
- On-site vaccinations
- Mobile vaccination carts
- Walk-in vaccinations
- Educational materials
- Communication campaigns

TRANSMISSION OF AIRBORNE VIRUSES (FIGS. 3A TO C)

Transmission of airborne virus can occur by direct contact with infected person or indirectly by touching objects contaminated with the virus. Infectious agents are transmitted to proximal person by droplets and to the distal person by droplet nuclei suspended in air. During aerosol-generating procedures, aerosols laden with infectious viruses are suspended in the environment with potential to cause infection in healthcare workers if not protected properly.[7]

Aerosol therapy remarkably rises aerosol concentration in the patient's surrounding. In vitro studies found that dispersion of exhaled air occurs with HFNC, NIV, and oxygen devices such as simple mask, Venturi mask, and nonrebreather mask. If there is good mask interface fit, exhaled air dispersion during HFNC and CPAP via different interfaces is limited.[8] When negative-pressure room was used in healthy human participants, NIV and humidified HFNC did not increase aerosol generation.[9] Similarly study by Agrawal et al. in COVID-19 pneumonia showed uncertain findings with regards to droplet dispersion and aerosol generation with HFNC.[10]

Hui et al. reported that aerosol spread does not increase if the HFNC is fitted properly to the face.[8] Cheung et al. discouraged the use of HFNC for patients with COVID-19.[11] Leonard et al. exhibited in a simulation that using a surgical mask over the HFNC likely reduces aerosol spread.[12] Kobayashi et al. concluded that aerosol spread is extensive during spontaneous breathing with HFNC as compared to spontaneous breathing without HFNC, thus recommending either avoidance of use of HFNC or implementing strict precautions against aerosol spread.[13]



Figs. 3A to C: (A) Aerosols generated during normal breathing; (B) Aerosols generated during procedures such as suctioning, intubation, or bronchoscopy; (C) Dispersion of aerosols during nebulization, noninvasive ventilation (NIV), and high-flow nasal cannula (HFNC).

TABLE 4: Tips to decrease aerosol.

Engineering controls	*Administrative controls*	*Environmental controls*
15 air exchanges per hour. To be assessed periodically	Proper disposal of respiratory secretions generated through suctioning in mechanically ventilated patients, as well as used personal protection equipment	Distribution of space for patients and healthcare workers in the designated ICU Individual cubicles curtails nosocomial infections and easy to disinfect
Air flow directional from room entrance to the back and outside	Visitor entry should be restricted to the minimum possible number	At least 12 air exchanges are recommended hourly, though more may be preferred
Air cleaning methods such as ultraviolet germicidal irradiation (UVGI) or HEPA filtration installed in closed air-conditioned suites		Surface cleaning (using cloth or mop moistened with water or a liquid detergent) should precede disinfection, to minimize aerosolization
N95 particulate respirators to be used by healthcare providers, both during procedure and while handling specimen		Intubated patients on mechanical ventilator with conditions of potential concern regarding airborne transmission, bacterial/viral filters should be used on exhalation valves and should be regularly changed and judiciously disposed off

(HEPA: high-efficiency particulate absorbing; ICU: intensive care unit)

TIPS TO DECREASE AEROSOL (TABLE 4)

- Adequate supply of PPE
- Use of N95 particulate respirators should be used along with PPE in procedures such as nebulization, cardiopulmonary resuscitation, intubation, manual ventilation, airway suctioning, and bronchoscopy-producing aerosols.
- Avoiding vented mask with NIV
- Avoiding use of HFNC or use of strict practices to avoid aerosol
- Use of snuggly fitted nasal prongs and placement of a surgical mask over the patient's face during HFNC.
- Placing a filter between a nonvented NIV mask and exhalation port
- Placing a filter between the resuscitator bag and mask during manual resuscitators
- Hand hygiene before and after removal of personal protective gear
- Respiratory hygiene and cough etiquette
- Ultraviolet germicidal irradiation (UVGI)
- True-HEPA (high-efficiency particulate absorbing) membrane filter in bronchoscopy suites, laboratories, ICU (rated to remove 99.97% of 1 micron particles)
- Use of negative pressure room

HEALTHCARE WORKER SAFETY DURING PATIENT TRANSPORTATION

Infectious cases may require intrahospital and interhospital transfer for many reasons. Potential breaches of infection control can occur during transportation of patient which may increase during transport of COVID-19 patients as accompanying staff has to wear cumbersome PPE **(Table 5)**.[14]

TABLE 5: Transportation involving potential breaches in infection control.

Intrahospital from	*Interhospital*
Emergency departments to the wards	For extracorporeal membrane oxygenation (ECMO)
General floor to the intensive care unit	For higher facility
From the wards to radiology suites	For transplant
From ICU or wards to endoscopy suits	

(ICU: intensive care unit)

TIPS TO PROTECT STAFF DURING TRANSPORT OF THE PATIENT[15]

Staff

- Trained staff
- Intubation of patients in distress before transportation
- N95 respirators and full PPE donning before transportation
- Use PAPRs with spare battery packs for PAPRs
- Dedicated housekeeping team in PPE for terminal cleaning of exclusive route and elevator after transport
- Doffing PAPRs and PPE at designated place after transport

Patient

- Surgical mask for patient during transport
- Polysheet cover on patient during transport
- Information to conscious patient and seeking cooperation from his side

Technical

- Avoid breathing circuits, HFNC, and NIV during transport.
- Use HEPA filters to endotracheal tubes for bagging and on the expiratory limbs of the breathing circuits for ventilators.
- Care to avoid breathing circuit disconnection.
- Preferable transportation for scan to be done in late hours to avoid exposure to many healthcare workers (HCWs) and allows for terminal cleaning of passages and areas used
- Terminal cleaning of ambulance after use

USE OF INTUBATION BOX

The aerosol or intubation box is a protective measure during airway management as it is a high-risk aerosol-generating procedure. Many simulations to ascertain the efficacy of the intubation box are available but lacks vast realistic data.[16] Begley et al. compared the intubation time without an aerosol box versus early-generation box and late-generation box and concluded that intubation time was much lesser without intubation as compared to any generation intubation box.[17]

Fig. 4: Transport of patient with face mask and plastic sheet.

In a study by Kartik et al., they observed 100% success in the first attempt of intubation without intubation box, 38.1% success in first attempt with intonation box, 28.6% patients required second attempt with intubation box with a combined favorable outcome of first and second attempts of endotracheal intubation using the box as 66.6%. Poor vision and inadequate space for maneuvering were limiting factors for use of intubation box. They too concluded that the intubation box increases the number of trials to successful intubation and thus increases patient–physician contact time.[16]

Thus, the use intubation box is still inconclusive for better for protection from aerosol-generating procedures.

SAFETY OF CRITICAL CARE PERSONNEL DURING EXTUBATION

Concerns about aerosol-generating procedures such as extubation lead to studies comparing of acrylic boxes and plastic sheets as protective barriers to noncoverage technique to assess the effectiveness under fluorescent condition. Laosuwan et al. compared droplet dispersion between acrylic box models (3.3–19.0%), plastic sheet (2.8%), and noncoverage technique (26.3%) during tracheal extubation. And showed that acrylic boxes had no contamination, whereas the plastic sheet caused contamination both on the chest and abdomen of anesthesia personnel.[18]

Shortcomings

- Higher cost
- Different models of acrylic box may result in different protective outcomes (more or less height of box, sloppy or flat top of box, door opening and hand slot).
- Cleaning methods are inconclusive.
- Hand slots limit hand movement for complicated airway procedures.
- Risk of minor trauma agitated or noncooperative patients

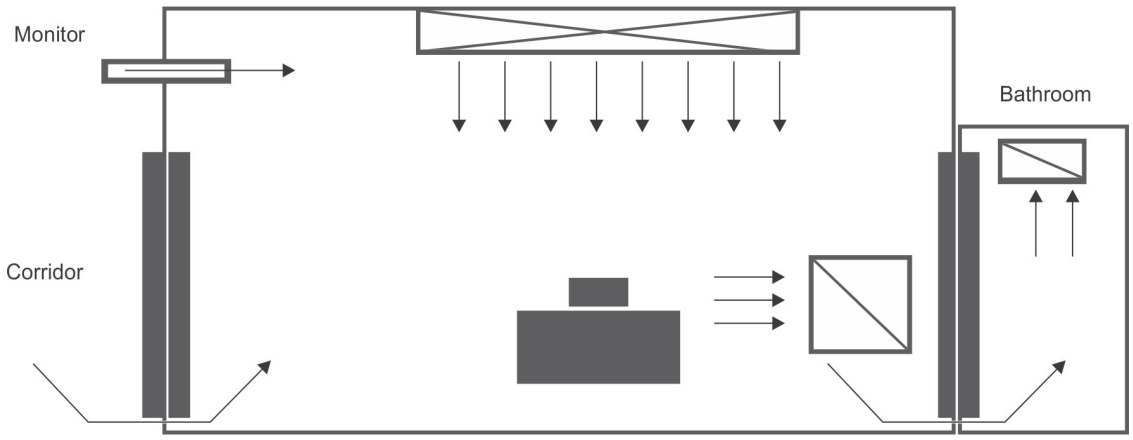


Fig. 5: Negative pressure room.

Advantages of Plastic Sheet[19]

- Less contamination (2.8%)
- Disposability
- Lower cost
- Less restriction to hand movement

Therefore, the barrier to prevent aerosol exposure should be chosen taking into consideration aspects such as availability, cost, disposition, and ease of use.

NEGATIVE-PRESSURE ROOM CONTROL FOR AIRBORNE INFECTION ISOLATION

Ventilation Specifications in Intensive Care Unit and Isolation Anteroom

Burnout

Though identified in 1970, burnout syndrome is gaining a lot of focus due to its increasing phenomenon during the testing pandemic times.[20] Health professionals' well-being is both physically and psychosocially valuable and thus it is important to protect staff by minimizing the risk of infection and the emotional burdens of filed work during this public health crisis. Mutual understanding and harmony in the department is must to have a healthy work life balance. Also, individually each doctor should decide and discern their work, ethics, and life balance.[21]

Psychological burden surfaces more in the healthcare providers, especially amongst the frontline workers due to increased working hours and increased workload in addition to scarcity of resources such as PPE, ICU beds, and ventilators. Occupational hazards is linked with high emotional impact in physicians who work on the front line due to highly contagious nature of SARS-COV-2.[22,23]

It negatively impacts not only the physician but also the organization and the patient. It has been seen that critical care personnel are the ones worst hit by burnout syndrome. Burnout in the ICU is multifactorial which can be attributed to workload, constantly stressful situation in ICU, expectation from patient attenders and organization for best results, catastrophes as well as due to personal reasons. It is therefore crucial to identify the factors causing burnout, addressing these factors and preventing it by making changes on personal and organizational level.

Burnout Prevention Tips (Table 6)

TABLE 6: Burnout prevention tips.

Identify and addressing the factors	*Personal efforts for prevention*	*Organizational amendments*
Stress	Adequate sleep	Adequate staffing
Workload	Healthy diet	Providing food of choice
Less appreciation on personal and financial level	Exercise	Appropriate working hours and holidays
Interpersonal conflicts	Mediation	Postnight duty off
Long working hours	Yoga	Rotation in different ICU of different severity of illness and workload
Night duties	Perusing hobby such as singing, painting, and photography	Proving gym and lounges
Insomnia	Spending time with family and friends	Psychological support
Health issues	Holiday from work	Appreciation of work and proper payment
Clerical work of documentation		Stress reduction therapy
Improper food habits		Support group
Physical fatigue		
Personal reasons		

Improving Compliance for Safety

- To ensure the necessary infrastructure
- Access to a continuous supply of required safeguarding equipment and material training and education at regular intervals
- Monitoring practices, infrastructure, and giving feedback
- Monitoring perceptions and knowledge among critical care personnel
- Taking feedback from staff
- Remind the importance of safety and practices
- Ensure active participation from institute and individuals

REFERENCES

1. WHO. Infection prevention and control-guidance to action tools. Copenhagen: WHO Regional Office for Europe; 2021. Licence: CC BY-NC-SA 3.0 IGO.
2. Beltrami EM, Williams IT, Shapiro CN, Chamberland ME. Risk and management of blood-borne infections in healthcare workers. Clin Microbiol Rev. 2000;13(3):385-407.
3. Busch MP, Satten GA. Time course of viremia and antibody seroconversion following human immunodeficiency virus exposure. Am J Med. 1997;102(Suppl. 5B):117-24.
4. Eron JJ, Benoit SL, Jemsek J, MacArthur RD, Santana J, Quinn JB, et al. Treatment with lamivudine, zidovudine, or both in HIV-positive patients with 200 to 500 CD4+ cells per cubic millimeter. N Engl J Med. 1995;333(25):1662-9.
5. Field RI. Mandatory vaccination of health care workers: whose rights should come first? PT. 2009;34(11):615-8.
6. Haviari S, Bénet T, Saadatian-Elahi M, André P, Loulergue P, Vanhems P. Vaccination of healthcare workers: A review. Hum Vaccin Immunother. 2015;11(11):2522-37.
7. Dhand R, Li J. Coughs and sneezes: their role in transmission of respiratory viral infections, including SARS-CoV-2. Am J Respir Crit Care Med. 2020;202(5):651-9.
8. Hui DS, Chow BK, Lo T, Tsang OTY, Ko FW, Ng SS, et al. Exhaled air dispersion during high-flow nasal cannula therapy versus CPAP via different masks. Eur Respir J. 2019;53(4):1802339.
9. Gaeckle NT, Lee J, Park Y, Kreykes G, Evans MD, Hogan CJ Jr. Aerosol generation from the respiratory tract with various modes of oxygen delivery. Am J Respir Crit Care Med. 2020;202(8):1115-24.
10. Agarwal A, Basmaji J, Muttalib F, Granton D, Chaudhuri D, Chetan D, et al. High-flow nasal cannula for acute hypoxemic respiratory failure in patients with COVID-19: systematic reviews of effectiveness and its risks of aerosolization, dispersion, and infection transmission. Les canules nasales à haut débit pour le traitement de l'insuffisance respiratoire hypoxémique aiguë chez les patients atteints de la COVID-19: comptes rendus systématiques de l'efficacité et des risques d'aérosolisation, de dispersion et de transmission de l'infection. Can J Anaesth. 2020;67(9):1217-48.
11. Cheung JC, Ho LT, Cheng JV, Cham EYK, Lam KN. Staff safety during emergency airway management for COVID-19 in Hong Kong. Lancet Respir Med. 2020;8(4):e19.
12. Leonard S, Atwood CW Jr, Walsh BK, DeBellis RJ, Dungan GC, Strasser W. Preliminary findings on control of dispersion of aerosols and droplets during high-velocity nasal insufflation therapy using a simple surgical mask: implications for the high-flow nasal cannula. Chest. 2020;158(3):1046-9.
13. Kobayashi H, Takimoto T, Kitaoka H, Kijima T. Aerosol spread with use of high-flow nasal cannulae: a computational fluid dynamics analysis. J Hosp Infect. 2020;106(1):204-5.
14. Wax RS, Christian MD. Practical recommendations for critical care and anesthesiology teams caring for novel coronavirus (2019-nCoV) patients. Can J Anaesth. 2020; 67(5):568-76.
15. Liew MF, Siow WT, Yau YW, See KC. Safe patient transport for COVID-19. Crit Care. 2020;24(1):94.
16. Ponnappan KT, Sam AF, Tempe DK, Arora MK. Intubation box in the current pandemic—helps or hinders? Anaesth Crit Care Pain Med. 2020;39(5):587-8.
17. Begley J, Lavery K, Nickson C, Brewster D. The aerosol box for intubation in COVID-19 patients: an in-situ simulation crossover study. Anaesthesia. 2020; 75(8):1014-21.
18. Laosuwan P, Earsakul A, Pannangpetch P, Sereeyotin J. Acrylic box versus plastic sheet covering on droplet dispersal during extubation in COVID-19 patients. Anesth Analg. 2020;131(2):e106-8.
19. Brown S, Patrao F, Verma S, Lean A, Flack S, Polaner D. Barrier system for airway management of COVID-19 patients. Anesth Analg. 2020.
20. Howell BAM. Battling Burnout at the Frontlines of Health Care Amid COVID-19. AACN Adv Crit Care. 2021;32(2):195-203.
21. McDougall RJ, Gillam L, Ko D, Holmes I, Delany C. Balancing health worker well-being and duty to care: an ethical approach to staff safety in COVID-19 and beyond. J Med Ethics. 2020;medethics-2020-106557.
22. Elbay RY, Kurtulmuş A, Arpacıoğlu S, Karadere E. Depression, anxiety, stress levels of physicians and associated factors in COVID-19 pandemics. Psychiatry Res. 2020;290:113130.
23. Gold JA. COVID-19: adverse mental health outcomes for healthcare workers. BMJ. 2020;369:m1815.

89

CHAPTER

Step-down Intensive Care Unit: Role in Present Healthcare Scenario

Gyanendra Agrawal, Smita Sharma, Ranvir Tyagi

INTRODUCTION

Step-down intensive care units (ICUs) are special units which offer highly specialized treatment and close monitoring in order to fulfill an intermediate role between the standard-care unit (SCU/ward) and the intensive care unit (ICU). Step-down ICUs are also known as "intermediate care units (IMC)", high-dependency units (HDUs), step-down units (SDU), transitional care units, level 2 care units or progressive care units.[1-8] The concept of step-down ICUs was first proposed and introduced by Gotsman and Schrire in 1968.[9] There is an ongoing debate in the medical fraternity as to whether and how step-down ICUs should be used. The major advantage of such units is to alleviate ICU congestion, better utilization of human resources (intensivists and nurses) and are less costly than ICUs to operate. Thus, this is a strategy to improve critical care cost-effectiveness and patient flow without compromising the overall quality.

PATIENT SELECTION

One particular patient in a hospital can be admitted to ICU, step-down ICU or standard-care unit (wards). Every hospital must have specific admission and transfer criteria to these units depending upon personnel and technical resource allocation in the hospital in these units agreed upon by treating teams. The allocation of patients to any unit depends upon severity of illness, experience of personnel (doctors and nurses), and technical resources [bedside monitors, pulse oximeter, portable noninvasive ventilation (NIV), infusion pumps, etc.] allocated to each of the unit in that hospital. The patient profile of step-down ICUs depends upon the ability to provide specific organ support and the nurse to patient ratio for these beds. The type of patients to be admitted to step-down ICUs are unstable patients who need nursing interventions, laboratory workup, and/or monitoring every 2–4 hourly. Patients with stable organ dysfunction with no hemodynamic instability can be managed in such units. Patients who should not be admitted to step-down ICUs include those with complicated myocardial infarction, acute respiratory failure, status epilepticus, catastrophic brain injury, multiple organ dysfunction, complex life-threatening conditions or those requiring invasive mechanical ventilation and heavy nursing care.[7] Guidelines published in Critical Care Medicine in 1998 based on expert consensus are helpful in establishing criteria for step-down ICU admission.[7] Nursing-to-patient ratios in such units is usually ≤1:3. The review of literature reveals a large percentage of ICU beds are occupied at any given time by patients requiring intermediate care.[1,3,10-13]

The patients in step-down ICU are classified into three groups:

1. The first is "step-down" patients who are received from ICU. Most of the critically ill patients require intermediate level of care before shifting to wards except few such as drug overdose, snake bite, etc.
2. The second is "step-up" patients from Emergency Department (ED) or regular ward with increased care requirements, such as those requiring noninvasive ventilatory support or those requiring acute renal replacement therapy.
3. The third is postoperative patients who have underlying comorbidities, who underwent prolonged complex surgeries or whose vitals are not stable.

LOCATION OF STEP-DOWN INTENSIVE CARE UNITS

There are many studies which have laid down the guidelines for structure and facilities in step-down ICUs.[3,14,15] Step-down ICU location with respect to ICU and ward can be of three types:

1. *Separate stand-alone units*: The unit independent in terms of space, organization, and staff is also termed as independent step-down ICU. The major disadvantage of such small units is less flexibility in planning of nursing rotas, requirement of full technical infrastructure of their own, loss of treatment continuity, and information and increased documentation during transfers.

2. *Co-located units*: The unit is co-located within ICUs or wards. The beds could be fixed or flexible as per patients' inflow. Co-location with ICU is also termed as *integration model in an intensive care unit*. The advantage of co-location within ICU is continuity of care, information, and ability to handle sudden influx of patients more easily. There is extremely high flexibility in terms of the assignment of personnel such as nurse:patient ratio and intensivist is always present. There is better human resource development that is, intermediate level nursing staff getting exposure of critical care. There is no need of two sets of equipment available such as arterial blood gas (ABG) machine, transport ventilator, ultrasound, ECG, defibrillator, etc. The major disadvantage is that every bed must be equipped with equipment for ICU care. There will be difficulty in categorizing patients to intensive care or intermediate care because of potential for conflict of interest of interdisciplinary units. The awake patients of step-down ICU have to bear loud and turbulent environment of an ICU.
3. *Adjacent but separate units*: The unit is located adjacent to ICU or ward. The unit adjacent to ICU is also termed as *parallel model on an intensive care unit*. The major advantage of being adjacent to ICU is to get coverage of trained nursing staff and intensivists, the common use of (technical) intensive care resources and treatment continuity with little loss of information during transfers. At the same time, patients are away from noisy environment of ICU.

HUMAN RESOURCE REQUIREMENT IN STEP-DOWN INTENSIVE CARE UNIT

The staffing in step-down ICU depends upon the location of unit. The intensivist-led teams take care if unit is co-located in ICU or adjacent to it. The stand-alone (independent) units or the units co-located or adjacent to ward should be headed by physicians trained in ICU, emergency care or anesthesia for a period of at least 1 year with specialist review as and when required.[7] The primary teams also take responsibility of stand-alone ICU, collocated in ward or adjacent to ward.[3] The nurse to patient ratio in these units is from 1:2 to 1:4 compared to ratios of 1:1 or 1:2 in ICU. The nurse-to-patient ratio in wards usually ranges from 1:6 to 1:10.[3]

STEP-DOWN INTENSIVE CARE UNIT IMPACT

The review of literature shows major benefit of step-down units in postoperative patients as they reduce postoperative complications and improve patients' pain control.[16,17] In a study by Suparerk Lekwijit et al., it was concluded that transitional care benefit was most evident among ICU patients with higher illness severity when they assessed the "Impact of Step-Down Unit Care" on patient outcomes after ICU discharge. In these patients, there were statistically significant reductions in mortality, ICU re-admissions and hospital length-of-stay.[18] In patients with lower severity, transfer to step-down ICU was associated with reduced hospital readmission rates.[18] The review of literature shows mixed results with respect to step-down ICUs because there is incomplete data with respect to outcomes. The paucity of data here may not reflect ineffectiveness of the step-down unit but rather a large gap in research to validate effectiveness.

ROLE OF STEP-DOWN INTENSIVE CARE UNITS IN INDIA

India has three different levels of healthcare: primary, secondary, and tertiary. India expenditure on healthcare is 1.8% of GDP, which is much less than that of developed nations (USA: 8.51%, UK: 7.86%). The first critical care unit in India was coronary care unit in 1968 at the King Edward VII Memorial Hospital, Mumbai, which was followed by one at Breach Candy Hospital in Mumbai. It is estimated that India has approximately 1.9 million hospital beds of which 95,000 are ICU beds; thereby ICU beds are approximately 5% of total hospital beds. The shortage of ICU beds in India leads to serious consequences and only the most critical patients are able to get good ICU care, which in turn contributes to high mortality both inside the ICUs as well as outside the ICUs (in the wards). There appears a strong need to increase the ICU beds to at least 10% of total beds in all hospitals; and even up to 15–20% in some leading public as well as private tertiary care centres.[19] Here, the role of step-down ICUs comes to play in providing better medical care in resource-limited environment.

STEP-DOWN INTENSIVE CARE UNIT ROLE DURING SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 PANDEMIC

Step-down ICUs have played a vital role in providing medical care to critical coronavirus disease 2019 (COVID-19) patients and in treating post-COVID complications. Step-down ICU played two major roles during pandemic. First role is reducing length of stay in ICU, which facilitates admission of new critically ill patients. Second role is by providing high-flow oxygen therapy via venturi mask, nonrebreathing mask, high-flow of nasal cannula (HFNC) or NIV to critical patients who may eventually require ICU care too (step-up). It also provided high-flow oxygen therapy to those who may not be candidates for mechanical ventilation due to concomitant conditions. In a retrospective analysis by Mónica Matute-Villacís et al., it was concluded that step-down ICUs are relevant in healthcare crisis and have a valuable role in management of acute respiratory patients.[20]

STEP-DOWN INTENSIVE CARE UNIT ECONOMICS

There are multiple benefits of step-down ICUs: (1) More critical care admissions without an increase in mortality. (2) Shortens ICU length of stay without increasing ICU re-admissions. (3) Decrease the proportion of step-down patients residing in ICU beds. However, a systematic review of the literature by Keenan and colleagues was unable to conclude whether these benefits translate into cost effectiveness.[4]

CONCLUSION

We conclude that step-down ICUs are extremely useful in resource limited Indian healthcare scenario. They play a pivotal role in acute health care emergencies like COVID-19 pandemic. Every medical care facility should have clear guidelines for admission and transfer of patient in three levels of care that is intensive care, step-down ICU, and standard-care units depending upon personnel and technical resources allocation to each unit in that hospital. Co-location with ICU (integration model in an ICU) and adjacent to ICU but separate units (parallel model on an ICU) are the two models of step-down ICU which have many advantages. With growing health infrastructure in India, we expect more establishment of step-down ICUs with more research in this direction leading to better systems, design, and optimization of capacity of critical care delivery. By this, we aim to give "Heath Care for All" in most cost-effective manner.

REFERENCES

1. Zimmerman JE, Wagner DP, Knaus WA, Williams JF, Kolakowski D, Draper EA. The use of risk predictions to identify candidates for intermediate care units. Implications for intensive care utilization and cost. Chest. 1995;108:490-9.
2. Nguyen Y, Wunsch H, Angus DC. Critical care: the impact of organization and management on outcomes. Curr Opin Crit Care. 2010;16:487-92.
3. Prin M, Wunsch H. The Role of Step down Beds in Hospital Care. Am J Respir Crit Care Med. 2014;190(11):1210-6.
4. Keenan SP, Massel D, Inman KJ, Sibbald WJ. A systematic review of the cost-effectiveness of noncardiac transitional care units. Chest. 1998;113:172-7.
5. Ambrosino N, Gabbrielli L. The difficult-to-wean patient. Expert Rev Respir Med. 2010;4:685-92.
6. American Association of Critical Care Nurses. (2014). American Association of Critical Care Nurses Progressive Care Task Force: Progressive care fact sheet. [online] Available from: http://www.aacn.org/wd/practice/content/progressivecarefactsheet.pcms?menu=practice [Last accessed February, 2022].
7. Nasraway SA, Cohen IL, Dennis RC, Howenstein MA, Nikas DK, Warren J, et al; American College of Critical Care Medicine of the Society of Critical Care Medicine. Guidelines on admission and discharge for adult intermediate care units. Crit Care Med. 1998;26:607-10.
8. Department of Health. Comprehensive critical care: a review of adult critical care services. London: Department of Health; 2000.
9. Gotsman MS, Schrire V. Acute myocardial infarction—an ideal concept of progressive coronary care. S Afr Med J. 1968;42:829-32.
10. Hilton G, Madayag M, Shagoury C. Development of a surgical/trauma intermediate care unit. Clin Nurse Spec. 1993;7:274-9.
11. Fox AJ, Owen-Smith O, Spiers P. The immediate impact of opening an adult high dependency unit on intensive care unit occupancy. Anaesthesia. 1999;54:280-3.
12. Henning RJ, McClish D, Daly B, Nearman H, Franklin C, Jackson D. Clinical characteristics and resource utilization of ICU patients: implications for organization of intensive care. Crit Care Med. 1987;15:264-9.
13. Pappachan JV, Millar BW, Barrett DJ, Smith GB. Analysis of intensive care populations to select possible candidates for high dependency care. J Accid Emerg Med. 1999;16:13-7.
14. Waydhas C, Herting E, Kluge S, Markewitz A, Marx G, Muhl E, et al. Intermediate care units: Recommendations on facilities and structure. MedKlin Intensiv Med. 2018;113:33-44.
15. Cheng DC, Byrick RJ, Knobel E. Structural models for intermediate care areas. Crit Care Med. 1999;27:2266-71.
16. Armstrong K, Young J, Hayburn A, Irish B, Nikoletti S. Evaluating the impact of a new high dependency unit. Int J Nurs Pract. 2003;9:285-93.
17. Jones HJ, Coggins R, Lafuente J, de Cossart L. Value of a surgical high-dependency unit. Br J Surg. 1999;86:1578-82.
18. Lekwijit S, Chan CW, Green LV, Liu VX, Escobar GJ. The Impact of Step-Down Unit Care on Patient Outcomes after ICU Discharge. Crit Care Explor. 2020;2:e0114.
19. Yeolekar ME, Mehta S. ICU Care in India—Status and Challenges. J Assoc Physicians India. 2008;56:221-2.
20. Matute-Villacís M, Moisés J, Embid C, Armas J, Fernández I, Medina M, et al. Role of respiratory intermediate care units during the SARS-CoV-2 pandemic. BMC Pulm Med. 2021;21:228.

CHAPTER 90

Team Building in Intensive Care and Liaising with Administration

Kunal Punamiya, Rahul Pandit

INTRODUCTION

Since the time intensive care services started in the 1950s, it has evolved into one of the most critical departments in terms of the reputation building of the hospital. While in the 1980s and 1990s, we did see hospitals in India starting critical care units; however, the intent of the management always remained to provide it as a supportive care area. Neither these units were really equipped with adequate necessary equipment nor staffed by personnel trained to handle critical care emergencies. With the formation of Indian Society of Critical Care Medicine (ISCCM) in 1993, there has been a concentrated effort to have a structure critical care department with appropriate protocols in place. However, it has taken the administration and the government bodies over 20 years to realize the importance of critical care, which has reinstated its requirement during the pandemic of COVID-19.

Also in the recent years, there has been an increased need of liaising between the intensive care unit (ICU) and the administration of the hospital. Apart from being a huge revenue generating source for the hospital, intensive care is an area wherein multidisciplinary teams treat patients, which can interfere with the standard protocol of the department. Further, escalating costs of treatment, requirement of high value equipment and drugs, and most importantly, the need to have trained staff across cadres make it necessary for the administration and the ICU to be on the same page and ensure that the right care is being delivered to the patients, which is measured through the outcomes.

TEAM BUILDING AND LIAISING OPPORTUNITIES

Traditionally the clinicians and paramedics have been involved in the clinical care of the patients, while the hospital administration has limited itself to all administrative working of the hospital as a whole. However, with the changing times, it has been seen that a synergistic liaising and exchange of ideas between these two teams lead to better functioning of the clinical departments and makes administrative decisions smoother.

Let's look at certain areas where a good teamwork between the two can produce better results.

Layout and Design

Often the layout and design of any department is discussed in details with architect and seldom with the doctors and nurses who will actually use them. Inputs from the clinical team would include details such as accessibility around the bed of the patient, equipment placement, electrical points [including uninterruptible power supply (UPS) backup], medical gas points, storage, and nursing station planning. Never underestimate the inputs of the users, as many a times the administration would look at cost-saving benefits, which may compromise clinical requirements. While ICU beds may be determined based on the clinical strength and the disease profile of the vicinity, it would be good to have ICU units of 12–15 beds for optimum human resource allocation.

Equipment Planning

After the operation theaters, the ICU is the most equipment intensive department. Right from the type of beds to monitors, syringe pumps, ventilators, etc., it all requires a lot of detailing. The inputs from the ICU team becomes utmost important as they would, based on their clinical strengths and type of disease pattern expected, give inputs on the features that are necessary for them. It becomes necessary to list the equipment that would be required. The biomedical department of the hospital would do a technical comparative of the equipment, followed by demonstrations before recommending a product for purchase, only after a sign-off from the clinical team. The administration at this point has to be mindful, that clinicians do have a tendency

to go overboard by demanding the latest technologies, and that is where the administration should be able to do a cost–benefit analysis to ensure that the hospital is not over- or underinvesting in technology.

Manpower Planning and Selection

An ICU is the heaviest department in terms of manpower. Basic types of manpower required are as follows:

- *Doctors*:
  - *Consultant*: One per 25 beds.
  - *Clinical associates*: One per one unit per shift.
  - *Registrars*: One per one unit per shift.
- *Nurses*:
  - *In-charge*: One per 25 beds.
  - *Team leaders*: One per unit per shift.
  - *Nursing staff*: In the ratio of 2.5 per bed.
- *Support staff*:
  - *Housekeeping:* Two per unit.
  - *Medical transcriptionist:* One per unit per shift. Not required during night shift.
  - *Clinical pharmacist*: One for two units per shift. May not be there during night shift.
  - *ICU clerk*: One per unit per shift. Not required during night shift.

In addition to the above, it is good to consider respiratory therapists in medical ICUs, as they can be extremely helpful for maintaining ventilated patients and any patients requiring any sort of mechanical ventilation. Further, in case a hospital has some than 30 beds of ICU, it would be prudent to consider having an ICU manager. A 30-bedded ICU is as good as a 60-bedded hospital, and a dedicated manager ensures that the liaising with the various departments to be taken care of without bothering the clinical team. Last but not the least, in a scenario, wherein there is a shortage of clinical staff, physician assistant is a category that needs to be explored for a role in the ICU.

Further, while selecting staff, especially doctors, the administration should be mindful of selecting clinicians, not only those who have adequate experience, but also have appropriate inclination toward research and academics, to enable the department to run teaching program, without which, it would be difficult to sustain manpower in an ICU.[1]

Clinical Pathways and Protocols

Intensive care unit invites admissions from physicians and surgeons across specialties, working patterns, and mindsets. While every treating physician and surgeon who like to have total control of his/her patient, one should remember that the intensivist is looking after the patient 24×7. Hence, it is a teamwork in the ICU, wherein we might have multiple specialty consultants taking care of a single patient. To ensure that the standard of care is maintained, it is of immense importance to have clinical pathways and protocols pertaining to various ailments, antibiotic policy, protocol for dialysis, blood transfusion, informing of critical values, and any change in course of treatment, apart from many others. In the absence of these pathways and protocols, one would not be able to control investigations and drugs prescribed and overprescribed to patients, which apart from not positively contributing to care, will also cause a huge escalation in the bills of the patient, leading to dissatisfaction and against the hospital. Management has to extensively work with the ICU team to ensure that while standards of care are kept optimally high, the clinicians, who bring in their patients, are also in synchronization and agreement with them.

Admission and Discharge Policies

Admission and discharge from the ICU is the decision of the ICU team. In a country such as India, where we have a dearth of ICU beds, and at the same time, the difference of care in ICU versus the wards is highly evident, a clear admission and discharge policy becomes important to ensure beds are occupied by the right patient and those who do not require critical care monitoring are shifted to the wards. For admissions, a major liaising is between the emergency department and the ICU and the administration should ensure proper channel of communication between the two departments. Further, the administration should push for transfer outs from the ICU first thing in the morning, so that the patient is shifted out to the ward during the normal working hours to avoid any mishap. Evening transfer outs are seen to have a greater incidence of return to the ICU. To ensure this, the administration should have a system in the pathology to ensure that all morning pathology samples of patients to be transferred out reach the pathology on time and reports made available before the morning rounds start. Also postdischarge, the ICU team should have one clinical associate, who should visit every patient transferred in the day, to be assessed and ensure that the clinical parameters are not raising any alarm.

Costing of Services

We have seen that the average billing in the ICU varies a lot per day, depending on the number of investigations done and antibiotics and other drugs prescribed. The billing for the patients getting admitted in the ICU is usually higher in the first few days, when investigations are more. The administration should, in conversation with the ICU team, devise investigation packages for patients to ensure that the

bills do not show alarming raise, as this is one of the most common reason for discontent amongst people toward the hospital. It would be prudent on part of the administration to monitor the bills of patients admitted in the ICU. Please note we are not trying to say that we do not investigate or prescribe the drugs.

Another area is bedside procedures. Optimum pricing of these services or packaging the common services such as central line or arterial line insertion and intubation can help keeping the cost considerations.

Privileges for Reference Consultants

We usually see consultants across specialties treating a single patient in the ICU, especially when multiple organ systems are involved. This has become a norm for most to avoid medicolegal hassles in the future. However, we must note that multiple people come in with multiple suggestions, which might be contradictory to each other. Further, the timings of different consultants may be different when they see the patient and this leads to negligible communication between consultants and multiple voices to the relatives. Hence, it is important that the reference consultants are privileged only to advice any addition, deletion, or change in course of treatment and investigations. Administration should ensure that the final call on any of the suggestions of the reference consultants is taken after affirmation of the treating consultant and the ICU team only. Further, in any patient where more than one reference consultant is involved, the management should ensure that there is a meeting of the clinical team, wherein all consultants come to the same page for the treatment of the patient.

Documentation and Communication

Document, communicate, and document what you communicate. This is a basic principle of maintaining medical records. Templates can be prepared to maintain daily medical records. Administration should try to provide electronic medical record (EMR) facilities to make it more and more convenient for the clinicians to document. Provide audio visual room facility to the clinicians to communicate with the relatives. In most of these meetings, the administration should ensure a representative from its end to be present.

Training, Education, and Research Activities

As highlighted in a point earlier, education and research has to be an integral part of the ICU working, since it would not only attract talent but help retain many. Continuous training on job is mandatory and the administration should work closely with the ICU team to ensure it happens. Identify candidates who are more inclined to learn and teach, and groom them as leaders for the future.

Quality Systems

Quality has to be a part of the daily activity of the ICU. Admin and the ICU team have to work closely together to ensure that the protocols and standard operating protocols (SOPs) are followed. Satisfaction levels of ICU care are not measured alone through the feedback of the patients, but also the consultants who bring their patients to the ICU. It is worthwhile to have an ICU user meeting at regular intervals, wherein feedback on the working of the ICU, challenges faced in aligning with various dependent departments of the hospital, and any queries or disagreements are discussed and sorted to ensure good collaboration amongst all, which will ensure good quality services.

Succession Planning

Intensive care is a highly demanding and stressful branch. While we see cardiologists, orthopedics, oncologists, and others work up to a very senior age, intensive specialists, would rather tend to slow down, while their counterparts in the other branches actively work. Hence, it is very important that a succession plan is built. Rather than hiring from outside, it is better if a member of the clinical team is elevated from within the system to take charge. Similarly in nurses, we need to build team leaders and show them the growth path toward becoming in-charges.

Expansion Plans

In today's time, the demand for ICU beds is rising and it also contributes to the revenue generation of the hospital in a huge way. The hospital administration should plan for ICU expansion as and when the bed occupancy in the ICU touches 85–90% consistently. At the same time, it is imperative to maintain an appropriate ratio of beds in wards to ensure there are enough beds available for transfer outs.

While planning expansions, it would help to see whether specialty ICUs can be made to elevate the level of care. This not only provides an opportunity to the administration to market the services of the hospital, but also gives an opportunity to the clinical team to develop skill sets in specific branches.

Support Mechanism

As part of liaising between the administration and the ICU team, the administration should ensure that in event of any calamity or adverse event, one senior representative of the administration is always present with the ICU team. The administration should ensure that the team feels safe and

protected in such events and lend appropriate support to the team as required.[2]

WAY FORWARD FOR THE INTENSIVE CARE UNIT

While the above covers some broad points over which the administration and the intensive care team can come together and liaise, every day-to-day activity of the hospital and the department of intensive care will involve challenges for both the clinical and administrative team to overcome and excel in order to ensure best practices and safety and care for the patient.

REFERENCES

1. Chakraborti C, Boonyasai RT, Wright SM, Kern DE. A systematic review of teamwork training interventions in medical student and resident education. J Gen Intern Med. 2008;23(6):846-53.
2. Agency for Healthcare Research and Quality. (2009). Team STEPPS: national implementation. [online] Available from: http://teamstepps.ahrq.gov/index.htm. [Last accessed February 2020].

CHAPTER 91

Interspecialty Communication: Finding the Right Balance

Simran J Singh

INTRODUCTION

Intensive care unit (ICU) is a place where interspecialty teams play an important role in the care of most critically ill patients. Within the hospital community, the ICU exists at an intersection of departments where multispecialty teams such as emergency, general medicine, nephrology, infectious diseases, surgical, anesthesia, and palliative care play a pivotal role in patient care and management.

The stakes are high in the ICU especially in view of patient care resources which are expensive and limited.[1] Care of critically ill patient is a team approach between intensivists and ICU nursing staff and intensivists and interspecialty teams.

The aim of these interspecialty and interdisciplinary teams should be toward providing a unified care and cultivate collective decision-making.

Effective management of an ICU requires not only good clinical skills and medical knowledge in managing complex critically ill patients but also good communication skills. It is an essential necessity on a daily basis when managing complex critical cases. Lack of communication does compromise patient safety resulting in many critical incidents.

In a recent survey, 43% surgeons reported experiencing conflicts with ICU teams about the goals of postoperative care and lack of proper communication played a major role.[2] Therefore, effective team communication and coordination are recognized as being crucial for improving quality and safety in acute medical settings such as the ICU.[3,4] ICU in particular is a nexus for interspecialty tensions because of its pivotal role in the care of the hospital's most critically ill patients and in the management of critical care resources. Within the hospital community, the ICU exists at the high-stakes intersection of emergency, surgery, internal medicine, and palliative care, an intersection where the patient care resources are expensive, in scarce supply, and a source of intense competition.

COMMUNICATION BETWEEN INTENSIVE CARE UNIT TEAMS AND NURSING STAFF

Care of critically ill patient is a team approach **(Fig. 1)**.

A well-structured collaboration in the ICU between intensivists, ICU trainee doctors, and nursing staff is fundamental in providing optimal care. Therefore, finding the right balance in team communication and collaboration becomes an essential aspect of all the team members looking after such a patient with vacillating and complex critical illness.

Any kind of conflict between nurses and physicians can threaten to disrupt this collaboration and can negatively influence patient outcomes.

Common sources of conflicts for instance are communication gaps—resulting in blame-game, lack of proper training, and paucity of regular interdisciplinary meetings and appropriate leadership. Studies show that

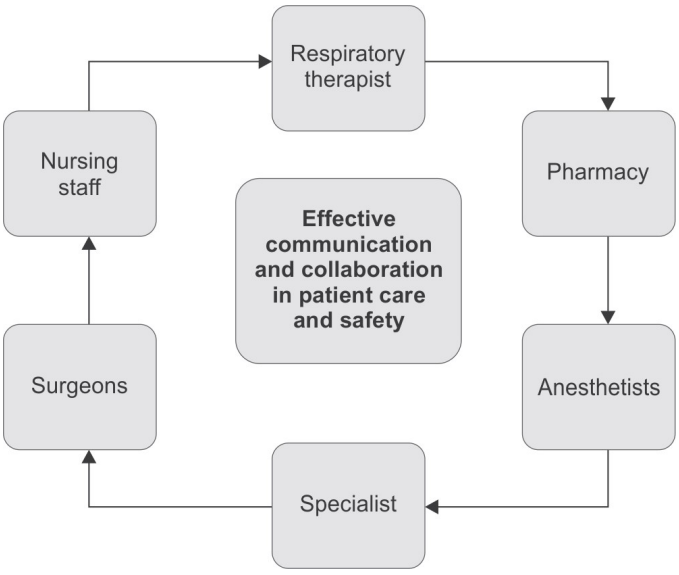


Fig. 1: Communication between intensive care unit (ICU) and specialist teams.

physicians and nurses differ in their expectations, and comprehensions about interdisciplinary communication.[5] To achieve an ICU environment conducive to an ethical workplace, the nurses and residents should be trained to speak up on any pertinent issues regarding quality of care and safety provided to the patients.

All constituents of the ICU team should be considered as equal partners with well-defined roles and responsibilities in the care of a critically ill patient.

The ICU team leadership should acknowledge and value the contributions of each team member and should support a less steep hierarchy.

COMMUNICATION BETWEEN INTENSIVE CARE UNIT TEAMS AND OTHER SPECIALTIES

Advanced technologies, therapeutic interventions, and increasing acuity of patients in the ICU require minute to minute assessments, planning, interventions, and evaluations. The complex, fluctuating, and vital nature of patient care in the ICU heightens the clinical significance of the role of interdisciplinary communication and the understanding of common goals of patient care in such a critical patient care environment.[6] Poor communication among physicians results in suboptimal patient care adding to morbidity and even mortality in some instances. Also such a behavioral pattern can encourage a similar pattern amongst junior trainee doctors. This can happen especially in a tertiary care medical center where patient management involves joint management by medical and surgical teams.

In such a dynamic environment, verbal communication may be a great source of building trust amongst clinicians. A study reported that failure in communication causes two-third of sentinel events in healthcare system.[7] In the same study, investigators noted that improper communication accounted for 91% of the medical errors which were contributory toward increasing costs to the healthcare institution.[7] However, the fact remains that interspecialty communications are far from optimal. Physicians themselves have reported significant deficits in their training related to communication skills with patients, family members, and colleagues.[8]

The ICU in particular is a nexus for interspecialty tensions because of its pivotal role in the care of the hospital's most critically ill patients and in the management of critical care resources. Within the hospital community, the ICU exists at the high-stakes intersection of emergency, surgery, internal medicine, and palliative care, an intersection where the patient care resources are expensive, in scarce supply, and a source of intense competition.

Studies have also shown that increased length of stay, increased patient harm, and increased resource utilization have been associated with ineffective communication.[9] On the other hand, clear and precise communication influences the quality of care, patient safety, and can result in favorable outcomes. It is the responsibility of physicians of all specialties to meet this challenge for the benefit of all patients.[10] Interspecialty conflicts commonly occur about goals of care and the role of life-sustaining interventions. Any clinical disagreements between ICU team and the referral teams require prompt negotiations and needs to be dealt with tactfully.

NEED OF THE HOUR: TO IMPROVE INTERDISCIPLINARY

Collaboration

"Collaboration in health care is the ability of every health care professional, to effectively adopt complementary roles within a team, share the responsibilities for problem-solving, and make a care plan for the patient."[11] The concept of collaboration must be more than mere "team cooperation."[1] It should be an interspecialty partnership aimed at contribution of technical skills and goal-driven execution of plans. This should essentially form the backbone of a good, quality-driven ICU setup.

Communication failures can emerge from junior team members being reluctant to communicate openly with senior team members because of a fear of either sounding incompetent, or of being vilified.[12]

Language and social barriers might also add to a hesitation in communicating and coordinating effectively.

Studies of communication failures in medical teams have pointed toward hierarchical factors also which can have an adverse influence on the junior medical staff.[12] Regular ward rounds with documented outcomes and review of defined treatment goals between the ICU team as well as nursing, medical staff, and preferably other specialties have shown to reduce length of ICU stay.[13] The way in which clinical disagreements with colleagues in contributing specialties are negotiated and settled has received little attention.

Clear communication is central to clarifying and resolving these disputes, but little is known about how this might be taught or improved. Ongoing contact with the referring consultant needs to be actively encouraged by intensivists to build a joint understanding of the patient's progress and prognosis.

It has been seen that conflicts were less likely to occur in ICUs that hold regular staff meeting.

HOW TO IMPROVE UPON COMMUNICATION SKILLS?

There is no current consensus or standard on the best way to teach communication. However, competency in communication is a core clinical skill, which must be taught, tested, and practiced. At academic medical centers, where complex patients routinely require management by medical and surgical specialists, an educational curriculum to improve communication skills between specialists is needed.

Trainee doctors in ICU acquire communication techniques by observing the practice of their senior colleagues. This method may result in a not so perfect a practice for these future intensivists. Without a real-time practice and active feedback by their seniors, trainees may never be able to improve upon their communication skills.

Simulators and mock examinations using varied case scenarios and communication strategies can provide a powerful learning tool for healthcare professionals.[14] An increase in interdisciplinary activities such as daily interprofessional grand rounds or multidisciplinary team meetings have a positive impact on patient outcomes.

Ongoing contact with the referring consultant needs to be actively encouraged by intensivists. Also they are more likely to speak the same language when interacting with each other, and with the patient's families. ICU team members should be encouraged to speak without fear of reprisal or embarrassment if they have any safety concerns or issues with the quality of care provided to patients. Other ways to improve communication are through multidisciplinary team meetings. Also multidisciplinary shift evaluations—where at the end of the shift, staff gather to discuss what went wrong and what needs to be improved upon—increase team accountability. It is also possible to conduct such meetings physically or virtually in the form of an interdisciplinary audit.

COMMUNICATION TECHNIQUES

There are several ways in which the teams can communicate amongst themselves which are as follows:

- *Direct person to person*: Face-to-face meetings might still be the most effective way to communicate allowing the interspecialty teams to more effectively share a complex range of information and a better view of patient management.
- *Telephonic communications* in situations with time constraints are equally effective.
- *Email techniques* can be adopted in not so urgent decision-making or in resolving conflicts and clearing any team miscommunication.
- *Virtual multidisciplinary meetings*—to enable clinicians to meet virtually to provide coordinated care to patients with complex needs. The COVID-19 pandemic brought about the switch to the virtual meetings. It is an effective alternative to conventional direct person-to-person meeting, provided an effective software is in place.
- *WhatsApp messages*: Method of communication is beneficial in the interest of patient care. It is cheap, very quick, and very easy to operate.[15]
- *Maintenance of daily patient goal sheet* which includes tasks to be completed, the care plan, and the communication agenda for the day has shown to reduce medical errors.
- *Structured postoperative handovers*: Multiple shift changes are an inevitable part of ICU and as a result handovers need to be done to maintain continuity of quality care. Also transition of patient care occurs postoperatively when a patient is shifted from the operating room to the ICU or vice-versa. Communication errors are common during such handovers and have been implicated in medical errors.[16]

All key personnel (e.g., surgeon, anesthesiologist, ICU attending, ICU nurses, and respiratory therapist) should be present during the transfer of technology and information. Each individual during such transfer should attend to their assigned task.

Such handovers generally consist of a document filled by the ICU registrar at the time of shifting the patient from the operating room or the catheterization laboratory/digital subtraction angiography (DSA) laboratory to the ICU by the anesthetist ideally in the presence of the operating surgical team.

Information given includes any intraoperative problems, nature of anesthesia, fluids, antibiotics administered, severity of blood loss, requirements of vasopressors, and plans for postoperative analgesia and sedation.

This protocolized transfer of care has been studied primarily in cardiac surgical patients. In a literature review, an interdisciplinary handover from the operating room to the ICU after cardiac surgery was associated with improved outcomes and prevention of adverse events.[17]

Examples of improvements in clinical outcomes include more timely administration of antibiotics, reduction in time to extubation, reduced need for respiratory and cardiovascular interventions, and reduced overall risk of postoperative complications.[18]

The impact of introducing such structured handover protocols is to improve upon information transfer and minimize communication and technical errors.

An illustration of a standard handover form practiced in our ICU is shown in **Figures 2 and 3**.

P. D. HINDUJA NATIONAL HOSPITAL & MEDICAL RESEARCH CENTRE

Veer Savarkar Marg, Mahim, Mumbai - 400 016

0117 / IPD / 2009

Anesthetist : Date :

Surgeopn : Time of Arrival AM/PM

Operative Procedure

Type of Anesthesia GA SA

PRE OPERATIVE STATUS

Mjor background illness IHD HT DM CRF COAD CIRRHOSIS SMOKER OTHER

Ejection fraction (LV)

Nutritional status REGULAR MEDICATIONS / ALLERGIES

Good Moderator Poor

INTRAOPERATIVE PERIOD

Duration of Anesthesia and Surgery

Difficult Intubation Y / N

Ventilation problems Y / N

Urine Output in O. T.

Estimated blood loss : ANY OTHER INTRA OPERATIVE PROBLEMS

Total Fluids administered :

RBC / WB :

FFB / Platelet Cryo :

Colloid :

Crystalloid :

Autotransfusion :

Bypass

Infusions Dop Dob Adr Amr NTG Sonide Lign Other

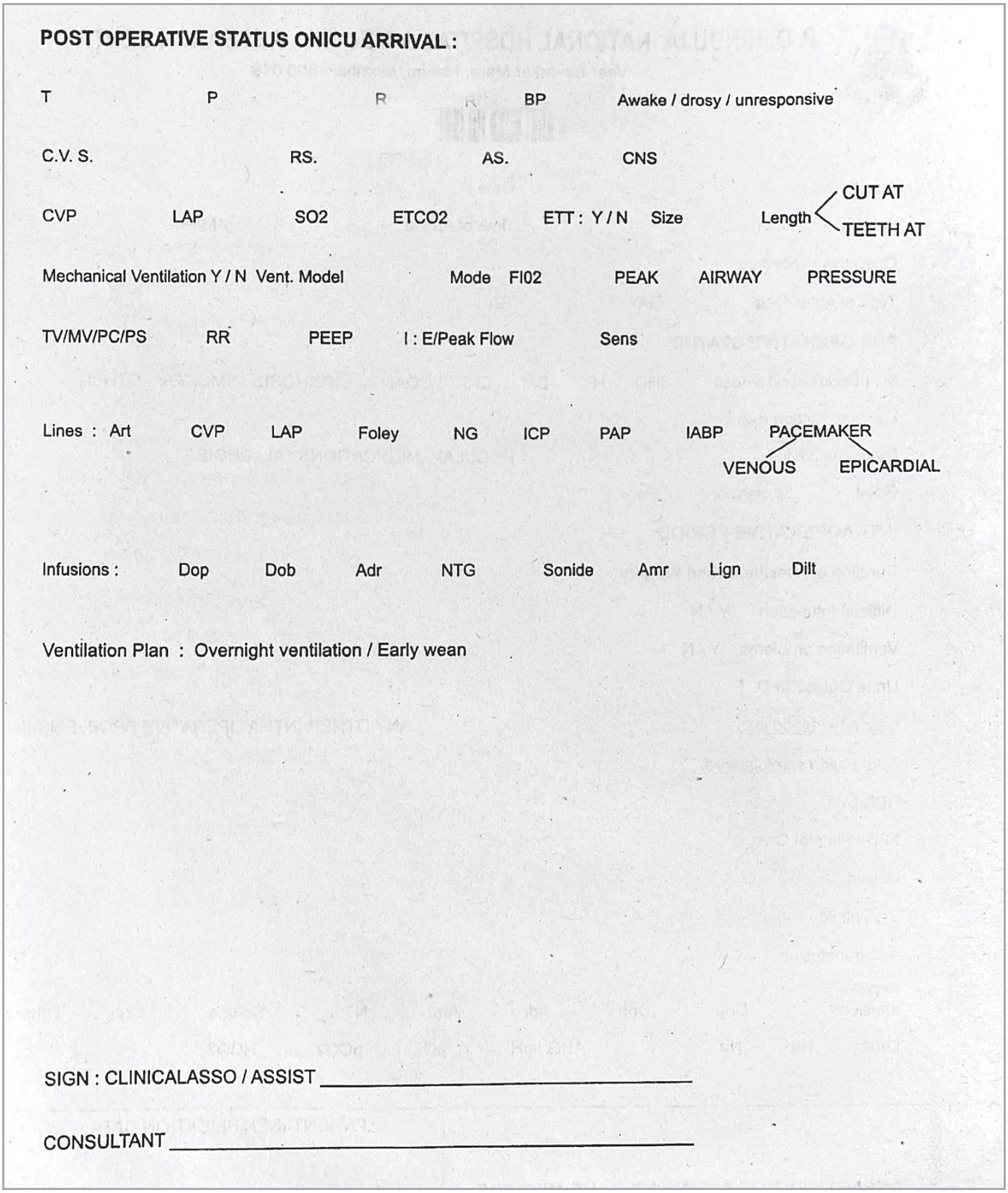
Labs Hb Na K ABG : pH pO2 pCO2 HCO3

Code No.: 0117/IPD/2009

DEPARTMENT OF INTENSIVE CARE MEDICINE
POST OPERATIVE PATIENT

PATIENT IDENTIFICATION DATA

Fig. 2: Intensive care unit (ICU) postoperative handover form.



POST OPERATIVE STATUS ONICU ARRIVAL :

T P R BP Awake / drosy / unresponsive

C.V. S. RS. AS. CNS

CVP LAP SO2 ETCO2 ETT : Y / N Size Length CUT AT TEETH AT

Mechanical Ventilation Y / N Vent. Model Mode FI02 PEAK AIRWAY PRESSURE

TV/MV/PC/PS RR PEEP I : E/Peak Flow Sens

Lines : Art CVP LAP Foley NG ICP PAP IABP PACEMAKER VENOUS EPICARDIAL

Infusions : Dop Dob Adr NTG Sonide Amr Lign Dilt

Ventilation Plan : Overnight ventilation / Early wean

SIGN : CLINICALASSO / ASSIST _____

CONSULTANT _____

Fig. 3: Continuation of postoperative intensive care unit (ICU) handover form.

CONCLUSION

In conclusion, suboptimal communication between interspecialty teams can be an impediment to optimal patient care. The current healthcare environment has made communication with colleagues time-consuming, infrequent, and sparse resulting in a communication breakdown. Patient safety research has shown such failures to be a causal factor in many ICU critical incidents. On the other hand, finding the right balance via effective communication

facilitates an environment in the ICU which favors interspecialty team collaboration in its truest sense. Communication skills training for ICU and interspecialty trainees using an evidence-based curriculum can improve their practice and improve the quality of care provided to critically ill patients resulting in better outcomes. This seems like the best way forward for the future of an exemplary interprofessional collaboration in the ICU.

REFERENCES

1. Lingard L, Espin S, Evans C, Hawryluck L. The rules of the game: interprofessional collaboration on the intensive care unit team. Crit Care. 2004;8(6):R403-8.
2. Paul Olson TJ, Brasel KJ, Redmann AJ, Alexander GC, Schwarze ML. Surgeon-reported conflict with intensivists about postoperative goals of care. JAMA. 2013;148(1):29-35.
3. Baggs JG, Schmitt MH, Mushlin AI, Mitchell PH, Eldrege DH, Oakes D. Association between nurse–physician collaboration and patient outcomes in three intensive care units. Crit Care Med. 1999;27(9):1991-8.
4. Reader T, Flin R, Lauche K, Cuthbertson B. Non-technical skills in the intensive care unit. Br J Anaesth. 2006;96(5):551-9.
5. Sexton JB, Thomas EJ, Helmreich RL. Error, stress, and teamwork in medicine and aviation: cross sectional surveys. BMJ. 2000;320(7237):745-9.
6. Pronovost PJ, Wu AW, Sexton B. Acute decompensation after removing a central line: practical approaches to increasing safety in the intensive care unit. Ann Intern Med. 2004;140(12):1025-33.
7. Sutcliffe KM, Lewton E, Rosenthal MM. Communication failures: an insidious contributor to medical mishaps. Acad Med. 2004;79(2):186-94.
8. Visser M, Deliens L, Houttekier D. Physician-related barriers to communication and patient- and family-centered decision-making towards the end of life in intensive care: a systematic review. Crit Care. 2014;18(6):604.
9. Zwarenstein M, Reeves S. Working together but apart: barriers and routes to nurse—physician collaboration. Jt Comm J Qual Improv. 2002;28(5):242-7.
10. Gauntlett R, Laws D. Communication skills in critical care. Contin Educ Anaesth Crit Care Pain. 2008;8(4):121-4.
11. Christensen C, Larson JR Jr. Collaborative medical decision making. Med Decis Making. 1993;13(4):339-46.
12. Edmondson A. Psychological safety and learning behaviour in work teams. Adm Sci Q. 1999;44(2):350-83.
13. Pronovost P, Berenholtz S, Dorman T, Lipsett PA, Simmonds T, Haraden C. Improving communication in the ICU using daily goals. J Crit Care. 2003;18(2):71-3.
14. Eddy K, Jordan Z, Stephenson M. Health professionals' experience of teamwork education in acute hospital settings: a systematic review of qualitative literature. JBI Database Syst Rev Implement Rep. 2016;14(4):96-137.
15. Ghani, Padha K, Rashid Anjam R. Effectiveness of WhatsApp application on smart phone as a communication tool in orthopaedic surgery. Int J Curr Res. 2015;7:16238-241.
16. Nagpal K, Vats A, Ahmed K, Vincent C, Moorthy K. An evaluation of information transfer through the continum of surgical care: a feasibility study. Ann Surg. 2010;252(2):402-7.
17. Hall M, Robertson J, Merkel M, Aziz M, Hutchens M. A structured transfer of care process reduces perioperative complications in cardiac surgery patients. Anesth Analg. 2017;125(2):477.
18. Agarwal HS, Saville BR, Slayton JM, Donahue BS, Daves S, Christian KG, et al. Standardized postoperative handover process improves outcomes in the intensive care unit: model for operational sustainability and improved team performance. Crit Care Med. 2012;40(7):2109-15.

92

CHAPTER

Career Path in Critical Care in India

Asish Kumar Sahoo, Prakash Shastri

INTRODUCTION

The journey of critical care medicine as a distinctive standalone branch in the past two decades in India has been remarkable. With the advances in the technology and better understanding of the disease processes, the outcomes in intensive care units (ICUs) have improved. The genesis of critical care in India started with setting up of coronary care units for cardiac patients in erstwhile Bombay state in 1960s and the same experience was then extended to the noncardiac serious patients.[1] Though the initial growth in this field was slow, the sheer, individual brilliance and passion of a few practitioners found a common platform and the Indian Society of Critical Care Medicine (ISCCM) was formed in 1993. It promoted academic and scientific activity, and started various courses to train young doctors in the field of critical care. This led to the recognition of critical care medicine as a distinctive super specialty course with statutory approval attained from the Supreme Court in 2011.

INFRASTRUCTURE OF PRESENT DAY INDIAN INTENSIVE CARE UNITS

The infrastructure for ICUs including the manpower in India is dismally variable across various regions in the country. The academic teaching institutes and large corporate chains do have the requisite infrastructure and manpower but are concentrated around the major cities. Although the exact number of fully equipped ICUs is difficult to ascertain, a recent study published in June 2020 estimated that India has roughly 95,000 ICU beds and 48,000 ventilators.[1] it is assumed that 5% of all hospital beds in both public and private facilities were ICU beds, and that 50% of all ICU beds were equipped with ventilators. Most of the critical care setups are concentrated in the private sector (ICU beds 59,262 private vs. 35,699 public and ventilators 29,631 private and 17,850 public). Most ICU beds and ventilators in India are concentrated in seven states—Uttar Pradesh (14.8%), Karnataka (13.8%), Maharashtra (12.2%), Tamil Nadu (8.1%), West Bengal (5.9%), Telangana (5.2%), and Kerala (5.2%). The present COVID-19 pandemic has only magnified the need for a robust critical care set up, and the required trained professionals to run it.

WHY CRITICAL CARE?

The core aspects of the specialty of critical care medicine revolve around providing life-support therapies under one roof to critically sick patients (medical, surgical and trauma, etc.). Before anyone starts the journey of critical care, they should be well aware of the requirements and the necessary trainings to have a successful career. Needless to say this branch requires utmost dedication and discipline. Critical care medicine combines the art of clinical medicine along with the new technologies requiring constant human and machine interactions. The dynamics of constant attention to ever-changing status and physical interventions needed to treat it or prevent further deterioration presents unique challenges. In addition, you need to be continuously updated with recent literature and guidelines. The same recommendation change very quickly in the light of newfound evidences as noticed during the recent COVID times. One has to lead by example as an ICU requires a collective effort of everyone involved to implement the strategies. Communication skills to foster a healthy relationship with colleagues from other specialties as well as the relations of the patient cannot be over emphasized. Training in critical care medicine deals with the cognitive, psychomotor, and affective domains to cover all learning objectives.

It is recommended that before making a conscious decision to take up critical care as your chosen specialty, an organized approach or a checklist can come in handy.[2] Specific questions which one should ask at this point include, but are not limited to:

- What do you want your future practice to look like?
- How will a fellowship get you there?
- Do you find a particular device or procedure desirable to manipulate/understand? [e.g., ventilators, extracorporeal

membrane oxygenation (ECMO), dialysis machines, pacemakers, ventriculostomy drains].

- Are there groups/teams of providers you feel most comfortable with? (e.g., surgeons, neurologists, pulmonologists, medical subspecialists).
- Are you a team player comfortable to work alongside different medical and surgical specialties?

COURSES AND TRAINING AVAILABLE

In the early days of development of critical care medicine, there were no structured critical care training programs in India. ISCCM, after its inception, started working on this lacuna and the first training course for critical care in India started in the year 1997.[3] Initially, a 1-year certificate course was started, which soon evolved into a 1-year diploma and a 2-year fellowship course. These persistent efforts by ISCCM led to recognition of the Doctorate in Medicine (DM) in critical care medicine in 2012 as a distinct super specialty course,[4] which is recognized by the erstwhile Medical Council of India (MCI), now known as the National Medical Commission (NMC), a regulatory body overseeing medical education in India. The National Board of Examinations (NBE), an autonomous body that came in to existence by an act of parliament, started the Diplomate of National Board in Critical Care Medicine (DNB), which is an equivalent super specialty course after postgraduation. Both DM (CCM) and DNB (CCM) are of 3-year duration after postgraduation in Internal Medicine, Anesthesiology, Chest Medicine, and Emergency Medicine. There are around 45 DM (CCM) and around 225 DNB (CCM) positions available for admission in various training institutes throughout India, a number which is bound to increase in the coming years. Admission to these courses is through National Eligibility Cum Entrance Test for super-specialty (NEET-SS) conducted by National Board of Examinations annually. There is a separate examination conducted by All India Institute of Medical Science (AIIMS) known as Institute of National Importance Combined Entrance Test (INI-CET) for admission in all AIIMS, as well as at JIPMER Puducherry and PGI Chandigarh. These are institutes of national importance enacted through an act of parliament and are not under NMC or NBE. Number of positions in these institutes keep on changing and the examinations are conducted semiannually.

Indian Society of Critical Care Medicine offers three courses for doctors in India through the Indian College of Critical Care Medicine (ICCCM).[4] One is offered post Bachelor of Medicine and Bachelor of Surgery (MBBS) and other two after postgraduation. Post-MBBS Certificate Course (CTCCM) is a 2-year course for fresh graduates. After postgraduation, one opt for Indian Diploma in Critical Care Medicine (IDCCM) and then the Indian Fellowship in Critical Care Medicine (IFCCM). The requisite qualification for entry is a postgraduate degree in Internal Medicine, Anesthesiology, Chest Medicine, and Emergency medicine. For doctors who have successfully completed IDCCM, the duration for IFCCM is 1 year. The selection process of above two courses is done directly by the institutions which are accredited by the ISCCM. The various courses and pathways available in India are shown in **Table 1**.

TABLE 1: Courses of critical care available in India.

Course	*Duration*	*Eligibility*
CTCCM (Certificate of Training in Critical Care Medicine), ISCCM	2 years	MBBS from NMC recognized medical college
Doctorate in Medicine (DM-CCM) National Medical Council	3 years	Postgraduate in anesthesia, internal medicine, pulmonary medicine, pediatrics, and emergency medicine
Diplomate of National Board [DNB (CCM)] by the National Board of Examination (NBE)	3 years	Postgraduate in anesthesia, internal medicine, pulmonary medicine, pediatrics, and emergency medicine
Indian Fellowship in Critical Care Medicine (IFCCM) ISCCM	2 years	Postgraduate in anesthesia, internal medicine, pulmonary medicine, pediatrics, and emergency medicine
Indian Diploma in Critical Care Medicine (IDCCM) ISCCM	1 year	Postgraduate in anesthesia, internal medicine, pulmonary medicine, emergency medicine, general surgery, and orthopedics

(ISCCM: Indian Society of Critical Care Medicine; MBBS: Bachelor of Medicine and Bachelor of Surgery; NMC: National Medical Commission)

RESEARCH AND ACADEMICS IN CRITICAL CARE

All the courses of critical care in India emphasize on instilling interest for research in young doctors. For DM and DNB candidates, it is mandatory to have an original thesis as a prerequisite for the exit examination. It is also expected from a candidate to present their work in national and international conferences. IFCCM candidates are also required to present an original research paper in one national conference or publish it in a journal related to critical care.

Critical care, being a predominantly service-oriented specialty, engages with almost all the medical and surgical branches. Therefore, a critical care trainee must have the basic knowledge of all the disease processes and their management.

CRITICAL CARE SUBSPECIALTIES

Specialized or focused critical care is another interesting avenue which needs to be explored in India. Evidence suggests that critically sick patients with similar pathology when treated in a specialized ICU tend to do better.[5] Although considered a new concept in India, segregation of ICUs for different specialties is standard in the developed world. After training a young doctor can tailor his practice to various subspecialties. Presently there is a 1-year postdoctoral fellowship in neurocritical care at AIIMS New Delhi and NIMHANS Bangalore. The Society of Neuro Critical Care (SNCC-India), in collaboration with the ISCCM plans to start FNCC (Fellowship of Neuro Critical Care), a postdoctoral fellowship program, aimed to provide quality training to candidates for the management of critically ill patients with neurological and neurosurgical insults.

JOB TRENDS IN CRITICAL CARE

With the rise in purchasing power among Indians, the health sector and specifically critical care has seen tremendous growth in the last two decades. Furthermore, the technological advancements and improved outcomes in ICU have led to a growing belief that many critically ill patients can be saved now, which was hitherto not possible. The recent COVID pandemic has sharply brought into focus the need for trained manpower and robust critical care setup in India. It is expected that all medical colleges and district level hospitals will have dedicated ICUs that will be manned by specially trained workforce. Thus, the job prospects in critical care are immense and likely to grow exponentially with each year. Not surprisingly the ever-increasing number of medical postgraduates taking the entrance examinations for critical care medicine have made entry into this specialty more competitive despite an increase in the number of seats.

CONCLUSION

Critical care or intensive care medicine is a fairly nascent specialty. With the rapid technical and pharmacological advances in medicine, physicians trained in critical care offer a unique skill set and will continue to be in high demand. Recent COVID pandemic has only further underlined the need for trained critical care specialists.

REFERENCES

1. Kapoor G, Hauck S, Sriram A, Joshi J, Schueller E, Frost I, et al. State-wise estimates of current hospital beds, intensive care unit (ICU) beds and ventilators in India: are we prepared for a surge in COVID-19 hospitalizations? medRxiv. 2020.
2. Hoffman JMW, Mayer K. Destination critical care: a roadmap for academic clinicians, educators, and mentors. AEM Educ Train. 2018;3(1):74-8.
3. Prayag S. ICUs worldwide: critical care in India. Crit Care. 2002;6(6):479-80.
4. Kulkarni AP, Zirpe KG, Dixit SB, Chaudhry D, Mehta Y, Mishra RC, et al. Indian Society of Critical Care Medicine. Development of critical care medicine in India. J Crit Care. 2020;56:188-96.
5. Chang CWJ. Focused subspecialty critical care training is superior for trainees and patients. Crit Care Med. 2019;47(11):1645-7.

93

CHAPTER

Intensive Care Unit in Night

Shakya Mohanty, Shivangi Khanna, Jeetendra Sharma

INTRODUCTION

Night time in an intensive care unit (ICU) can be specially challenging due to multiple anticipated and unanticipated problems, which comprise of various clinical, logistic, and staffing issues along with the obvious defiance of the normal biological circadian rhythms of the patients as well as the healthcare personnel. All individuals have different sleep wake cycles called chronotypes.[1] The enforced variation in circadian rhythms due to shift work is known as "social jetlag," which leads to fatigue and reduces performance.[2] This social jetlag is further complicated by comparatively more emergency and critically ill admissions at night, requiring prompt decision-making along with complex diagnostic and therapeutic procedures, which are usually urgent and whose postponement can have serious implications on the patient prognosis. Maintenance of performance and patient care in resource (staffing, equipment, trained personnel) limited settings is particularly difficult. Therefore, proper understanding of the ICU functioning at night is important for patients as well as healthcare personnel's well-being and for provision of good quality care at all times.

PROBLEMS COMPLICATING INTENSIVE CARE UNIT ENVIRONMENT AT NIGHT

The environment of an ICU at night is starkly different from that during the day. Factors causing difficulty are:

- *Light*: Nocturnal light levels in an average ICU can range from 2.4 to 145 lux and those during the procedures can be as high as 10,000 lux.[3] This high intensity of light has the capacity to decrease melatonin secretion during the night and cause disruption of sleep, which in turn leads to sleep deprivation-induced delirium and dysfunctional behavior.
- *Noise*: Though the ideal noise levels in ICU during day and night are defined, these targets are difficult to meet in the real world scenario **(Table 1)**.

  Continuous positive airway pressure (CPAP) hood can be as noisy as loud music at a disco [100 dB(A)]. Noises above 50 dB(A) can also lead to cardiovascular implications, increased heart rate variability, and have been sighted as a cause of more readmissions to the coronary unit.[6] Noise can cause stress in healthcare workers as well.
- *Temperature*: The recommendations for normal ambient temperature in adult ICUs are 21–24°C by the USA and 16–25°C by the Indian guidelines.[7,8] Cooler temperatures have been found to result in sleep disruption, while warmer temperatures enable sleep.
- *Limited staffing and resources*: There might be a dearth of paraclinical and support staff during night shifts, especially when there is sudden unexpected rise in admissions. Also, all the investigations, especially the advanced imaging studies are generally not available round the clock.
- *Limited availability of consultants and senior supervision*: Although consultants are available throughout in modern ICUs and clinical decision-making is not delayed or hampered in tertiary care hospitals, this might not be true for resource-limited settings. Also, the insight provided by senior and most experienced physicians is accessible during morning rounds only.
- *Compromised performance due to social jetlag:* As described previously

TABLE 1: Noise level in intensive care unit (ICU).

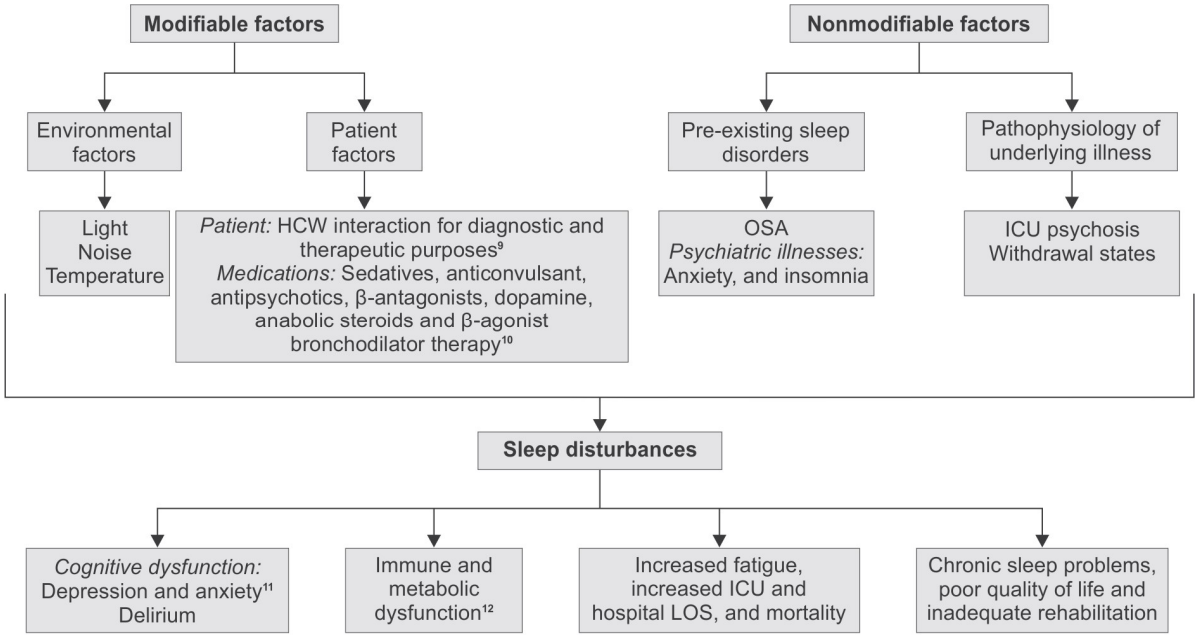
	Ideal noise threshold (WHO)[4]	*Actual average noise levels in ICU*[5]
Day	<30 dB(A)	60–70 dB(A) with peak up to 90 dB(A)
Night	<40 dB(A)	60–70 dB(A)

(dB(A): A-weighted decibels; WHO: World Health Organization)

EFFECTS ON PATIENTS

Multiple factors may coexist simultaneously at a particular time, which may adversely affect the patients. Some of these

Flowchart 1: Factors affecting patients during night.



(HCW: healthcare worker, OSA: obstructive sleep apnea, LOS: length of stay)

factors are modifiable, while many of them, especially the disease-related factors, are unmodifiable. These are depicted in **Flowchart 1**.

EFFECT ON HEALTHCARE WORKERS

"Shift work disorder" is a syndrome seen in shift workers (incidence varying from 24.4 to 44.3%) characterized by alteration in circadian rhythm, insomnia, excessive daytime sleepiness, and fatigue.[13]

The following problems are commonly seen in healthcare providers with shift duty:

- Poorer psychological and mental health causes higher incidence of irritability, interpersonal sensitivity, anxiety, obsessive compulsive disorder, altered mood, and paranoid disorders leading to negative impact on social life also.[14]
- Cardiovascular and gastrointestinal systems can also be adversely affected.
- Chronic fatigue and poor mental health leads to poor job performance and reduced job satisfaction, which can eventually result in increasing absenteeism due to various reasons and also can end up in consumption of psychotropic drugs.
- The cognitive abilities of intensivists are significantly altered following a night shift in the ICU, regardless of either the amount of professional experience or the duration of sleep during the shift. Cognitive decline is evident in the following areas, i.e., working memory capacity, speed of processing information, perceptual reasoning, and verbal processing, in complex problem-solving skills and cognitive flexibility, all of which can eventually result in impaired decision making. Hence, it is advisable to delay nonurgent procedures or decisions until some senior experts come in morning hours.

However, this degradation in psychomotor performance does not always lead to a degradation in clinical skills or in significant patient harm. This is more relevant in the ICU setting as multidisciplinary team involvement and a team-based approach in the ICU alleviates any impact of individual poor psychomotor performance.[15] Several studies have also proven that presence of some physician in ICU at night (including trainees) does not change the patient outcome significantly compared to presence of more senior/well rested physicians at night.[16,17]

POTENTIAL SOLUTIONS

Both patients and healthcare workers face varied spectrum of challenges at night inside ICUs. From the patient's perspective, it is advisable to work on the modifiable environmental and patient factors to make them more comfortable.

Addressing Patient Problems

Changes in certain clinical practices, processes, and ICU environment can address patient related problems/issues effectively **(Table 2)**.

Addressing Healthcare Workers Problems

Healthcare workers, from doctors and nurses to paraclinical staff, have unique issues at night. A common denominator across them contributing to stress is the high burden of

TABLE 2: Suggested solutions related to patients.

Noise	• Maintaining baseline noise levels below 40 dB[7] • Effort by nursing staff or paraclinical staff to turn down the volumes of alarm on monitoring equipment Prespecified protocolized timings to turn down or turn up the alarm volume to maintain uniformity
Light	• Using lights of lower luminosity around awake patients who do not require aggressive monitoring • Turning down the lights after completion of procedures and rounds
Temperature	• Maintaining optimum temperatures as per guidelines[7,8] • Providing extra blankets and warmers to susceptible patients like elderly who cannot communicate well
Patient cohort	• Within large ICUs trying to cohort patients according to the severity of illness, need for constant monitoring, and high activity around patients such as diagnostic therapeutic procedures and dialysis • Shifting relatively stable patients to HDUs or cabin rooms
Diagnostic procedures	• Blood sampling to be done in waking hours in nonemergent cases • Imaging studies, diagnostic procedures requiring patient to be shifted out of ICU to be done during the day
Nutrition	Respecting patients' regular mealtimes as much as possible
Bowel and bladder	Promptly addressing bladder and bowel needs by the paraclinical staff
Medications	• Limiting sleep inducing medications to late evening/night • Planning sedation breaks only during the day time. Avoiding sedation breaks during night unless medically indicated • Medications for adequate pain relief • Melatonin at regular bed time for restoring sleep pattern
Substance withdrawal	Differentiating withdrawal states from ICU psychosis and initiating appropriate treatment
Physical restraints	• As physical restraints can exaggerate aggression in few patients, therefore limiting its use only to selected patients • Appropriate use of sedatives/antianxiety medications can help settle milder cases
Miscellaneous	• Having open visiting policies • Using eye masks and ear plugs during sleeping hours

(ICU: intensive care unit; HDU: high dependency unit)

healthcare in the face of limited resources at night. The following measures can help to overcome these problems to some extent:

- Decreasing the overall burden of healthcare in the night shift:
  - Major diagnostic and treatment decisions should be taken during the day, preferably in the morning half.
  - Completing planned diagnostics including blood sampling and procedures during the day
  - Completing all interdepartmental consultations during the day
  - Family counseling and addressing all the queries and grievances after morning rounds
  - Maintaining patient–nurse ratio of 1:1 in severely critically ill patients. Provision of extra staff in case of unusually high number of sick patients/mass casualty.
- *Remote monitoring/tele-ICU*: Telemedicine was a fledgling concept, especially in developing countries where majority of population does not have access to technology. However, the global COVID-19 pandemic has been a game changer in this aspect. Tele-ICU models are being more frequently used, especially in resource poor conditions.

  Remote monitoring and control of ICU offer the greatest advantage when the ICU and the command center of remote control are located in different time zones. Night time in ICU corresponding to day time at the command center provides additional monitoring, vigilance, and decision-making assistance to the floor ICU staff as it is provided by more attentive staff at the remote monitoring center.

  Previous studies have shown its cost-effectiveness, however more studies on the safety and efficacy of tele ICU are required before it becomes a norm during nonpandemic times.[18]
- *Automatization*: In ICUs treating the sickest of sick patients, vast amount of data is generated by the multitude of ICU devices. The most prevalent system to analyze data is to use alerting systems that warn staff when a patient's condition deteriorates and needs immediate attention. This is hard to monitor and causes alarm fatigue.

  Commercial aviation faced a similar dilemma and has developed automation models to create safer airplanes and make their operations more reliable. This is yet to happen in healthcare industry. Drawing on the aviation industry, Principles of Automation for Patient

Safety in Intensive Care (PASPIC) framework uses Billings' principles of human-centered aviation (HCA) automation to help healthcare providers retain control and swiftly respond to failure. This is based on the premise that human operators must remain in command, so that they are continuously informed and actively involved in all aspects of system operations. PAPSIC proposes three key characteristics: (1) integration and better interoperability, (2) multidimensional analysis, and (3) enhanced situation awareness. As the healthcare provider is at the center of the loop, this is better described as "cooperative automation" where there is coordination between humans and machines.[19]

- *Environmental factors for healthcare workers*: Small breaks by rotating team members have shown to reduce burn out effect and fatigue as well as help in enhancing the attention and efficiency of the team members. Several methods to reduce sleepiness and insomnia while improving performance in night shift workers: Short naps (20–30 minutes), intake of caffeine at the beginning of shift, not allowing prolonged duty hours, regulation of working hours, not allowing continuous night duties, and providing offs after night duties. Provision of adequate duty rooms, refreshments, and restroom facilities to maintain a standard of comfort during the long shift hours is advisable.

CONCLUSION

Intensive care embarks upon the ability to provide seamless healthcare 24 hours of the day and 7 days a week and that too in a very proficient and empathetic manner. This makes shift work and rotating schedules of the doctors and nurses mandatory for maintenance of continuity of care. Maintenance of performance and patient care in resource (staffing, equipment, and trained personnel) limited settings is particularly difficult. Therefore, proper understanding of the ICU functioning at night is important for patients as well as healthcare personnel's well-being and for provision of good quality care at all times. Multiple modifiable factors give a scope for improving ICU environment at night and improve patient wellbeing. Adequate staffing and decreasing the burden of care can improve healthcare worker fatigue leading to better outcomes.

REFERENCES

1. Vetter C, Schernhammer ES. Early, but not late chronotypes, are up during their biological night when working the night shift. Occup Environ Med. 2015;72(3):235.
2. Wittmann M, Dinich J, Merrow M, Roenneberg T. Social jetlag: misalignment of biological and social time. Chronobiol Int. 2006;23(1-2):497-509.
3. Verceles AC, Liu X, Terrin ML, Scharf SM, Shanholtz C, Harris A, et al. Ambient light levels and critical care outcomes. J Crit Care. 2013;28(1):110.e1-8.
4. Berglund B, Lindvall T, Schwela DH. Guidelines for Community Noise. Geneva: World Health Organization; 1999.
5. Wenham T, Pittard A. Intensive care unit environment. Contin Educ Anaesth Crit Care Pain. 2009;9(6):178-83.
6. Hagerman I, Rasmanis G, Blomkvist V, Ulrich R, Eriksen CA, Theorell T. Influence of intensive coronary care acoustics on the quality of care and physiological state of patients. Int J Card. 2005;98(2):267-70.
7. Centers for Disease Control and Prevention. Guidelines for environmental infection control in health-care facilities: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC) (2003). Updated in 2017.
8. Rungta N, Zirpe KG, Dixit SB, Mehta Y, Chaudhry D, Govil D, et al. Indian Society of Critical Care Medicine Experts Committee Consensus Statement on ICU Planning and Designing, 2020. Indian J Crit Care Med. 2020;24 (Suppl 1):S43-S60.
9. Celik S, Oztekin D, Akyolcu N, Işsever H. Sleep disturbance: the patient care activities applied at the night shift in the intensive care unit. J Clin Nurs. 2005;14(1):102-6.
10. Young JS, Bourgeois JA, Hilty DM, Hardin KA. Sleep in hospitalized medical patients, part 1: factors affecting sleep. J Hosp Med. 2008;3(6):473-82.
11. Marcks BA, Weisberg RB, Edelen MO, Keller MB. The relationship between sleep disturbance and the course of anxiety disorders in primary care patients. Psychiatry Res. 2010;178(3):487-92.
12. Irwin MR, Wang M, Campomayor CO, Collado-Hidalgo A, Cole S. Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. Arch Intern Med. 2006;166(16):1756-62.
13. Ferri P, Guadi M, Marcheselli L, Balduzzi S, Magnani D, Di Lorenzo R. The impact of shift work on the psychological and physical health of nurses in a general hospital: a comparison between rotating night shifts and day shifts. Risk Manag Healthc Policy. 2016;9:203-211.
14. Bjorvatn B, Dale S, Hogstad-Erikstein R, Fiske E, Pallesen S, Waage S. Self-reported sleep and health among Norwegian hospital nurses in intensive care units. Nurs Crit Care. 2012;17(4):180-8.
15. Rubulotta F, Scales DC, Halpern SD. Night shifts, human factors, and errors in the ICU: a causal pathway? Intensive Care Med. 2016;42(3):456-7.
16. Kerlin MP, Harhay MO, Kahn JM, Halpern SD. Nighttime intensivist staffing, mortality, and limits on life support: A retrospective cohort study. Chest. 2015;147(4):951-8.
17. Wallace DJ, Angus DC, Barnato AE, Kramer AA, Kahn JM. Nighttime intensivist staffing and mortality among critically ill patients. N Engl J Med. 2012;366(22):2093-101.
18. Yoo BK, Kim M, Sasaki T, Melnikow J, Marcin JP. Economic evaluation of telemedicine for patients in ICU. Crit Care Med. 2015;44(2):266-74.
19. Dominiczak J, Khansa L. Principles of automation for patient safety in intensive care: learning from aviation. Jt Comm J Qual Patient Saf. 2018;44(6):366-71.

94

CHAPTER

How to Mitigate Ill Effects of High Staff Attrition Rates in ICU?

Neeru Gaur, Pradeep Bhatia, Revathi Aiyer

INTRODUCTION

Staff retention and managing their shift duties are the most intense challenges faced in intensive care unit (ICU), especially during pandemics, because the rate of attrition is very high, especially among the critical care nursing staff as well as residents and exponentially rising in the past few years. Shortage of staff nurses, "the backbone of any healthcare sector," is more difficult to cope with, in the developing countries, as they are unable to stand in competition with variability in work culture, the work output, salary, professional development, and variability offered in developed countries. Attrition, the abandonment of a position due to retirement, resignation, or other similar reasons, is a critical issue affecting the growth of any organization, thus it is essential to retain its skilled staff.[1]

CAUSES OF ATTRITION: IDENTIFY THE CAUSE

20 good reasons for the attrition of staff nurses can be:

1. *Emigration*: Brain drain of intelligent staff from developing country to developed country in pursuit of greener pastures—better lifestyle and financial status.
2. *Voluntary exits*: Due to personal, social issues such as marriage, pregnancy, and childbirth, especially in case of female staff.
3. *Change of job from one institute to another*: Usually for better payment structure and sometimes for ease of work and stability as offered in government sector.
4. *Severe debilitating illness*: Hospital-acquired Koch or other infectious diseases or death.
5. Retirement.
6. Less number of recruitments rather than actually needed to run a particular health system.
7. Decreasing enrolment in nursing education programs.
8. Lack of motivation and feeling of identity crisis with increased demand for nurses, especially in less equipped and overwork situations.
9. When there is a compromise in safety and security.
10. Unequal distribution of salary among the staff without any basic mandatory standards leads to dissatisfaction and mutiny.
11. Absence of training and quality check services.
12. Absence of counseling and effective communication.
13. Difficult working conditions, especially during 2020 pandemic.
14. Unequal educational opportunities and support.
15. Perceptions of favoritism among staff by management or by superiors.
16. High workloads and double shifts.
17. Highly stressful (physical or mental) work environment.
18. Working as substituting nurse as well in other wards than their own due to insufficient resources.
19. Need to perform non-nursing jobs as well such as computer work, accounting due to lack of ancillary staff.
20. Lack of incentives compared to competing institutions.

THE 10 ILL EFFECTS AND CONSEQUENCES OF ATTRITION

1. Economic loss.
2. Emotional loss.
3. Reduced efficiency at work place and poor patient satisfaction.
4. Poor performance outcomes and results.
5. Very high stress levels of all the working staff, doctors, and management.
6. Huge loss of public resources spent on education and training of health workers.
7. Increased workload as well as worse working conditions for the remaining workforce and feeling of dissatisfaction.
8. Affects the overall institutional capacity of the health standards of basic and advanced care.
9. Loss of valuable knowledge and experience.
10. Loss of team competence.

Above mentioned ill effects[2-4] and their consequences on the overall performance are deleterious to the health infrastructure, hence solutions to timely *identify the issue*

(common causes mentioned above), assess, and plan ways to mitigate the staff attrition are needed.

ASSESS

Demographic characteristics such as age, the role values, personality traits, and particular hospital conditions were crucial in staff retention.

Though it is difficult to control the attrition rate within the hospital, the decreased nurse attrition rate is positively associated with higher job satisfaction, older nurses, and resident relationships.[5]

- Recognize early to anticipate turnover or upcoming shortage of staff.
- Timely action to retain good staff.
- Recruitment of new ones with proactive planning.
- *Turnover remedy:* Four elements of turnover remedy:
  1. Recruiting
  2. Onboarding
  3. Training
  4. Engagement

PLAN: METHODS TO MITIGATE ILL EFFECTS OF STAFF ATTRITION

- *Hire*
- *Train*
- *Motivate*
- *Retain*

The best way is to empower staff to teach, guide, learn, and motivate each other by means of recognition, celebration, and sharing—throughout the organization. It is observed that employees were feeling lonely, stressed, and isolated during the pandemic. More than half said that receiving or giving a "thank you" has helped ease their anxiety and almost two-third said that these moments of recognition have motivated them to work harder.[6]

25-FIVE SUGGESTIONS TO MITIGATE STAFF ATTRITION[7-13]

1. *Appreciation for staff*: By the peer, seniors, relatives, patients, and management in their workplace. When people feel recognized, valued, appreciated, and empowered, they respond with greater energy to invest themselves in their respective area.
2. *Authenticity*: Hire the right people—proper selection as per the need of organization.
3. *Acceptance*: Define the role clearly, accept and respect their selection, and work with continuous quality check.
4. Agile performance model with the main components of continuous learning, frequent check-ins, building trust, and connection to the work.
5. Make them feel safe and energized.
6. Avoid negative working conditions and sharing of overwork of peer staff.
7. Empowerment and work engagement.
8. *Training*: Nursing supervisors can support newly recruited nurses' professional practice behavior, by providing and empowering supportive and professional practice environments.
9. Care of psychological factors such as paying attention to the shift demands of staff, having children, and the need to receive emotional support from the workplace.
10. Encourage prosocial good behavior in your employees, commend and give them a sense of ownership of their domain. The peer award can be instituted accompanied by a thanks and an inspirational story which also creates a permanent record of the good work done.
11. Working plan and protocols in the workplace with regular surveillance.
12. Role of head nurse is most important to support the staff nurses' personal problems in their family or a work dispute with the in-charge doctor, thus encouraging them in their work tasks. This would be the most effective way toward retention without creating sense of fear among staff.
13. *Salary*: The quantum and timely payment of reward and salary appropriate to the workload, which is fair and competitive with other organizations.
14. Compensation and benefits in the form of long-term investments and health insurance for employees.
15. Proper working shifts and total working hours.
16. Good work environment factors that support their professional practice behaviors and high-quality patient care will help in professional growth with job satisfaction and retention of new staff.
17. Give warnings, memos, and fire people who do not fit or those found to be inefficient, corrupt, and can be deleterious to the institution.
18. *Offer flexibility*: Modifiable workplace options for further promotions and profile change can play an important role in influencing new graduate nurses and doctors. Also, flexible shift duties and vacation policy should be practiced.
19. Give opportunities for development and growth.
20. Keep performance reviews and improve performance management by regular appraisals to ensure employee trust and satisfaction.
21. Offer the staff a strong vision, purpose, and goals of work and increase their sense of belonging and loyalty to your institute as part of NABH (National Accreditation Board for Hospitals & Healthcare Providers) survey trainings and infection control drills.
22. *Demonstrate and cultivate respect*: Creates a magnetic culture and it will help in higher retention.

23. Maintaining one's autonomy rather than breathe down their necks all the time.
24. Opportunities for innovation.
25. *Last but not least*: *Enrolling your institute for educational courses in critical care* would help in not only producing good quality staff-doctors and nurses, but also retaining them for the period of the course and later on with additional incentives in the form of higher cadre posts and salary, which would ensure continuum of good quality of care as well as additional trained staff who will help in training the new staff.

CONCLUSION

Staff attrition in ICU is a global problem, but a major issue in developing counties like us in India is mainly due the brain drain and emigration of good qualified intelligent ambitious staff to the developed western countries or the paying Arab countries in search of better financial and lifestyle options. It would be impossible to stop this culture unless we have good corporate hospitals which would ensure good quality patient care as well as good renumeration and long-term benefits for the trained medical personnel. Although mandatory monetary bonds implemented by the governmental institutions may deter a few, only a strong patriotism can stop the others.

The factors such as good conducive healthy working environment and a good short-term and long-term financial security and growth would probably be the major factors which would mitigate staff attrition from one ICU to another competitive one, which is the problem faced by most of us today.

REFERENCES

1. Campbell J, Buchan J, Cometto G, David B, Dussault G, Fogstad H, et al. Human resources for health and universal health coverage: fostering equity and effective coverage. Bull World Health Organ. 2013;91(11):853-63.
2. Kollar E, Buyx A. Ethics and policy of medical brain drain: a review. Swiss Med Wkly. 2013;143:1-8.
3. Ono T, Lafortune G, Schoenstein M. Health workforce planning in OECD countries: a review of 26 projection models from 18 countries. [online] Available from: https://www.oecd-ilibrary.org/social-issues-migration-health/health-workforce-planning-in-oecd-countries_5k44t787zcwb-en. [Last accessed February 2022].
4. Cometto G, Tulenko K, Muula AS, Krech R. Health workforce brain drain: from denouncing the challenge to solving the problem. PLoS Med. 2013;10(9):e1001514.
5. Dovlo D. Wastage in the health workforce: some perspectives from African countries. Hum Resour Health. 2005;3(1):1-9.
6. Workhuman. (2021). The Human Workplace Is The New Work Paradigm. [online] Available from: https://www.workhuman.com/resources/globoforce-blog/the-human-workplace-is-the-new-work-paradigm. [Last accessed February 2022].
7. Campbell N, McAllister L, Eley DS. The influence of motivation in recruitment and retention of rural and remote allied health professionals: a literature review. Rural Remote Health. 2012;12:1900.
8. Schoo A, Stagnitti K, Mercer C, Dunbar J. A conceptual model for recruitment and retention: allied health workforce enhancement in Western Victoria, Australia. Rural Remote Health. 2005;5(477):1-8.
9. Lassiter SS. Staff nurse retention: strategies for success. J Neurosci Nurs.1989;21(2):104-7.
10. Chen LC, Perng SJ, Chang FM, Lai HL. Influence of work values and personality traits on intent to stay among nurses at various types of hospital in Taiwan. J Nurs Manag. 2016;24(1):30-8.
11. Flinkman M, Salanterä S. Early career experiences and perceptions–a qualitative exploration of the turnover of young registered nurses and intention to leave the nursing profession in F inland. J Nurs Manag. 2015;23(8):1050-7.
12. Takase M, Teraoka S, Yabase K. Retaining the nursing workforce: Factors contributing to the reduction of nurses' turnover intention in Japan. J Nurs Manag. 2016;24(1):21-9.
13. Cicolini G, Comparcini D, Simonetti V. Workplace empowerment and nurses' job satisfaction: a systematic literature review. J Nurs Manag. 2014;22(7):855-71.

95

CHAPTER

Purchasing New Devices for Intensive Care: What do I Look for?

Vipul Pranlal Thakkar, Lalit Gupta, Vijay Mishra

INTRODUCTION

In any medical establishment including hospitals, devices and equipment hold a central and pivotal role. These equipment enable various tasks including medical diagnosis and treatment without which no medical services could be offered. With rapid technological advancements, hospitals procure newer equipment improvising on the quality of services offered. Procuring healthcare equipment is way different from common consumer purchases. Numerous aspects including but not limited to hospital infrastructure and logistics (ease of accommodation and transfer), manufacturer terms and conditions, maintenance and repair, user training and service, cost effectiveness, recurring expenses, human resources and their associated costs, and return on investment are involved. If the medical equipment is for critical care, the challenges faced are also more critical and complex. The critical care unit is the most dynamic area of hospital, wherein the clinical condition of the patient is usually at high risk, which is handled by a multidisciplinary intensive care unit (ICU) team offering monitoring, diagnostic, supportive, and therapeutic services using numerous devices for a favorable outcome. Thus, added considerations for critical care hospital equipment include personalized training, equipment and support service, ethics, and research and use of latest technology including bioprinting and artificial intelligence. For example, mechanical ventilation is common ICU interventions, wherein sedation and analgesia are important but show significant interpatient variability. This interpatient variability along with clinician's decision variability can be reduced by use of artificial intelligence tool. The hospital/ICU procurement committee in close association with an intensivist does the selection of the critical care equipment.

This chapter will serve as guide for purchase of an ICU device; aiding in the decision-making, considering important factors, checklists, and safety issues.

WHEN IS THE RIGHT TIME TO PROCURE A NEW INTENSIVE CARE UNIT DEVICE?

Myriads of devices in a critical care unit exist depending on the level and quality standards of the ICU; aiming different diagnostic, preventive, supportive, therapeutic, and/or palliative goals. These devices range from small to large size, single-use to multiple uses, either stationary or used for/during transfer of patients. Thus, let us classify devices.

Classification of Medical Devices

There are several ways to classify medical devices considering the (1) risk level involved in its operation; (2) purpose of usage, and (3) user interface (UI) design.[1]

Risk Level Categorization

According to Global Harmonization Task Force (GHTF), a voluntary group of representatives from medical device regulatory authorities and the regulated industry has classified medical devices into four classes—A, B, C, and D based on risk associated with its design as shown in **Table 1**.

Intended Usage Categorization

This categorization of devices is based on its purpose of use such as monitoring clinical parameters (monitoring

TABLE 1: Risk level medical device categorization.

Class	*Risk level*	*Device example*
A	Low risk	ECG machine
B	Low-moderate risk	Patient monitoring system, USG machine, syringe pump, and ABG machine
C	Moderate–high risk	Ventilator machine, ECMO machine, and ETO sterilizer
D	High risk	Defibrillator

(ABG: arterial blood gas; ECG: electrocardiogram; ECMO: extracorporeal membrane oxygenation; ETO: ethylene oxide; USG: ultrasonography)

TABLE 2: Intended usage medical device categorization.

	Category	*Device example*
1	Monitoring devices	Patient monitoring system
2	Therapeutic devices	Ventilator machine, defibrillator, syringe pump, and CRRT machine
3	Diagnostic devices	ECG, USG, and ABG machine
4	Supplementary devices	ETO sterilizer

(ABG: arterial blood gas; CRRT: continuous renal replacement therapy; ECG: electrocardiogram; ETO: ethylene oxide; USG: ultrasonography)

devices); during the therapies (therapeutic devices), in diagnosis (diagnostic devices), and availing various support services/facilities (supplementary devices). **Table 2** depicts intended usage categorization.

On-screen User Interface Design Categorization

In modern era, onscreen UI is an important feature for interaction with users for monitoring real-time status of patient and changes over time. Devices such as mechanical ventilator, continuous renal replacement therapy (CRRT) machines, have major UI on screen, while devices such as syringe pump or ECG machine may not have or have minor onscreen UI.[1]

For procurement of a medical ICU device at the right time, an intensivist needs to be abreast of new developments in the field by referring various journals, scientific programs, colleagues, or device-manufacturing companies. A continuously updated selection policy should be in place referred by medical, nursing, and concerned ICU staff for suggestions and feedback on both required new equipment and the existing ICU equipment.[2]

The responsibility for procurement or replacement of ICU equipment needs to be shouldered by team of key stakeholders of procurement committee, where an intensivist is a crucial member as a frontline user who can initiate the need of new device. Various factors influence the device selection process, which could be mitigated with the help of a checklist. Based on device logistics, the checklist could be divided as:

- *Preprocurement checklist*: This includes request by the user team, engineer review, and procurement committee approval. It includes assessment of need and value analysis process; review plan and inputs from engineers, and equipment providers/distributors; in-house evaluations from operations, nursing, medical staff, and other relevant departments before acquisition.
- *Procurement checklist*: It includes items related to equipment selection and validation. The engineering and maintenance department should be consulted to determine *space* requirements, *electrical safety and environmental* standards for optimal equipment functioning and its feasibility in the ICU. This checklist should include:
  - Accuracy, safety, and quality check.
  - *Infection control methods*: Cleaning, disinfection, and sterilization process.
  - Compatibility with existing systems.
  - *Ergonomic and operational factors including*: Ease of operation and maintenance.
  - Operating and maintenance costs throughout the use
  - Ease of transport or relocation (if necessary).
  - Low cost with broad application.
  - Availability of adequate maintenance centers, team, and training support staff.
- *Postprocurement checklist*: This includes items related to receipt and evaluation of device, its setup, orientation and training, cleaning, sterilization, and proper maintenance. It is recommended to keep a copy of the manufacturer's operator manuals accessible to all ICU staff at the location of the equipment. An assessment of the environmental impact of purchasing decisions will become increasingly important as the importance of the environmental impact of health care is recognized.[3] Some ICU equipment are being available as single-use device, which should be preferred for prevention of cross-infection if cost-effective. While considering it, one should take into account not only the cost of the reusable equipment, but that of sterilization, time, manpower, extra numbers required, storage space, etc., also. Examples of such items are bedpans, thermometer, flexible bronchoscopes, etc.[2]

Findings of literature review from low- and middle-income countries suggest that equipment cost, specialist recommendations, and technology regulatory approval are the primary procurement influencing factors **(Fig. 1)**. Authors also cautioned that procurement stakeholders underestimate the true cost of medical equipment, as they do not consider maintenance, servicing, and user training requirements.[4]

TECHNICAL ANALYSIS, EVALUATION, AND ADMINISTRATIVE PERSPECTIVE OF DEVICE

Technical Analysis

Technical analysis is generally done by the biomedical engineering department. As intensivist, one has to take technical expert's opinion and comments into consideration without being biased. However, it is intensivists' prerogative as an end-user, to give adequate weightage to clinically relevant usability factors for decision-making. It is advisable to call all vendors within a short and fixed time-span (for example, within 48–72 hours.) in the presence of important stakeholders at a time instead of scattered meetings. This

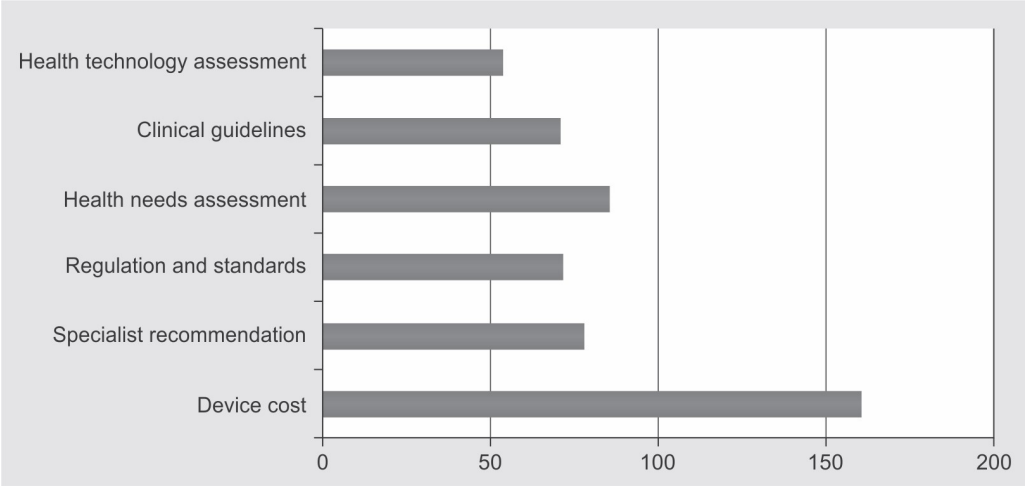


Fig. 1: Citation frequency of factors and evidence inputs considered in procurement planning.

helps to have a clear, updated impression and comparative evaluation of important technical issues, pros and cons of each device brand. Mandatory presence of each stakeholder helps to have different views and counter-views, which complement each other helping to build a consensus with the best decision statement. Human variables research has shown the significance of including all partners in medical device and software evaluations and successful implementation of innovation.[5,6] Also, device demonstration on patient is always preferred. Collaborating with allied departments has advantages of bulk purchase, wherein purchase from same vendor is preferred for illustration, selecting the same ventilator model from a single company. This not only reduces cost, but also makes it more users friendly.[2] Thus, a range of factors, including financial resources, opinion of clinicians, politics, evidence from literature, and consumer opinion, affect organizational decisions about medical equipment purchasing.[7]

Evaluation and Administrative Perspective of a Device

Medical equipment is a love asset for any healthcare facility. Thus, it is very important to ensure medical equipment safety and effectiveness, for which there is a need to understand its associated management methodology, which should be done systematically by optimizing and understanding the life cycle of the device. The methodology involves human, material, structural, organizational, and financial resources.

The administration also plays a pivotal role in procuring new equipment. Some important sequential steps involved in the process stand are as follows:

- *Acquisition*: Identification of device need usually begins with users of technology, i.e., the medical staff (physicians and nurses). Hence, before aiming at introducing new devices, a direct feedback from frontline users must be done about its various aspects.
- *Delivery and incoming inspection*: The biomedical engineering department should ensure that an inspection of the equipment is done which should include possible equipment damage/compliance with the specifications mentioned/verifying accessories, manuals, electrical safety, and operation should all be according to the policies.
- *Inventory and documentation*: After procuring an equipment and conducting inspection, it is vital to plan and make a device record file, which should be active throughout the life span of the device.
- *Installation*: Arranging of installation should be done in accordance with standard policies for medical equipment installation.
- *User training*: In order to have the best outcome and functioning of any given medical device, it is extremely important to train the equipment user as well as equipment maintenance and repair team. Frontline users (physician and nurses) should be acquainted with information like the functioning of equipment and its limitations, preventive maintenance, and sterilization of equipment.

STRENGTH AND PITFALLS OF INDIVIDUAL AND GROUP DECISION-MAKING: INFERENCE FROM EXPERIENCE AND EVIDENCE

Involvement of End Users

While evaluating safety-related knowledge in syringe pump, purchase process at three hospitals in US revealed potential problems with the composition of the purchasing groups. End users have the greatest knowledge of a device's strengths and weaknesses and of the environment and tasks to be performed with the device, yet none of the three purchasing teams included end users. Further, it was found limited consideration was given to the alternative device across all hospitals.[8]

Behavioral and Cognitive Differences Amongst End Users

Studies have repeatedly shown that human decision-making behavior rarely conforms to the strict logic of classical decision-making theories (e.g., Bayesian theory). Due to cognitive and situational constraints, humans rarely engage in probabilistic computations of expected utilities of different options.[9] Instead, they rely on a limited set of heuristics principles that allow them to reduce complex computational tasks to simplified but more manageable ones, but this leads to various bias. Patel and Arocha[10] suggest that three types of factors—cognitive, social, and environmental/cultural—are key elements in collaborative decision-making. By and large clinical and administrative culture are similar across hospitals; hence, they affect device selection processes in similar ways. The writing on this subject recommends numerous manners by which data innovation can help with expanding patient safety and reducing medical errors (e.g., implementing computerized order entry systems, using computerized alert systems, etc.).[11]

Safety and Quality Concerns Influencing Device Purchase

Many investigations have exhibited that numerous user errors are identified classic interface problems (e.g., poor feedback, ambiguous display messages, etc.).[12] Redesigning the interface using human factor guidelines has shown to decrease device programming time, minimize users' mental workload, and reduce the number of programming errors.[13] A retrospective analytical study on an infusion pump purchase in a large urban hospital suggests that while all participants view device safety as an important factor in selection process, there is absence of an overall collective perception where all perspectives are represented.[3] In brief, every stakeholder is conscious about patient safety and quality offered by equipment, but there is no surrogate parameter to measure it. It is seen distinctively by various partners.

In general, for patient safety offered by equipment, healthcare provider must be aware of its user interface, patient safety alarms (if applicable), and its interpretation as well as infection prevention measures.

Another important factor for patient safety is duration of battery backup in some devices, a feature that is very important during transfer of patients and in situation of electricity failure.

International certification [e.g., approval by the Food and Drug Administration (FDA), a CE mark in the European Union (EU), inclusion in a World Health Organization (WHO) prequalification scheme] most of the time serves as a proxy for technology safety, a desired feature of device to be procured.[14-16]

Demerits of Improper Selection of Device

- No benefit to patient, in fact may harm and add to cost burden [e.g., poor functioning of deep vein thrombosis (DVT) prophylaxis device].
- Nonacceptance by end-user.
- Economic loss to hospital.
- Nonavailability when in real need (especially when maintenance repair takes long time without replacement of only device, e.g., capnograph).
- Physical harm to patient and staff or surrounding.

LEARNING LESSONS FOR PANDEMIC SITUATIONS

The aftermath of COVID-19 pandemic has led to faltering economy and healthcare system. In these difficult times, cost cutting and limited infrastructure have affected the hospital segment as well. We have realized that hospital system and healthcare provider must respond in different and unique ways. Prioritizing of supplies and equipment must be done. To avoid any vulnerability in supply chain always, alternative agents and supply channels must be identified.

While opting for purchase in such disaster scenarios, clinician and technical team need to make prompt choices and decisions. Every effort should be directed toward provision of necessary devices with minimum acceptable performance and high safety standard, considering its utility after pandemic. Optimization and strategic allocation of resources is the key to overcoming any crisis.

CONCLUSION

Medical devices and their adequate functioning are the key to a successful and satisfactory functioning of a critical care unit. Suboptimal use of a medical ICU device relates to the failure of the hospital procurement process, which is often linked, to incomplete allocation of financial and human resources as well as inadequate consideration given to maintenance, postpurchase services, and user training. Early involvement of all stakeholders with focus on important technical and administrative aspects will help purchaser of device make the procurement process more meaningful for patients care and cost-effective for the hospital.

REFERENCES

1. Ganesh B, Shahaji D. Medical Equipment and Automation (Mar-April 2012). [online] Available from: https://www.researchgate.net/publication/285474310_Vital_Medical_Devices_in_Intensive_Care_Unit. [Last accessed February 2022].
2. Rungta N, Zirpe KG, Dixit SB, Mehta Y, Chaudhry D, Govil D, et al: Indian society of critical Care Medicine Expert Committee consensus statement on ICU planning and designing 2020. Indian J Crit Care Med. 2020;24(1):S43-60.

3. Thomas AN, Roberts JC. Standard for Equipment in Critical Care. The Intensive Care Society. [online] Available from: https://www.cc3n.org.uk/uploads/9/8/4/2/98425184/equipment_in_cc__1_.pdf. [Last accessed February 2022].
4. Diaconu K, Yen-Fu C, Carole C, Moyao GJ, Manaseki-Holland S, Lilford R. Methods for medical device and equipment procurement and prioritization within low- and middle-income countries: finding of a systemic literature review. Global Health. 2017;13(1):59.
5. Nielsen J. Usability Engineering. San Diego: Morgan Kaufmann; 1993.
6. Chan W. Increasing the success of physician order entry through human factors engineering. J Healthc Inf Manag. 2002;16(1):71-9.
7. Farmer J, Williams D. Decision-making by health purchasing organizations in Scotland: the role and influence of evidence from the research literature. J Inf Sci. 1997;23(1):59-72.
8. Johnson TR, Zhang J, Patel VL, Keselman A, Tang X, Brixey JJ, et al. The role of patient safety in the device purchasing process. Adv Patient Safety: From Research to Implementation. 2005;1:341-35.
9. Keselmen A, Vimla L, Todd R, Zhang J. Institutional decision-making to select patient care device: identifying venues to prompt patient safety, Science Direct- Journal of biomedical Informatics; 2003;36(1-2):31-44.
10. Patel VL, Arocha JF. The nature of constraints on collaborative decision making in health care settings. In: Salas E, Klein G, (Eds). Linking expertise and naturalistic decision making. Mahwah, NJ: Erlbaum; 2000. p. 383-405.
11. Bates D, Cohen M, Leape L, Overhage JM, Shabot MM, Sheridan T. Reducing the frequency of errors in medicine using information technology. JAMIA. 2001;8(4):299-308.
12. McConnell E, Cattonar M, Manning J. Australian registered nurse medical device education: a comparison of simple vs. complex devices. J Adv Nurs. 1996;23(2):322-8.
13. Lin L, Isla R, Doniz K, Harkness H, Vicente KJ, Doyle DJ. Applying human factors to the design of medical equipment: patient-controlled analgesia. J Clin Monit Comput 1998; 14(4):253-63.
14. Matai S, Peel D, Wandi F, Jonathan M, Subhi R, Duke T. Implementing an oxygen programme in hospitals in Papua New Guinea. Ann Trop Paediatr. 2008;28(1):71-8.
15. Dyer R, Reed A, James M. Obstetric anaesthesia in low-resource settings. Best practice and research. Clin Obstet Gynecol. 2010;24(3):401-12.
16. Briggs C, Carter J, Lee S, Sandhaus L, Simon-Lopez R, Vives Corrons JL, et al. ICSH guideline for worldwide point-of-care testing in haematology with special reference to the complete blood count. Int J Lab Hematol. 2008;30(2):105-16.

96

CHAPTER

Smart Intelligent Bedside Monitoring and Infusion Pumps

Khusrav Bajan

A well and holistically monitored patient, seldom crashes suddenly in ICU which is a nightmare for most intensivists.

INTRODUCTION

A critically ill patient is often in a dynamic process of the disease, resulting in sudden deterioration of vitals. A close smart and intelligent monitoring of such patients is a mandate in the intensive care unit (ICU). Since "One size does not fit all," there is no gold standard monitoring tool and hence an amalgamation of portable, comprehensive, and well-connected bedside monitors is the key to patient safety and outcomes. In spite of these measures, medical errors are more frequently encountered in ICUs due to unstable vitals, unconsciousness, and/or unknown medical history of patients. Moreover, the inability of ICU patients to monitor or respond to side effects of medications further leads to serious consequences. A recently published study on improving patient safety in pediatric intensive care reported medical errors in up to 77% cases.[1] Similar statistics are reported by other intensivists who suggested approximately 1.7 errors occurring per day in ICUs accounting to 78% of serious medical errors.[2]

CHALLENGES FACED IN INTENSIVE CARE UNIT

From an organizational perspective, the commonly faced challenges are:

- Multiple sourcing of patient information (through charts, multiple staff members, and smart devices).
- Lack of interactive monitors (indicating all vitals on a single screen).
- Changing shifts of nurses leading to multiple handovers of patient information.
- Lack of interdepartmental collaboration among medical officials.
- Lack of specialized nurses and junior doctors manning the ICUs 24×7.

Critical care in itself is overwhelming and demands high cognitive abilities to process patient information and deliver accurate and timely prescriptions. The above challenges limit the ability of intensivists to efficiently manage critically ill patients. It is equally challenging for untrained junior doctors/critical care nurses to operate and manage the instruments throughout the day. This leads to vital signs being missed, eventually causing harm and death. Thus, the need for upgraded and more sophisticated smart and intelligent bedside monitoring systems arises to overcome the challenges faced in ICUs.[3]

INTENSIVE CARE MONITORING SYSTEMS

The monitors in ICU are designed to provide an overview of the physiological status of patients that help in detecting, diagnosing, and treating them. The physiological monitoring displays, introduced in the 1970s, can currently portray over 36 critical physiologic patient variables in real time. These monitor designs use a single-sensor–single-indicator approach to visualize the vital signs of patient in the form of raw waveforms or translated numerical data.[4] A system-wise patient monitoring is carried out simultaneously in the ICUs to design treatment plans based on the stability of observed vitals. An outdated single reading gadget to more sophisticated continuous monitoring modules for checking body temperature and glucose is now easily available.

System-Wise Monitoring of Critically Ill Patients

Neurological Monitoring

Earlier, neurological monitoring was done based on frequent clinical examinations to record subtle changes in brain activity. This made it extremely challenging to detect asymptomatic acute neurological deterioration. Even today, with the technological advancements, none of the available systems can efficiently monitor all neurological parameters. Instead, the multimodal neurocritical monitoring (MMM) is encouraged to examine the pathophysiological variations in patients.[5] The neuromonitoring tools have advanced recently as compared to other physiological monitors. For instance, the intracranial monitors became popular between 1980 and 2000 followed by several other monitors for detection of brain oxygenation and blood flow **(Table 1)**.

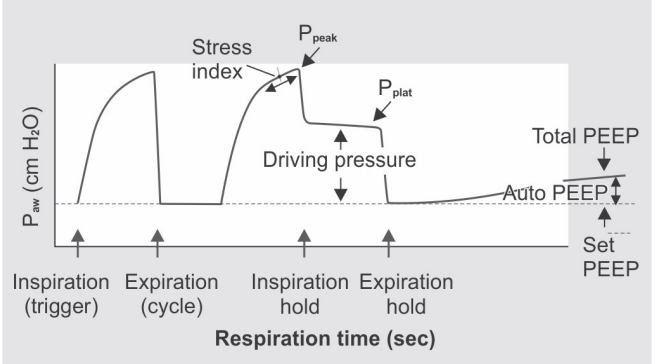
With the help of these monitors, it is now possible to predict subtle changes and allow timely interventions that can prevent secondary injuries and advances in disease conditions. Although the MMM systems have helped in significant improvement of neurocritical conditions, it remains a challenging task. The key challenge is to assess the condition of the patient who is unconscious, or under anesthesia, for carbon dioxide narcosis, status epilepticus hypoxia, and traumatic brain injuries.[6] For these reasons, the scoring systems are still followed to grade the functioning of neurological parameters as prediction models for making rapid and timely decisions during critical life-threatening events. A good clinical exam can never be replaced but only can be complimented with smart intelligent monitors.

Pulmonary Monitoring

Noninvasive and invasive mechanical ventilators are not a treatment but a mere supportive tool until the underlying condition, such as acute respiratory distress syndrome (ARDS) and pulmonary edema, settles. A supportive therapy should have a zero tolerance to worsen the condition of the patient, thus stressing the principle of "*PRIMUM NON NOCERE*"—DO NO HARM. An unprecedented level of sophistication occurs in these systems due to utilization of several microprocessors to monitor and analyze multiple variables. Moreover, these variables are converted into measurable tools to calculate lung functions to further analyze the respiratory mechanics **(Fig. 1)**. All forms of ventilator monitoring and graphics should be a bedside norm to prevent the dreaded complication ventilator-associated lung injury. An understanding of peak, plateau, and driving pressures makes it a comprehensive and safe way to ventilate a patient in the ICU. **Table 2** enlists commonly used pulmonary monitors in ICU. To assist pulmonary monitoring, the pulse oximetry is the basic and most important tool to detect early signs of inadequate oxygenation leading to lung injury. The measurement of airway pressures can help in optimization of positive end-expiratory pressure (PEEP) to prevent alveolar overdistension which, in turn, increases end-expiratory lung impedance. The alveolar pressures also provide critical information during simple respiratory maneuvers to assess treatment response and predict successful weaning.[6,7]

TABLE 1: Neurological monitoring aids in intensive care unit (ICU).

Monitors	***Uses***
Intraventricular catheter, subdural screw (bolt), epidural sensor, tympanic membrane displacement, optic nerve sheath diameter	Intracranial pressure
Cerebral microdialysis	Assessment of ischemia/stroke/brain injury by measurement of common brain metabolites, markers of tissue injury, energy failure, and cellular stress
Jugular vein bulb oximetry	Oxygen saturation in brain
Positron emission tomography, magnetic resonance angiography, computed tomography, Doppler flowmetry, transcranial Doppler ultrasonography, near-infrared spectroscopy	Cerebral blood flow



Average airway pressure

$$\bar{P}_{aw} = (PIP - PEEP)\left(\frac{T_i}{T_T}\right) + PEEP$$

Constant flow volume ventilation

$$\bar{P}_{aw} = 0.5(PIP - PEEP)\left(\frac{T_i}{T_T}\right) + PEEP$$

Compliance

$$C = \frac{V_T}{P_{plat} - PEEP_{tot}}$$

Inspiratory resistance

$$R_t = \frac{PIP - P_{plat}}{\dot{V}_I}$$

Expiratory resistance

$$R_E = \frac{P_{plat} - PEEP_{tot}}{\dot{V}_{Emax}}$$

Work of breathing

$$W = \frac{PIP - (0.5)P_{plat}}{100}.V_T$$

Fig. 1: Respiratory mechanics.
(P_{aw}: average airway pressure; PIP: peak inspiratory pressure; PEEP: positive end-expiratory pressure; T_i: inspiratory time; T_T: total respiratory cycle time; V_{Emax}: peak expiratory flow; V_i: inspiratory flow; V_T: tidal volume)

TABLE 2: Pulmonary monitoring aids in intensive care unit (ICU).

Monitors	*Uses*
Ventilators	Lung pressure and respiratory rate
Pulse oximeter	Oxygen saturation of lungs
Capnography	Partial pressure of carbon dioxide in respiratory gases and confirmation of an appropriately placed endotracheal tube
Automated FRC	Assessment of aerated lung available for ventilation
EIT	End-expiratory lung volume
VC	Assessment of respiratory muscle strength
Blood gas analysis	Assessment of partial arterial pressure of oxygen and carbon dioxide (PaO_2, $PaCO_2$), arterial hypoxemia and hyperoxia, hypercapnia, and hypocapnia

(EIT: electrical impedance tomography; FRC: functional residual capacity; VC: vital capacity)

TABLE 3: Hemodynamic monitoring aids in intensive care unit (ICU).

Monitors	*Uses*
Arterial catheter; external pressure cuff	Blood pressure
Pulmonary artery (PA) catheter, central venous pressure, right atrial pressure, PA pressure	Intravascular and intracardiac pressures, CO, mixed venous oxygen saturation (SvO_2), and cardiac output
Electrocardiogram waveform	Electrical activity of the heart
Transesophageal echocardiography	Cardiac output during surgery

Hemodynamic Monitoring

Since their introduction in the medical practice, the electrocardiography and echocardiography remain the most accurate tool for hemodynamic monitoring. The former evaluates electrical activity of the heart to measure heart rate, rhythm, conduction disturbances, and pacemaker functions, whereas the latter uses sound waves for anatomical imaging of the heart. Other hemodynamic monitoring aids used for determining the blood flow and oxygen delivery to organs are indicated in **Table 3**.

Hemodynamic monitoring is also critically essential for detection of myocardial ischemia and arrhythmias. For detection of these conditions, the preload and volume responsiveness are assessed using static and dynamic indices. The systolic pressure variation, also indicating fluid responsiveness, can be used to estimate cardiac contractibility. Altogether, the factors such as preload, contractility, and afterload determine the stroke volume, which along with heart rate define the patient's cardiac output.[6] Technically, the problem arises due to the inability of monitoring systems to measure these factors accurately. Precisely, the preload (i.e., sarcomere tension) cannot be measured in absolute terms. However, several relative indicators such as right atrial pressure and central venous pressure reflect static measurements of right ventricular preload. Similarly, the central venous pressure and passive leg raising maneuver are helpful in detecting fluid responsiveness.[6,8] Various indices and algorithms used in hemodynamic monitoring are represented in **Figure 2**. Commercially available All-in-one monitors such as VGILEO and VOLUVIEW not only guide us in advanced hemodynamic monitoring such as knowing pre- and afterload but

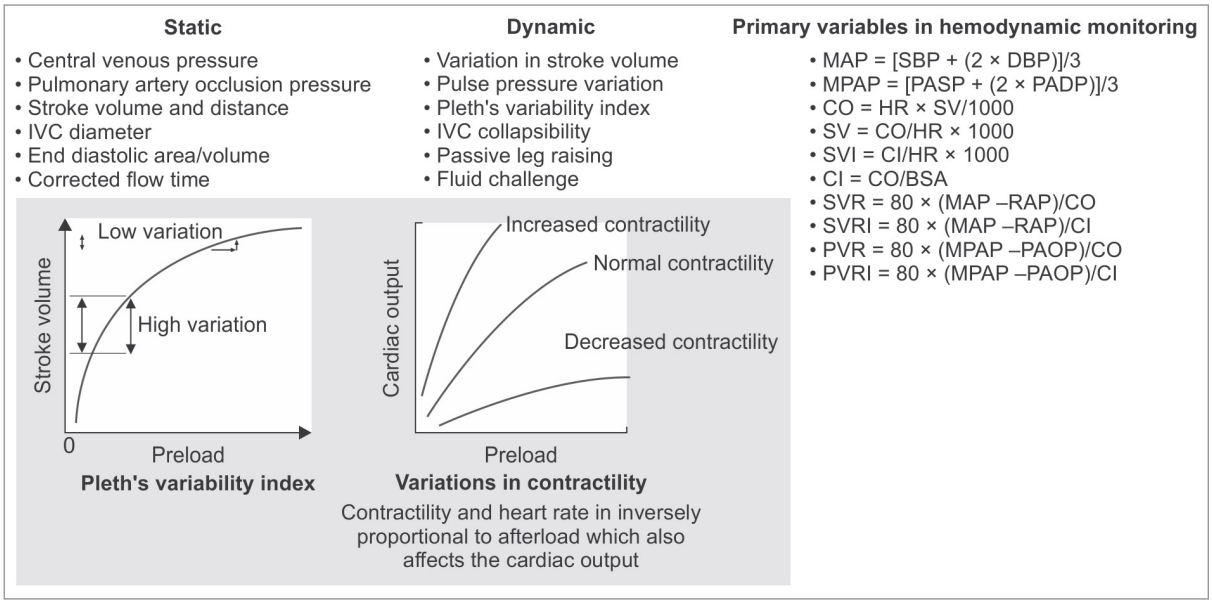


Fig. 2: Hemodynamic monitoring.
(BSA: body surface area; CO/I: cardiac output/index; HR: heart rate; IVC: inferior vena cava; MAP: mean arterial pressure; MPAP: mean pulmonary artery pressure; PASP/PADP: pulmonary artery systolic/diastolic pressure; PAOP: Pulmonary artery occlusion pressure; PVR/I: pulmonary vascular resistance/index; RAP: right atrial pressure; SBP/DBP: systolic/diastolic blood pressure; SV: stroke volume; SVR/I: systematic vascular resistance/index)

also parameters such as extravascular lung water (EVLW) and erythrocyte velocity in Global End-diastolic Volume (GEV) to help us in knowing the bad effects of excess fluid therapy.

Microcirculation and Tissue Perfusion Monitoring

With the recent insights in physiological monitoring of critically ill patients, a new paradigm of independent components of microcirculation and tissue perfusion has been identified. This paradigm change indicates that the microcirculatory parameters including arterial pressure, heart rate, or cardiac output may stabilize in critically ill patients. However, this does not necessarily indicate normal tissue perfusion. These conditions more commonly arise during acute circulatory failure in critically ill patients. Hence, bedside systems have been developed to monitor venous oxygen saturation and venous blood circulation **(Table 4)** to monitor tissue perfusion.[9]

Besides the oxygenation monitors, a popular biomarker of tissue perfusion is serum lactate. This is because the lactate levels increase during cellular hypoxia or low peripheral perfusion. Similarly, increased levels of lactate are found to be associated with, and hence used as a predictor for monitoring, septic shock. Consequently, increased clearance of serum lactate has been evidently useful in monitoring improved outcomes.[10]

Portable Monitoring Systems Using Point-of-care Ultrasound

Besides the use of sophisticated monitors and indices, portable systems for point-of-care ultrasound (POCUS) enable bedside diagnosis, assessment, and guided therapeutic interventions in critical care of patients. For instance, the POCUS-RUSH potential is used for *R*apid *U*ltrasound assessment of *S*hock and *H*ypotension through systematic examination of RUSH components that include heart, inferior vena cava, Morrison's/FAST abdominal views, aorta, and pneumothorax. Since increased intracranial pressure is among the first signs of neurological defects, rapid diagnostic techniques are increasingly sought for patient monitoring. In neurocritically ill pediatric patients, the POCUS of optic nerve sheath diameter (POCUS-ONSD) allows rapid diagnosis of increased intracranial pressure.[11,12] In contrast to bedside portable ultrasound, the benefit of POCUS is that it can be used for outpatient care during trauma and transport in the ambulance.

TABLE 4: Microcirculation monitoring aids in intensive care unit (ICU).

Monitors	*Uses*
Videomicroscopy using orthogonal polarization spectral (OPS), side stream dark field (SDF) imaging, incident dark field (IDF) imaging; vascular occlusion tests (VOTs)	Sublingual microcirculation
Transcutaneous tissue PO_2, SvO_2, tissue CO_2 (gastric tonometry, abdominal compartment pressure monitors, transcutaneous CO_2), lactate physiology, near-infrared spectroscopy (NIRS)	Tissue oxygenation

LIMITATIONS OF INTENSIVE CARE MONITORING SYSTEMS

The bedside monitors provide multiple vital parameters of patients through complex and continuous monitoring systems. However, this is accompanied with a surge of unprocessed clinical information that is challenging to relate to each other. Many a times, multiple factors are continuously monitored manually by ICU staff and recorded in patient charts or smart devices based on memory recollection after uneven monitoring schedules. To make matters worse, the high cognitive demand to follow up mass casualty events impedes rapid intervention measures that detriment the patient condition. During neurological monitoring, these challenges are further enhanced due to nearly impossible means of manual integration of patient information such as clinical values, imaging reports, and other medical records that are required for assessment of critically ill patients.[2,3] Besides, the smart bedside intelligent monitors are not only expensive but also need a great deal of training and hands-on time for an intensivist to interpret the available data and use it for better patient outcomes.

POSSIBLE SOLUTION

To prevent medical errors in processing of above information, a virtual checklist protocol of key components is evaluated by intensivists on a regular basis to optimize bedside monitoring of patients. For instance, the FAST HUGS BID **(Fig. 3)** principle is followed as a general care for all

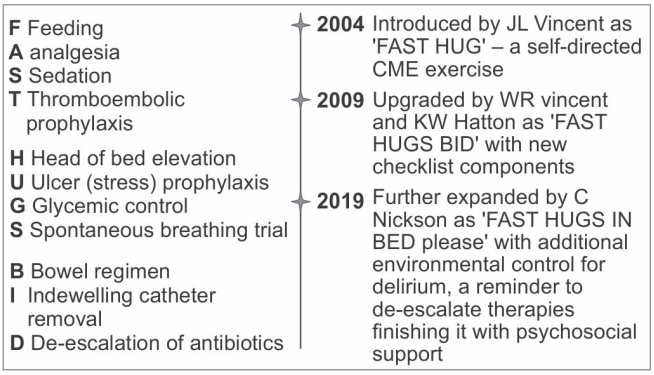


Fig. 3: Mnemonic for critical care of patients.
Sources: Vincent JL. Give your patient a fast hug (at least) once a day. Crit Care Med. 2005;33:1225-9. Vincent WR, 3rd, Hatton KW. Critically ill patients need "FAST HUGS BID" (an update mnemonic). Critical Care Med. 2009;37:2326-7. Nickson C. (2019). Life in the fastlane. Available from: http://litfl.com/fast-hugs-in-bed-please/[Last accessed February, 2022].

critically ill patients. However, it does not overcome the challenges faced in ICU. A potential solution to this limitation is the application of artificial intelligence in development of electronic ICUs to enable monitoring from a central console.

EVOLUTION OF MONITORING SYSTEMS

The monitoring systems have evolved over time, with every new phase integrating more sophisticated approaches such as use of sensors or artificial intelligence in the existing systems. The invasive approaches are largely replaced by minimally- or noninvasive procedures today. Also, instead of overall systemic monitoring, estimating performance output of individual organs is now possible. These advancements gradually led to the development of scoring systems to grade the functioning of physiologic parameters. The evolution of these grading systems is represented in **Figure 4**.

Many advances are also made in patient monitoring systems to consolidate patient information and ensure reliable and secure communication between patient and healthcare providers. Several approaches are already in practice whereas others are currently in different phases of clinical trials that may be implemented in near future. Among these advances, the integrated implementation of Internet of Things (IoT) and cloud computing are most promising technologies to improvise the "smart health" notion in health care by enabling remote monitoring systems. Consequently, the most beneficial aspect of these technologies is the improved accessibility to remote and rural areas, and during home-care of patients.[13]

Prototypes for Intelligent Monitoring

Several prototypes are in the developmental process that can combine patient information from multiple monitoring systems and translate them into practical workflow to prevent communication and manual errors. For instance, telemetry is an automated communication process whereby data is collected remotely and transmitted to receiving equipment for monitoring. An advancement of this prototype is VitalPAD—a mobile/tablet/computer operated prototype, currently under clinical trial, which is predicted to reduce over 22% of preventable errors in ICUs.[14]

Hub and Spoke Model

A more advanced example of artificial intelligence–enabled monitoring prototypes is the Hub and Spoke model that may truly revolutionize critical care of patients. It is an organizational model that is set up at a primary establishment (Hub) and is connected to multiple secondary establishments (Spokes). The aim of this model is to deliver intensive care to all patients in a hub and adjoining spokes and ensure critical management and operational efficiency of extremely ill patients by referring them to hub establishments. The Tata Memorial Centre, India, is among the first few research centers that aim to reach out to approximately 45–50 million cancer patients by setting up over 30 Hub and 100–130 Spoke throughout the country in near future.[15]

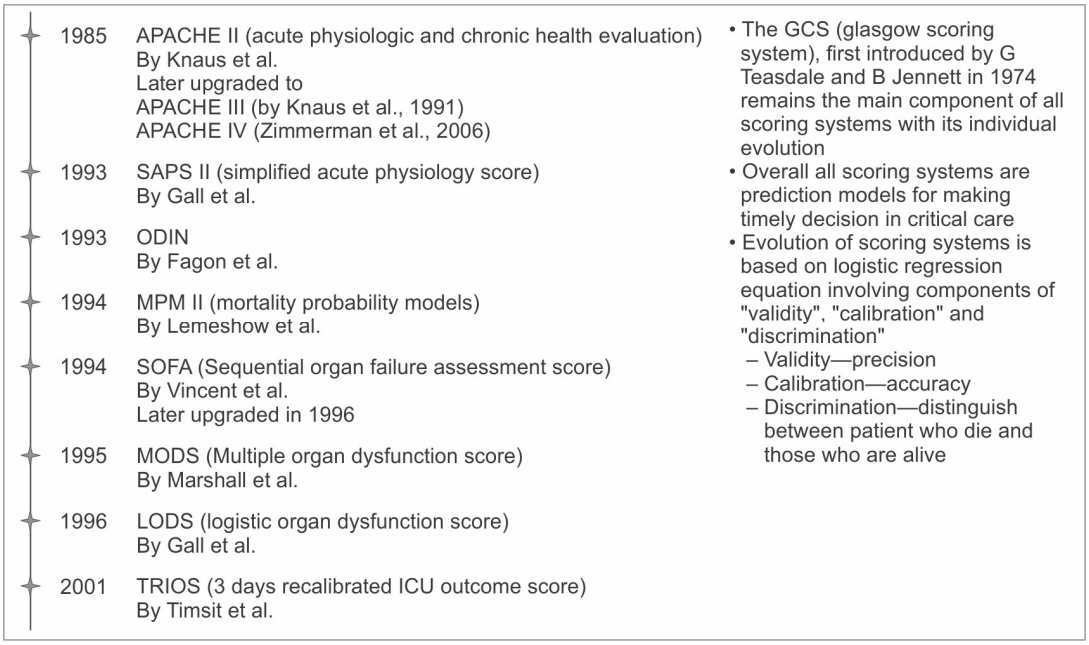


Fig. 4: Timeline of evolution of intensive care unit (ICU) scoring systems.
(GCS: Glasgow Coma Scale)
Source: Pellathy TP, Pinsky MR, Hravnak M. Intensive Care Unit Scoring Systems. Crit Care Nurse. 2021;41(4):54-64.

BEDSIDE MONITORING DURING COVID-19 PANDEMIC

The challenges faced in ICUs were more apparent during the provisional care of coronavirus disease-19 (COVID-19) patients during the recent pandemic. Besides the routine challenges of intensive care, the physical exhaustion and continuous uncertainty of patient outcome further added to the psychological burden of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection leading to situational helplessness of intensivists. The integrated approach based on Hub and Spoke model proved extremely useful when implemented by health providers during the COVID-19 crisis. The efficient management of the above situation was achieved by retaining clinical experts and resources at the hub establishment, while mobilizing the hospital staff and physicians throughout the Spoke centers.

EVOLUTION OF INFUSION PUMPS

During early medical care, the infusion pumps were primarily used for feeding and administering cardiovascular drugs. With the technological breakthrough in the development of electronically erasable programmable read-only memory (EEPROM) in the 1990s, the IV care transformed into "smart pumps." These smart pumps allowed customized programming options to meet the changing needs of different patients during critical care. At the same time they have safety limitations, which can be programmed by hospitals, to prevent infusion in adverse cases. Due to these factors, the scope of IV pumps has been extended in pain management (epidural), anesthesia, and multichannel general-purpose pumps to administer medications and fluids, thus evolving them into therapy-specific device. This evolution has benefitted the health care in:

- Standardization of dosing units based on the monitoring system to prevent variation in infusion practices.
- Setting a drug dose limit.
- Prevention of manual errors.
- Enabled wireless connectivity.

Besides, the smart pumps act as "treasure trove" of infusion data and allow identification of preventable programming errors. However, the artificial smartness of these pumps has various limiting factors such as:

- They cannot be assigned to specific patients.
- They do not prevent mixing of drugs and do not identify incorrect library selection by healthcare staff.
- They do not document infusion records or patient/nurse information.
- They cannot reason for alert overrides.
- Poor communication in real time and poor compliance with Barcode Medication Administration (BCMA).

Thus, significant advances are made during the evolution of infusion systems into smart pumps, but they lack the ability to ensure responsiveness and documentation criteria met through "five rights" of drug, dose, route, patient, and time. Although challenging, these limitations have paved the way toward improvised and advanced programming of smart pumps to further transform them into intelligent infusion systems. In addition to optimizing the infusion practices, the intelligent infusion systems shall overcome the above limitations in near future and enable tracking and reporting of patient status in real time, thereby promoting continuous quality improvement and compliance with the existing BCMA approach.[16,17]

CONCLUSION

In order to focus on patient safety and better outcomes, a robust, smart, easy-to-use portable, and intelligent monitoring system has become an integral part of the ICU. Over the past 5 decades, ICU monitoring has witnessed a full circle from heavy, basic, single-parameter, nonportable gadgets to noninvasive highly portable monitoring systems. Technological progress at rocket speed makes monitoring of the physiology, pathology, and even the tissue microcirculation available at the blink of an eye. A comprehensive and holistic monitoring supplemented by a thorough clinical acumen makes an ICU environment safe and happy. Finally, we as healthcare professionals should not become slaves to technology but rather utilize and interpret data for better interventions and thus patient outcomes.

"It is not the Tool that makes a difference but what the physician makes of the tool that strikes a positive change."

REFERENCES

1. Frey B, Doell C, Klauwer D, Cannizzaro V, Bernet V, Maguire C, et al. The morbidity and mortality conference in pediatric intensive care as a means for improving patient safety. Pediatr Crit Care Med. 2016;17(1):67-72.
2. Farzi S, Irajpour A, Saghaei M, Ravaghi H. Causes of medication errors in intensive care units from the perspective of healthcare professionals. J Res Pharm Pract. 2017;6(3):158-65.
3. Matlakala MC, Bezuidenhout MC, Botha AD. Challenges encountered by critical care unit managers in the large intensive care units. Curationis. 2014;37(1):1146.
4. De Georgia MA, Kaffashi F, Jacono FJ, Loparo KA. Information technology in critical care: review of monitoring and data acquisition systems for patient care and research. Sci World J. 2015;2015:727694.
5. Yang MT. Multimodal neurocritical monitoring. Biomed J. 2020;43(3):226-30.
6. Rhodes A, Waldmann C, Handy J, Soni N (Eds). Oxford Desk Reference: Critical Care, 2nd edition. New York: Oxford University Press; 2019.
7. Rackley CR. Monitoring during mechanical ventilation. Respir Care. 2020;65(6):832-46.

8. Vincent JL, Joosten A, Saugel B. Hemodynamic monitoring and support. Crit Care Med. 2021;49(10):1638-50.
9. Donati A, Tibboel D, Ince C. Towards integrative physiological monitoring of the critically ill: from cardiovascular to microcirculatory and cellular function monitoring at the bedside. Crit Care. 2013;17(Suppl 1):S5.
10. Scorcella C, Damiani E, Domizi R, Pierantozzi S, Tondi S, Carsetti A, et al. MicroDAIMON study: Microcirculatory DAIly MONitoring in critically ill patients: a prospective observational study. Ann Intensive Care. 2018;8(1):64.
11. Smallwood N, Dachsel M. Point-of-care ultrasound (POCUS): unnecessary gadgetry or evidence-based medicine? Clin Med (Lond). 2018;18(3):219-24.
12. Lin JJ, Chen AE, Lin EE, Hsia SH, Chiang MC, Lin KL. Point-of-care ultrasound of optic nerve sheath diameter to detect intracranial pressure in neurocritically ill children: a narrative review. Biomed J. 2020;43(3):231-9.
13. Filho IMB, Aquino G, Malaquias R, Girao G, Melo SRM. An IoT-based healthcare platform for patients in ICU Beds during the COVID-19 outbreak. IEEE Access. 2021;9:27262-77.
14. Flohr L, Beaudry S, Johnson KT, West N, Burns CM, Ansermino JM, et. Clinician-Driven Design of VitalPAD: an intelligent monitoring and communication device to improve patient safety in the intensive care unit. IEEE J Transl Eng Health Med. 2018;6:3000114.
15. Menon N. (2019). Hub and spoke – the future of cancer hospitals in India. [online] Available from: https://docmode.org/hub-and-spoke-the-future-of-cancer-hospitals-in-india/#:~:text=It%20is%20an%20organizational%20model,intensive%20treatment%20to%20the%20hub [Last accessed February, 2022].
16. Vanderveen T. (2014). From smart pumps to intelligent infusion systems – The promise of interoperability. [online] Available from: https://www.psqh.com/analysis/from-smart-pumps-to-intelligent-infusion-systems-the-promise-of-interoperability/ [Last accessed February, 2022].
17. Lehr J, Vitoux RR, Evanovich Zavotsky K, Pontieri-Lewis V, Colineri L. Achieving outcomes with innovative smart pump technology: partnership, planning, and quality improvement. J Nurs Care Qual. 2019;34(1):9-15.

97

CHAPTER

Critical Care Trainees Competencies: How to Map and Maintain?

Subhash Todi

INTRODUCTION

Critical care as a stand-alone specialty is still in the nascent stage when compared to other established medical and surgical specialties. Various diploma, fellowship, and certificate courses are conducted by the Diplomate of National Board (DNB) and Indian Society of Critical Care Medicine (ISCCM). The training period varies from 1 to 3 years based on the basic degree of the candidate. Various syllabi and formats of examination have been suggested for these courses. Recently, an expert group was convened by DNB to formulate a detailed competency-based syllabus for a 3-year DNB program. This chapter will review an important part of this document which is also available at the DrNB website.[1] There are also various international training syllabi by various organizations such as European Society of Critical Care Medicine (ESICM)[2] and American College of Graduate Medical Education (ACGME) which are also of a similar nature.[3]

A structured framework for acquiring professional skill consists of domains, competencies, and aggregated syllabus. Domains consist of broad skill set which need to be acquired during the training period. Competencies are specific skill set within each domain. These competencies may further be acquired through skill sets enumerated in aggregated syllabus, which is classified systematically and within each system should consist of basic and applied anatomy and physiology, pharmacology, clinical examination skills, procedural skills, data interpretation, equipment knowledge, and disease management skills. As critical care is a rapidly advancing science with need of new skill set, changes in previous skill are needed as new evidence accumulates; any training syllabus should be used as a general guide and not as an all-inclusive document. Moreover, as critical care is a broad specialty, all of the knowledge and skill set may not be covered in any syllabus **(Boxes 1 and 2)**.

BOX 1: Domains.

- Resuscitation
- Disease management: Diagnosis/monitoring/supportive care
- Procedure
- Perioperative care
- Transport
- Ethics/end-of-life care/prognostication
- Quality and patient safety
- Administration/clinical governance
- Research/teaching
- Professionalism/communication
- Medicolegal
- Organ donation

BOX 2: Competencies.

- *Resuscitation:*
  - Assess and stabilize patients with shock/respiratory failure/other organ failure
  - Manage rapid response/cardiorespiratory arrest and postarrest care
  - Manage trauma/burn/environmental hazards
  - Disaster management and mass casualty management
  - Triaging
  - *Resuscitation in special situations*: Obstetrics/pediatrics
- *Disease management: Diagnosis/monitoring/supportive care/definitive care:*
  - History-taking
  - Focused physical examination
  - Relevant investigation/imaging
  - Provisional and differential diagnosis
  - Interdepartmental consultation
  - Documentation
  - General monitoring
  - Organ-specific monitoring
  - Hemodynamic support
  - Respiratory support
  - Renal support
  - Nutritional support
  - Neurological support
  - Hematological support
  - Metabolic support
  - Immunological support
  - Physiotherapy
  - Definitive care

Contd…

Contd…

- *Procedures:*
  - Organ-specific procedures
- *Perioperative care:*
  - Perioperative care of high-risk surgical patient
  - Perioperative care in cardiac surgery
  - Perioperative care in neurosurgery
  - Perioperative care in transplant surgery
  - Perioperative care in thoracic surgery
  - Perioperative care in trauma surgery
- *Transport:*
  - Intrahospital transport of high-risk patient
  - Interhospital ground/air transport of high-risk patient
  - Transport of patient with contagious disease
  - Documentation/handover
- *Ethics/end of life/prognostication:*
  - Prognostication scoring systems
  - Withholding and withdrawing life support: Communication
  - Principles of medical ethics
  - Palliative care
  - Empathy toward family and religious belief
- *Quality and patient safety:*
  - Structure, process, and outcome data on quality
  - Root cause analysis of near misses and medical errors
  - Medication safety and adverse drug reaction monitoring
  - Auditing and benchmarking performance
  - Environmental hazards and safety of patient and healthcare staff
  - Infection-control measures
- *Administration/clinical governance:*
  - Human resource/design/equipment/budgeting
  - Conflict resolution
  - Team leader role
  - Critical care outreach team
  - Critical care follow-up clinic
  - Admission and discharge planning
  - Developing ICU policies and protocols
- *Research/teaching:*
  - Plan research project
  - GCP training
  - Critically appraising a research paper
  - Participate in departments teaching/research programs
  - Simulation training
  - Teaching nurse/allied healthcare professional
  - Presentation in scientific meetings
- *Professionalism:*
  - Professional attitude/communication toward patients, family, colleagues
  - Patient care-related documents
  - Respects privacy, confidentiality of patient's data
  - Involves patient and family in decision-making
  - Promotes team management and multidisciplinary care
  - Patient and family centered care
  - Understand principles of reducing cost while maintaining quality
- *Medicolegal:*
  - State and national laws
  - Medical negligence
  - Informed consent
  - Medical indemnity
- *Organ donation*:
  - Certifying brain death
  - Managing organ donor/organ transport

(GCP: good clinical practice; ICU: intensive care unit)

LEARNING OBJECTIVE

Applied Anatomy and Physiology[4]

A knowledge of anatomical landmarks is required for various procedures performed in an intensive care unit (ICU). Few common examples of these are landmarks for anterior triangle of neck for internal jugular venous access, cricothyrotomy, intercostal drain, percutaneous tracheostomy, lumbar puncture, abdominal paracentesis, etc. Areas of applied physiology such as heart–lung interaction, Starling's curve, oxygen/carbon dioxide dissociation curve, cardiac output determinant, ventilation–perfusion mismatch, physiological dead space, right-to-left shunt, and respiratory drive need to be familiar with in order to interpret various pathological states seen in critically ill.

Pharmacology

A knowledge of common drugs used in critical care with their indication, contraindication, and adverse effects need to be known. There are many applications and ready references available for these and should be used at the bedside during daily clinical duties. Various drugs such as vasopressors, inotropes, antiarrhythmics, thrombolytics, crystalloids, colloids, bronchodilators, sedatives, analgesics, neuromuscular blocking agents, and diuretics need to be familiarized.

Clinical Skills[5]

These skills constitute a focused history from the patient or caregivers and focused physical examination. Many a times, these need to be performed in two steps of initial preliminary examination during resuscitation and later in depth when the patient has stabilized. The second step is equally important and sometimes not performed. Many clues about the patient problems emerge only during the later detailed interrogation and examination. The history and examination findings need to be documented in the clinical records. In the high-technology environment of ICU, bedside clinical skills are sometimes forgotten. There are inherent limitations of any technology and they are prone to error and clinical observations may be able to detect these. Moreover, initial clinical examination will also allow for a judicious ordering of tests and procedures which are relevant to patient care. History taking in the ICU many a times need to be taken from family members and other caregivers and should include patient's level of activity and preferences. This will help in making an informed decision regarding the intensity of treatment. Common pitfalls which a trainee should be cognizant about while performing clinical examination are not examining the patient fully due to time constraint or missing a new finding which is not expected; failure to inspect wounds, catheter sites, or recently done dressings; failure to inspect urine color, secretions, and

drained fluids; and not performing fundoscopy, rectal, or pelvic examination where indicated. These are equally applicable regardless of the resources available, as many a times false-positive laboratory or imaging results may lead to inappropriate therapeutic measures.

Practical Skills (Procedures)

Various procedures need to be performed under supervision initially and then unsupervised during the training period. Skills need to be acquired both from conventional anatomical landmark and from ultrasound-guided procedures. A log book needs to be maintained mentioning complications whenever they occur. This log book needs to be countersigned by the supervisor. Once the candidate has acquired sufficient skills to perform the procedure unsupervised, he/she can undertake training of new trainees. Usually, 20–30 procedures need to be done supervised and similar number unsupervised to get an adequate competency. Many institutions will grant privileges for performing these procedures once they are satisfied with the trainee's performance. Important practical skills that need to be acquired include adequate cardiopulmonary resuscitation, airway management skills, central line insertions, temporary pacing, intercostal drain insertion, and at an advanced stage of training, performing a percutaneous tracheostomy.

Use of Equipment

A basic knowledge of various equipment used in the ICU with familiarity of their operational aspects should be developed during the training period. Troubleshooting of important malfunctions should be acquired as many a times, these can happen unexpectedly without any backup support. The important equipment include defibrillators, ventilators, temporary pacemaker, transducers, syringe pump, pressure bags, heat and moisture exchanger (HME) filters, humidifiers, ventilator circuit, suctioning devices, blood warmers, advanced hemodynamic monitors, etc.

Data Interpretation

Intensive care is a data-driven environment, with multiple data acquired continuously by various monitors, laboratory reports, and imaging. It is imperative that a judicious use of these data on the background of a clinical context should be acquired during the training period. These data are also an important part of OSCE (Objective Structured Clinical Examination) in various assessment examinations. These data could be of biochemistry, hematology, coagulation, hepatic, renal, or any other organ system. These could also be related to imaging data, various ventilatory waveforms, or hemodynamic waveforms. During the training period, different sets of data patterns, images, and waveforms related to important clinical presentations should be recognized.

Management Skills

After initial resuscitation, critically ill patients essentially require supportive management which includes organ-specific and disease-specific management. This is usually done in collaboration with specialty consultants. Familiarity with various organ-supportive therapies, such as dialysis, mechanical ventilation, hemodynamic support, and intracranial pressure management, should be acquired during the training period. Acute cardiopulmonary emergencies such as pulmonary embolism, aortic dissection, hypertensive emergencies, and pericardial tamponade need to be managed during the training period. Disease- or syndrome-specific management such as management of acute heart failure, acute coronary syndrome, arrhythmias, chronic obstructive pulmonary disease (COPD) exacerbation, acute asthma, acute respiratory distress syndrome (ARDS), and acute liver failure also needs to be learnt during the training period.

Environmental Hazard/Trauma/Burns/ Perioperative/Transplantation/Inter- and Intrahospital Transport

Working knowledge of miscellaneous subjects, separate from the mainstream systems, needs to be familiarized with during the training period. Management of polytrauma including being a productive member of the trauma team needs to be learnt. Management of various drug overdoses, especially the common ones such as organophosphorus, benzodiazepines, and calcium channel blocker, needs to be familiarized with. Temperature-related injuries such as burns, inhalation injury, and hypo- and hyperthermia need to be managed. Envenomation, electrical hazards, radiation hazard, near-drowning, and partial hanging are some of the important environmental hazards that need to be familiarized with during the training period. Organ transplantation-related issues such as brain death certification, management of brain-dead organ donor, and familiarity of transplant immunology are imperative for imbibing broader critical care skills.

Nonclinical Skills

Use of computers, electronic medical record and other communication, and data recording technology need to be familiarized with. Basics of clinical governance which include education, periodic audit, quality improvement program, and risk management should be learnt.

The principles of research in intensive care, study design, biostatistics, grant funding, protocol writing, and manuscript writing are fundamental to furthering one's career in academic institutions. The ethical and legal aspects of critical care medicine such as withholding or withdrawal of therapy, major ethical principles, living will, durable

power of attorney, and Indian laws pertaining to critical care need to be familiarized with. As a trainee needs to be groomed as a future consultant, the basics of administrative and management skills need to be learnt. These include design of ICU, budgeting, resource allocation, manpower requirement, capital expenditure processing, developing clinical practice guidelines, and discussion with hospital administrators.

Courses/Workshops

Structured courses such as Comprehensive Critical Care Courses (4C, ISCCM), Fundamental Critical Care Support, Society for Critical Care Medicine (FCCS, SCCM), Advanced Trauma Life Support (ATLS), Advanced Cardiac Life Support (ACLS), Advanced Pediatric Life Support (PALS) are didactic and hands-on workshop should be attended by the trainees. During the initial period of training, they should attend the provider course and later, they should be competent to take the instructor course and be certified as an instructor in these courses. Many of these courses are available online, but hands-on skills can only be obtained by in-person training program. In future, a hybrid mode may be feasible with didactic lectures to be taken online and only hands-on workstations and discussion to be taken in person. Some of the courses provided by international organizations are expensive, and similar indigenous structured courses are also available for trainees. Focused workshops such as airway and hemodynamic monitoring and mechanical ventilation may also be helpful to get specific knowledge in these areas. Apart from these core workshops, the trainees are encouraged to attend specialized workshops during the advanced training period, such as echocardiography/ultrasonography, simulation, extracorporeal membrane oxygenation (ECMO), bronchoscopy, research methodology, and subspecialty workshops such as critical care neurology, obstetrics, and renal replacement therapy. These will broaden the knowledge areas of the trainees. They might choose the workshops in which they want to subspecialize after their training period. They should also maintain the skills acquired in these workshops by periodically attending these in various forums. A successful completion certificate of these courses needs to be logged in the trainee folder.

REFERENCES

1. DrNB—Critical Care Medicine. 2021. Guidelines for competency based training program. [online] Available from: https://nbe.edu.in/mainpdf/curriculum/DrNB%20-%20Critical%20care%20Medicine%202021.pdf [Last accessed February, 2022].
2. European Society of Intensive Care Medicine. Competency-based training in intensive care medicine in Europe (CoBaTrICE). [online] Available from: http://www.cobatrice.org/Data/ModuleGestionDeContenu/PagesGenerees/en/03-Syllabus/19.asp [Last accessed February, 2022].
3. ACGME Program Requirements for Graduate Medical Education in Critical Care Medicine. https://www.acgme.org.
4. Pinsky MR, Brochard L, Mancebo J (Eds). Applied Physiology in Intensive Care Medicine, 1st edition. New York: Springer; 2006.
5. Dankl D, Dünser MW, Mer M, Petros S (Eds). Clinical Examination Skills in the Adult Critically Ill Patient, 1st edition. New York: Springer; 2018.

98

CHAPTER

How to Improve Compliance to Protocols in Intensive Care Unit?

Arvind Baronia, Gautham Raju, Nitin Rai

INTRODUCTION

Quality control is the intrinsic component of any large dynamic organization or establishment. Worldwide, the importance of quality-improvement strategies [e.g., Total Quality Management (TQM), USA] was recognized from the early part of the 20th century. This momentum was largely attributed to USA, Europe, and Japan.

Total quality management pioneered in the USA focused on "process improvement." This was extended in "statistical quality control" (SQC) tools to optimize quality, performance, and the leadership governing the same organizations. Currently, quality controls and processes are being standardized across different industries starting from manufacturing industry to service sector, especially healthcare services.

RELEVANCE IN HEALTH CARE

A landmark report "To Err is Human: Building a Safer Health System" on healthcare issues was published by the Institute of Medicine (IOM), of the National Academy of Sciences, Engineering, and Medicine, in 1999. The report documented gaps between the established medical knowledge and practices, discrepancies in effective utilization of available tools, and possible adverse events and errors, and their impact on public health in the USA.[1] It reiterated the use of three components of quality care described by Avedis Donabedian, i.e., structure, process, and outcome—a framework when addressed individually sought to manage and control quality in health care with the help of specific tools.[2] The IOM refined Donabedian described attributes into six aims: (1) safety, (2) effectiveness, (3) patient-centeredness, (4) timeliness, (5) efficiency, and (6) equity.[3]

Healthcare protocols have been designed to apply the aforementioned factors and bring about changes in behaviors of healthcare givers, process control being one of the main aspects of quality control, specially so in intensive care unit (ICU) settings.

QUALITY CONTROL IN INTENSIVE CARE UNIT

Intensive care unit quality improvements require specific tools for specific areas. Several quality indicators (QIs) have been designed for application and evaluation. Capture of data, comparison, collation, and disclosure of various metrics by everyone involved in the ICU are necessary for continuous performance appraisal and improvement.

Several international societies review the relevant QIs and revalidate them based on ever-changing scientific evidence, tools, and techniques available and recommend their application (QI) by consensus to ensure delivery of high-quality health care and minimize human error/shortcomings.

The Society of Critical Care Medicine (SCCM) advocates a systematic and stepwise approach to QI while engaging inter- and intradisciplinary teamwork and fostering proactive leadership. The European Society of Intensive Care Medicine (ESICM) task force for quality and safety proposed nine indicators for measurement and improvement performance in any ICU across the world. The nine indicators included three regarding ICU structure, two process related, and four outcome measures.[4]

The main goal is to provide safe, reliable, and efficient health care with specific focus on ICU.

Efforts have been made by several researchers to identify key elements specific to each of the three components described by Avedis Donabedian:

1. Structure
2. Process
3. Outcome.

Intensive care unit protocol compliance can be elaborated based on the above three components as given in the following text.

Structure

Structure-related components in health care involve the metrics that provide an overview of the provider (hospitals or institutions) with respect to infrastructure, processes, and

capacity to provide high-quality care. General guidelines on minimum standards are available in every country. In India, it is governed by The Clinical Establishments (Registration and Regulation) Act, 2010 which prescribes minimum standards for facilities and services of healthcare establishments in general. The Indian Society of Critical Care Medicine (ISCCM) specifies the same for ICU design and function. The ISCCM has issued guidelines based on international best practices.

At the institutional level, quality management system can be incorporated and standards from the International Standards Organization such as ISO 9000 series, can be adapted to a healthcare facility. It promotes focus on the patient. Adhering to such standards is beneficial as it entails the following: gains efficiency, reduces cost, provides for improvements in quality and reliability, and increases potential for regulatory support from accrediting agencies such as Joint Commission on Accreditation of Healthcare Organizations (JCAHO) on the international level and National Accreditation Board for Hospitals and Healthcare Providers (NABH) at the national level.

The NABH specifically provides for evaluations in standards and objective elements with respect to the following. It can be applied to institution in general as well as ICU systems.[5]

- *Organization-centric standards*:
  - Continuous quality improvement
  - Responsibility of management
  - Facility management and safety
  - Human resource management
  - Information management system. For example, EMR (emergency medical response)/pager/message/alert—critical events alert.

  Among the above, human resources management commands special attention. ICU staffing with dedicated ICU consultant and adequate staffing with respect to doctors and a high nurse-to-patient ratio has been associated with improved mortality, morbidity, and other composite outcomes in ICU patients.[6] Currently, staffing and specialist availability in India remains constrained with a high degree of heterogeneity in staffing numbers in ICUs across the country.
- *Patient-centric standards*: Patient-centric standards include patient care, assessment, and continuity of care while ensuring compliance to prescribed protocols, medication management, patient rights and education, and hospital infection control.

  The ISCCM also advocates setting up of local and national databases and performance evaluation and optimization of individual institutions along with creating a database for specialized units looking at a specific subset of patients.[7] Quality improvement and compliance to related processes can be enhanced by application of core tools such as Plan-Do-Check-Act cycle.[8]

Compared to the structural component, process and outcome measures are amenable for better objective evaluation in terms of execution of protocols or failure of the same by using standards, guidelines, and/or indicators.[9]

Process and Outcomes

Process and outcome measures are evaluated by various QIs laid out by national and international bodies. The most important indicators as per international consensus are as follows:[4]

- *Infection-related QIs:*
  - Ventilator-associated events (VAEs)
  - Central line-associated blood stream infection (CLABSI)
  - Catheter-associated urinary tract infection (CAUTI)
- *Mortality indicators*: Standard mortality ratio (SMR)
- *Morbidity indicators*:
  - Unplanned extubations
  - Extubation failures (reintubation within 48 hours).

There are other outcome measures for which benchmarks and standards have been proposed by the ISCCM. Studies on adherence to protocols and processes with regard to ICU quality are scarce in India due to challenges in data availability. In a study conducted by Kartik et al., it was noted that in India, the ICU's average overall compliance to ICU protocols was about 70–85% with respect to human resources, infection control, and quality and policy issues.[10]

CHALLENGES TO IMPLEMENTATION

Despite established frameworks to follow and maintain quality, there remains a constant challenge to maintain the consistency of standard practices among healthcare workers. It can happen due to certain factors as follows:[11]

- Protocol misalignment
- Impact misattribution.

"*Protocol misalignment* is a mismatch between the context in which a protocol is developed and the context in which it is implemented." For example, a certain protocol developed as best practice methods assumes homogeneity in knowledge and competence of the personnel involved in application. If the protocol is too far demanding or too less in relation to the physician who applies at the bedside, it may lead to excessive pressure leading to unsafe practices or dilution of the existing good standards, respectively.

"*Impact misattribution* is a mismatch between the proposed versus actual reasons offered to explain how a protocol resulted in improved outcome." For example, application of evidence which is proven for specific aspects of certain disease processes misattributed to

general ICU population and inadvertent extrapolation to all patients. Such "misalignment" or "misattribution" can equally occur with guidelines, checklists, or protocols.[4,11]

To overcome this, the process of quality improvement is approached with core elements of the Plan-Do-Study-Act (PDSA) cycle:[12]

- *Defining quality*: Standards, guidelines, protocols, outcomes defined and measured against established standards.
- *Measuring quality*: Measuring quality includes data capture, monitoring, and audits. Frequency of monitoring and measurements can range from daily, weekly, monthly, quarterly or yearly depending on the component being measured. Compliance with process of care standards needs frequent measurements whereas outcome measures may need less-frequent measurements.

  Monitoring strategies:
  - Observations may be done by physicians, nursing staff, and other healthcare workers.
  - Data-collection tools may be combined with checklists and specially designed questionnaires.
  - Among such tools, checklists have been among the forefront. Daily checklist usage has been proven to improve compliance with wide range of ICU protocols and evidence-based best clinical practices.[13]

  Data collection and trend analysis:
  - *Measurement and review of data*: It is of great importance that the captured data regarding both clinical indicators [ventilator-associated pneumonia (VAP), CLABSI, etc.] and managerial indicators (waiting time, discharge time, cost estimates, percentage of satisfactory feedback, etc.) is reviewed, and the ICU unit collates and manages relevant statistical information on a timely basis.

  Trends across time as compared with updated standards and benchmarks can indicate whether quality improvement measures in the unit or institution perform as expected. Further upgrading or due diligence is performed as necessary.

  For example, in infection control, implementation of care bundles is captured as trendlines and compared against the International Nosocomial Infection Control Consortium (INICC) benchmarks.

  Flowcharts and dashboards: With regular capture of data and trend monitoring, the ongoing resultant analysis can be illustrated on a dashboard shared between individuals, units, and the healthcare establishment giving a clear idea of status and success in application of quality-control tools.

Improving Outcomes

A systematic review of strategies to improve implementation of care bundles found that the three most important strategies used to improve compliance were education, reminders and audit, and feedback.[14]

1. *Education*:
   - *Credentialing and privileging:*

     Credentialing: It means establishing qualifications of all the ICU personnel to entrust appropriate position and responsibilities. It also includes certification, education and training, and primary source verification as appropriate.[15]

     Privileging: ICU personnel are granted privilege/authority to deliver certain services according to their credentials or experience/expertise. For example, junior residents are allowed to take history and postgraduates are authorized to perform specific procedures. Periodic additional training and upgradation are done.
   - *Reminders and audit*: Unit handovers, reminders, and audits are followed across a large number of ICUs; however, the consistency and regularity are heterogenous.

   It is recognized that careful handovers and reminders about critical issues can mitigate oversight and patient complications.[16]

   Systematic communication and documentation during ICU stay and after discharge remain a challenge. To address this, the National Institute for Health and Care Excellence (NICE) published "Clinical Guideline 50" which give a framework for "a structured handover of care" along with a written plan, including a summary of the critical care stay, plans for ongoing treatment, and any specific needs identified.[17]

   Audits: Regular checklist-based audits, pre- and postinterventions/process review, and regular reminders using interpersonal and online tools improve compliance to various bundles/protocols despite the workload and stress in the ICU environment.[18]
2. *Feedback*: The mental and physical challenges innate with working in ICUs necessitate proactive communication among team members with periodic breaks to step back and reassess the situation. Factors that can help are as follows:
   - *Empathy, endorsement, and encouragement*: At any given point of time, ICU involves healthcare personnel with different levels of training, experience, expertise, and competence. This can place a significant strain on optimal human resource utilization unless there are proactive attempts to address such issues empathetically to minimize loss of interest/attrition of valuable human resources.

- *Rewarding and recognition of compliance*:
  Incentivizing efforts: The World Health Organization (WHO) recommends financial and nonfinancial incentives to recognize and appreciate consistency in adherence to protocols. It is to encourage, enable, and motivate healthcare personnel to inculcate and sustain a diligent approach to clinical care.

OTHER TOOLS TO IMPROVE COMPLIANCE

Other tools to improve compliance are given in the following text.

Patient-safety Best Practices

There are methods and practices outside the boundaries of regulatory requirements which may have impact on ICU care and compliance and consequent successful improvements in clinical outcomes.

- *Teamwork:*
  Teamwork in ICU—ICU being a critical environment, best practices can be adapted from other critical and high-risk fields such as military and airline industry with regard to teamwork.
  The Agency for Healthcare Research and Quality (AHRQ) in collaboration with US military developed "Team Strategies and Tools to Enhance Performance and Patient Safety (TeamSTEPPS)" to enhance teamwork and collaboration in identifying, interacting, assessing, and delivery various processes and outcome measures.[19]
  It focusses on team leadership, situation monitoring, mutual support, and communication and was found that it improved teamwork, compliance, and patient safety metrics.
- *Simulation*: Simulation in health care is a promising tool to improve patient safety.[20] It enables trainees to engage in near-realistic patient environment and hone their skills, knowledge, and responsiveness with regard to clinical assessment, procedures, communication, and teamwork in critical situations. It has been inculcated in medical curriculum to retrain and revalidate. Simulator-based teaching may help bridge gaps in upskilling healthcare personnel in real-life scenarios or clinical situations which may be uncommon, widely spaced/unavailable, or relatively unsafe to be independently performed.
- *Telemedicine*: In India, 24-hour presence is seen only in 37% of our ICUs due to lack of trained specialists.[10] Lack of trained specialists at many places may be bridged by bringing expert assistance remotely through telemedicine. The current coronavirus disease-19 (COVID-19) situation has brought audiovisual communication to the forefront which can be leveraged in ICUs to ensure quality of care and compliance to protocols.
- *Review and research:* An important aspect of any ICU, especially those involving critical processes with significant implications on the health, is to do a thorough review and research. The Japanese Principle of "Kaizen" or "continuous improvement" should be intrinsic and applied to all aspects of ICU management to ensure that benchmarks and standards continuously evolve for the better.

SUMMARY

- ICU is one of the most important areas in the hospital where quality-control measures and their continuous evaluation are crucial in ensuring patient safety and help improve outcomes.
- Quality improvement depends on continuous evaluation of performance metrics. It includes close monitoring and improvement of "processes," both existing and new, to improve patient outcomes and overall clinical care.
- The Institute for Healthcare Improvement (IHI) introduced care bundles to provide clear direction to guide quality control.
- Care bundles are designed around specific elements of patient care and consist of three to five key interventions or elements and have been observed to improve outcomes.[8]
- Performance of QIs and their compliance can be promoted by education, reminder and audits, feedback and reward, teamwork, simulation-based training and revalidation, and adopting telemedicine tools.
- Regular research and review of all quality-control measures across each of the components of structure, process, and outcome will ensure better clinical outcomes in hospital in general and ICU in particular.

REFERENCES

1. Kohn LT, Corrigan JM, Donaldson MS (Eds). Committee on Quality of Health Care in America, Institute of Medicine: To Err Is Human: Building a Safer Health System. Washington, DC: National Academies; 2000.
2. Donabedian A (Ed). Aspects of Medical Care Administration: Specifying Requirements for Health Care. Cambridge, MA: Harvard University Press; 1973.
3. Committee on Quality of Health Care in America, Institute of Medicine. Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, DC: National Academies Press; 2001.
4. Rhodes A, Moreno RP, Azoulay E, Capuzzo M, Chiche JD, Eddleston J, et al. Prospectively defined indicators to improve the safety and quality of care for critically ill patients: a report from the Task Force on Safety and Quality of the European Society of Intensive Care Medicine (ESICM). Intensive Care Med. 2012;38(4):598-605.

5. National Accreditation Board for Hospitals and Healthcare Providers. (2020). Hospital accreditation program. General information brochure. [online] Available from https://www.nabh.co/Images/PDF/nabh_gib_hos.pdf [Last accessed February, 2022].
6. Pronovost P, Thompson DA, Holzmueller CG, Dorman T, Morlock LL. Impact of the Leapfrog Group's intensive care unit physician staffing standard. J Crit Care. 2007;22(2):89-96.
7. Ray B, Samaddar DP, Todi SK, Ramakrishnan N, John G, Ramasubban S. Quality indicators for ICU: ISCCM guidelines for ICUs in India. Indian J Crit Care Med. 2009;13(4):173-206.
8. Institute for Healthcare Improvement Model for Quality Improvement. In: Langley GJ, Moen RD, Nolan KM, Nolan TW, Norman CL, Provost LP (Eds). The Improvement Guide: A Practical Approach to Enhancing Organizational Performance, 2nd edition. San Francisco: Jossey-Bass; 1996.
9. Curtis JR, Cook DJ, Wall RJ, Angus DC, Bion J, Kacmarek R, et al. Intensive care unit quality improvement: a "how-to" guide for the interdisciplinary team. Crit Care Med. 2006;34(1):211-8.
10. Kartik M, Gopal PB, Amte R. Quality indicators compliance survey in Indian intensive care units. Indian J Crit Care Med. 2017;21:187-91.
11. Kavanagh BP, Nurok M. Standardized Intensive Care. Protocol Misalignment and Impact Misattribution. Am J Respir Crit Care Med. 2016;193(1):17-22.
12. United States Agency International Development. (2006). Technical Manual: An Introduction to the Field of Quality Improvement in Health Care: Applications in Central Asia. [online] Available from https://pdf.usaid.gov/pdf_docs/Pnadg932.pdf [Last accessed February, 2022].
13. Byrnes MC, Schuerer DJE, Schallom ME, Sona CS, Mazuski JE, Taylor BE, et al. Implementation of a mandatory checklist of protocols and objectives improves compliance with a wide range of evidence-based intensive care unit practices. Crit Care Med. 2009;37(10):2775-81.
14. Borgert MJ, Goossens A, Dongelmans DA. What are effective strategies for the implementation of care bundles on ICUs: a systematic review. Implement Sci. 2015;10:119.
15. Healthcare Quality Improvement Act 42 USC 11101. 1986.
16. Metnitz PGH, Fieux F, Jordan B, Lang T, Moreno R, Le Gall JR. Critically ill patients readmitted to intensive care units—lessons to learn? Intensive Care Med. 2003;29(2):241-8.
17. National Institute for Health and Clinical Excellence. (2007). Acutely ill patients in hospital. Recognition of and response to acute illness in adults in hospital. [online] Available from: https://www.nice.org.uk/guidance/cg50/evidence/full-guideline-pdf-195219037 [Last accessed February, 2022].
18. Al-Harthy A, Mady AF, Rana MA, Al-Etreby W, Asaad T, Al-zayer W, et. al. Complete audit cycle: CLABSI bundle compliance in ICU. Int J Health Sci Res. 2015;5(2):70-4.
19. Mayer CM, Cluff L, Lin WT, Willis TS, Stafford RE, Williams C, et al. Evaluating efforts to optimize TeamSTEPPS implementation in surgical and pediatric intensive care units. Jt Comm J Qual Patient Saf. 2011;37(8):365-74.
20. Nishisaki A, Keren R, Nadkarni V. Does simulation improve patient safety? Self-efficacy, competence, operational performance, and patient safety. Anesthesiol Clin. 2007;25(2):225-36.

CHAPTER 99

Trigger Tools in Intensive Care Unit

Himanshu Pandya, Pradip Bhattacharya, Samir Patel, Jay Prakash

INTRODUCTION

In the intensive care unit (ICU), trigger tools are methods of identifying and recording patient harm through a systematic record review process on a randomly selected group of medical records employing triggers as patient harm flags. Trigger tools are a simple, cost-effective methodology for identifying, quantifying, and recording patient harm in order to enhance the quality and safety of patient care services in hospitals and general practices. The goal is not just to count the number of harms, but also to figure out what is causing them so that steps may be carried out to reduce the risk of harm and improve patient care. As a result, this method generally finds the more prevalent day-to-day "harms" that have an impact on patient care but do not meet the reporting threshold.

Jick established the concept of a "trigger" or "hint" to detect adverse events in the medical records in 1974.[1] Later, Classen upgraded the approach by employing electronic triggers within hospital information system to identify and review the records for adverse events.[2] The Institute for Healthcare Improvement (IHI) first introduced the use of triggers with manual record reviews in 1999 to detect only adverse drug events (ADEs). Patients in intensive care units are at a greater risk of experiencing adverse events and errors, thus IHI developed the IDMS (Idealized Design of Medication System) group to build a safer and more cost-effective medication system.[3] They are also exposed to a wide range of drugs, procedures, and healthcare professionals. Adverse events are associated with poor prognosis, including an increased risk of death. The most commonly used adverse event detection tool is adverse event reporting; however, it should be supplemented with other tools such as trigger tools, chart review, and direct observation. However, despite the fact that adverse event reporting is critical for the continuous quality improvement process and is associated to an improved safety culture, it is underutilized.

An adverse drug event is defined as follows by the World Health Organization's (WHO) Collaborating Centers for International Drug Monitoring: *"Noxious and unintended and occurs at doses used in man for prophylaxis, diagnosis, therapy, or modification of physiologic functions."*[4] The following is the harm definition used in the IHI Global Trigger Tool: *unintended physical injury resulting from or contributed to by medical care that requires additional monitoring, treatment, or hospitalization, or that result in death.*[3] For example, a patient is prescribed anticoagulation who subsequently suffered a stroke due to intracerebral hemorrhage would be considered as an adverse event.

The trigger tool was first used to detect medication-related adverse events via computerized linkage to pharmacy records. The pharmacy record was searched for specific "triggers" that may be connected to the medical data. When the chart was examined, the concurrent nature of the review allowed for prompt identification of potential or actual adverse effects such as an allergic reaction. The targeted evaluation allows for the examination of a large number of charts in a short period of time. Based on this technique, the IHI developed a manual "low-tech" trigger review based on focused and efficient retrospective chart review, which became fundamental components of the Trigger Tool methodology, as described by Classen et al.[2]

Unanticipated event in the ICU is the event which is generally not expected to occur during illness are also included in the ICU trigger tool. Because numerous factors influence the rate of ADEs in the ICU, ICU rates range from 5.1 to 87.5 ADE/1,000 patient-days.[5] Adverse event rate is calculated (exposure adjusted) by the number of subjects exposed to the drug and experiencing a certain event divided by total exposure time of all subjects who are at risk for the event. For example, out of 100 patients who are on tablet levofloxacin, how many develop seizure. A study conducted in the USA revealed heterogeneity in the literature, owing to methodological discrepancies in the definition of adverse event and detection methodologies.[6]

Most of the institute's data on ADE come from voluntary case reporting; however, underreporting is a major drawback.[7,8] Another approach is patient chart review or medical record review, which is considered more credible because it involves skilled medical experts scanning medical record data in depth and comprehensively. Examining the files by picking signals that could indicate the existence of ADE, as in the "Trigger Tool,"[9] is an alternative to this procedure. This method was established by the IHI, in which reviewers analyze charts retrospectively utilizing cues to change the risk of harm. Thus, the trigger tool is a simple approach for identifying ADEs and calculating their rates of occurrence. The main benefit is that it does not necessitate a lot of technology or financial resources.[3]

DEVELOPMENT OF INTENSIVE CARE UNIT ADVERSE EVENT TRIGGER TOOL

The goal of developing an ICU adverse event trigger tool is to look for potentially detrimental occurrences in the ICU from the patient's perspective. Adverse events might occur because of a medical error or consequences that have an undesirable outcome. The tool's main goal is to identify harm and reduce it in the ICU over time, either through prevention, mitigation, or simply by bringing the issues to light.

The IHI Global tool adapts classification from NCC MERP (National Coordinating Council for Medication Error Reporting and Prevention) comprising categories from A to I.

Accordingly, the following categories are excluded from the tool because these describe errors that do not cause harm.

- *Category A*: Circumstances or events that have the potential to lead to errors.
- *Category B*: An error that was not communicated to the patient.
- *Category C*: An error that reached the patient but did not hurt them.
- *Category D*: An error that reached the patient and necessitated further monitoring or intervention to ensure that the patient was not harmed.

Therefore, following categories are included in the tool which is resulting in harm to patients.

- *Category E*: The patient suffered temporary injury that necessitated action.
- *Category F*: Temporary harm to the patient that necessitates readmission to the ICU or prolongs hospitalization
- *Category G*: Permanent patient harm.
- *Category H*: Intervention is required to keep a person alive.
- *Category I*: Patient mortality.

The ICU adverse event trigger tool consists of the following components:

- Validity of triggers and methods used to identify triggers
- Patient record review selection process
- Techniques for reviewing patient records and training recommendations
- Rules and standards
- A training aid based on a case study
- Worksheet for the trigger tool.

Over 86 institutions and >3,000 patient record reviews have established a rich base for triggers to find ADEs. The ICU triggers were developed from the input of experienced critical care physicians. The ICU adverse event trigger tool provides "clues" to possible underlying adverse events. If triggers are positive, then patient's record is reviewed to establish presence of actual events. For example, drug trigger such as vitamin K is found in medication administration record, then review the laboratory value section to find laboratory trigger.

Patient records are randomly selected. It is recommended to review 10 patient records who are in ICU for at least 2 days every 2 weeks.

Two trained individuals should each review all 10 randomly selected records as per your local institution rules. Set 20-minute limit to review each patient record and "20-minute rule" applies to any record regardless of its size. Initially it might be difficult to review entire record within 20 minutes but it is important to note that Trigger Tool methodology is not meant to identify every single adverse event. The only area of the patient record that needs detail review is ICU course unless an event started in the unit and ultimate harm to the patient occurred outside of the unit.

The discharge summary and coding section should be read completely as it gives the outline of care. The first group of triggers can quickly review by looking at the laboratory values followed by physician medication orders and finally radiology and procedure notes. If any time remaining within 20-minute time limit, nursing notes can be reviewed. Physician or consultation notes are usually not reviewed.

All the information on findings while reviewing the patient records should be documented by reviewers using the ICU Adverse Event Trigger Tool Worksheet, which lists all ICU triggers.[3] For each trigger identified in the record, specific area of the record should be examined. For example, if the trigger "hypoglycemia" is identified on a given date and time, go to that date on the record and see if there is any evidence of a harmful event. If none, stop that trigger. If the trigger is positive, then identify the level of harm on the worksheet using categories from E to I.

Training

The physician and the primary record reviewers should be trained as a team. The training should ideally be conducted by someone who is familiar with the tool. If that is not possible, the next best choice is to follow these guidelines as precisely as possible and ask questions in the IHI discussion

groups, especially if the adverse event rates are significantly higher or lower than those reported in other hospitals. All patient records should be reviewed by both trainers and trainees during training. The trainer will be able to answer queries and ensure that the process is standardized because of this. If there are more than two reviewers, staggering the assignments for specific reviewers, such as alternating who reviews each month, may be advantageous.

For reviewer training, IHI provides five sample patient records. These training records should be used for the first part of training. The sample records were chosen with care to emphasize crucial issues. Each of the primary reviewers, as well as the physician, should go over all of the training records. Trainers will have already evaluated these records, but they should brush up on their knowledge of the material. During training, the "20-minute rule" should not be used so that reviewers may focus on understanding the process without feeling rushed. Schedule a debriefing session for all trainees and trainers to go through the findings and the main points from each of the sample records.[3]

When choosing primary reviewers (experienced nurses, pharmacists, or others) and physician reviewers, look for people who can complete the reviews on a regular basis. All patient records should be reviewed by both trainers and trainees during training. The trainer will be able to answer queries and ensure that the process is standardized because of this. If there are more than two reviewers, staggering the assignments for specific reviewers, such as alternating who reviews each month, may be advantageous.

For reviewer training, IHI provides five sample patient records. These training records should be used for the first part of training. The sample records were chosen with care to emphasize crucial issues. Each of the primary reviewers, as well as the physician, should go over all of the training records. Trainers will have already evaluated these records, but they should brush up on their knowledge of the material. During training, the "20-minute rule" should not be used so that reviewers may focus on understanding the process without feeling rushed. Schedule a debriefing session for all trainees and trainers to go through the findings and the main points from each of the sample records.[3]

When choosing primary reviewers (experienced nurses, pharmacists, or others) and physician reviewers, look for people who can complete the reviews on a regular basis for at least 1 year. Identify who will oversee each phase in the process. Identify a resource/time in the information or medical records department to "randomly" locate the required number of discharged patients' records (making sure deaths are also included as possible record pulls). Identify a meeting location for the review team to conduct the record review. Ascertain that this area has a secure storage location for the records. Wait until the team has collected at least 12 data points before drawing conclusions from the record review rates. Have a defined mechanism for releasing the information after a team has created a number of appropriate data points.[3]

Training Example

A 54-year-old male admitted for microvascular decompression surgery for refractory trigeminal neuralgia.

Reviewer found abrupt drop in hemoglobin level postoperatively as a trigger. In this event, it was found that venous sinus was accidentally punctured leading to massive blood loss and need for ICU admission due to unstable hemodynamics, transfusion of multiple blood products, and prolong hospital stay. This harm is category F.

Learning point in any complication during surgery is always an adverse event even though it is a known complication.

Important standards for ICU adverse event are as follows:

- Overdosing on purpose is not a side effect.
- Events that occurred outside of the ICU were only counted if they began while the patient was in the ICU.
- Treatment complications are referred to as adverse events.
- Death should not be regarded an event unless it was caused by a process that was not part of a regular biologic process.
- Arrhythmias that do not cause harm should not be regarded events.

Multiple triggers may be linked to a single event; however, the Trigger Tool only counts one event for evaluating ADEs. For example, ICU patient developing hypotension may be due to myocardial dysfunction, acute kidney injury, and multiorgan dysfunction leading to death.

HOW TO IMPROVE?

The Model for Improvement is the framework that IHI utilizes to lead improvement efforts. Associates in process established the Model for Improvement, which is a simple yet effective instrument for accelerating improvement. This model is not meant to replace existing change models; rather, it is aimed to help organizations develop faster. The principles of the Model for Improvement and employing Plan-Do-Study-Act (PDSA) cycles to test improvements on a small scale are: It consists of forming the team, setting aims, and establishing measures. The team will select a change which results in improvement and implement it.[3]

CONCLUSION

In summary, ICU adverse event trigger tool is very useful tool to identify adverse events and harm to the patient. It provides insight into quality of patient care in ICU and helps in making protocols for patient's safety. Ongoing changes are implemented to increase patient safety and decrease adverse events.

REFERENCES

1. Jick H. Drugs—remarkably nontoxic. N Engl J Med. 1974; 291(16):824-8.
2. Classen DC, Pestotnik SL, Evans RS, Burke JP. Description of a computerized adverse drug event monitors using a hospital information system. Hosp Pharm. 1992;27(9):774,776-9, 783.
3. Griffin FA, RESAR R. Global trigger tool for measuring adverse events. [publicação online]. IHI Innovation Series white paper. Cambridge, MA: Institute for Healthcare Improvement. 2009. [online] Available from: http://www.ihi.org/resources/_layouts/download.aspx?SourceURL=%2fresources%2fKnowledge+Center+Assets%2fTools+-+IHIGlobalTriggerToolforMeasuringAdverseEvents_df8a18b6-52cc-4674-8258-030941832115%2fIHIGlobalTriggerToolWhitePaper2009.pdf [Last accessed March 2022].
4. World Health Organization Publication DEM/NC/84.153(E), June 1984. [online] Available from: https://apps.who.int/iris/handle/10665/61950?locale-attribute=pt&. [Last accessed March 2022].
5. Wilmer A, Louie K, Dodek P, Wong H, Ayas N. Incidence of medication errors and adverse drug events in the ICU: a systematic review. Qual Saf Health Care. 2010;19(5):e7.
6. Rothschild JM, Landrigan CP, Cronin JW, Kaushal R, Lockley SW, Burdick E, et al. The Critical Care Safety Study: The incidence and nature of adverse events and serious medical errors in intensive care. Crit Care Med. 2005;33(8): 1694-700.
7. Ratz Y, Shafir I, Berkovitch S, Sharristh M, Jacoby M, Kozer E, et al. The importance of the pharmacist in reporting adverse drug reactions in the emergency department. J Clin Pharmacol. 2010;50(10):1217-21.
8. Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Determinants of under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2009;32(1):19-31.
9. Aikawa G, Sakuramoto H, Ouchi A, Ono C, Hoshino T, Kido T, et al. Development of the Japanese version of the Intensive Care Unit Trigger Tool to detect adverse events in critically ill patients. Acute Med Surg. 2021;8(1):e672.

100

CHAPTER

Newer Critical Care Apps

Tapas Kumar Sahoo, Lalit Singh, Pankaj Anand

INTRODUCTION

In the last decade, we have experienced a particularly rapid period of technological advancement. Through the development of intricate and advanced technologies and their incorporation in health care, we have overcome enormous barriers in providing better patient care. Mobile devices have now become commonplace in the field of health care, with an ownership rate of 87% of healthcare professionals (HCPs) at their workplace,[1] and this has expedited the development of Apps or medical applications for these devices. Innumerable Apps have become available to assist HCPs in accomplishing important tasks including information and time management, health-record maintenance and access, communications and consulting, reference and information gathering, patient management and monitoring, clinical decision-making, and medical education and training. Additionally, these Apps provide access to point-of-care tools which assist in more sound decision-making and improve patient outcomes.

NEED FOR MOBILE TECHNOLOGIES IN THE CRITICAL CARE SETTING

Critical care and its pathophysiology are time-sensitive, involve complex decision-making, and are data-intense, thus making technology an indispensable aid in such settings. The most time-sensitive of syndromes such as shock, cardiopulmonary resuscitation, and trauma need concise yet precise bundle strategies backed by practical guidelines and algorithmic management plans executed through an organized team play. Technologies have been developed to aid practitioners to formulate a diagnostic approach and management plan, communicate with other specialists, and put together a well-rounded patient care plan.

MOBILE APPLICATIONS: THE ROAD TO EVOLUTION OF MODERN MEDICINE

Mobile applications used in health care have been broadly classified into five groups: (1) *Administration,* (2) *Health record maintenance and access,* (3) *Communications and consulting,* (4) *Reference and information gathering, and* (5) *Medical education* **(Table 1)**.[2] With such a vast array of uses, developers have come up with a wide variety of mobile applications that can be directly downloaded onto smartphones via online application stores such as App store and Google Play store for free, or often with a nominal subscription fee.[2]

Information and Time Management

Information management software and cloud-based storage services have gained popularity among HCPs as they provide easy transfer, storage, and retrieval of data. Additionally, these Apps allow real-time activities such as writing and dictating notes during rounds, recording audio, and taking photographs. Collected information can be categorized within a searchable electronic database which can be accessed via a cloud-based storage and file-sharing service compatible with one's mobile device. Moreover, these software allow sharing of documents and photographs without any hassle and safety concerns associated with exchanging pen drives and hard drives. Most cloud-based storage software offer the first few gigabytes (GB) of storage free of cost after which users are required to pay a nominal fee. The drawback however is that most of these Apps are not compliant with both the Health Insurance Portability and Accountability Act (HIPAA) and the Health Information Technology for Economic and Clinical Health (HITECH) Act and therefore may be unsuitable for data exchange and transfer. HIPAA was enacted in 1996 and laid the foundation for the variety of protections that govern the safety of an individual's health information. It was designed to prohibit HCPs from unauthorized disclosure of protected health information.[3] The HITECH Act was enacted in 2009 by building on HIPAA's encouragement for the use of health information technology (IT). It stimulated the adoption of electronic health records (EHRs) by offering incentives to medical groups that proved "effective" implementation of EHR tech.

TABLE 1: Uses of mobile devices and Apps by healthcare professionals.

Information management	*Time management*	*Health record maintenance*	*Communications and consulting*
• Write notes • Dictate notes • Record audio • Take photographs • Organize information and images • Use e-book reader • Access cloud service	• Schedule appointments • Schedule meetings • Record call schedule	• Access EHRs and EMRs • Access images and scans • Electronic prescribing • Coding and billing	• Voice calling • Video calling • Texting • E-mail • Multimedia messaging • Video conferencing • Social networking
Reference and information gathering	***Clinical decision-making***	***Patient monitoring***	***Medical education and training***
• Medical textbooks • Medical journals • Medical literature • Literature search portals • Drug reference guides • Medical news	• Clinical decision support systems • Clinical treatment guidelines • Disease diagnosis aids • Differential diagnosis aids • Medical calculators • Laboratory test ordering • Laboratory test interpretation • Medical examinations	• Monitor patient health • Monitor patient location • Monitor patient rehabilitation • Collect clinical data • Monitor heart function	• Continuing medical education • Knowledge assessment tests • Board examination preparation • Case studies • E-learning and teaching • Surgical simulation

(EHRs: electronic health records; EMRs: electronic medical records)
Source: Ventola CL. Mobile devices and Apps for health care professionals: uses and benefits. Journal for Formulary Management 2014;39(5):356-64.

Health Record Maintenance and Access

Hospital information systems (HISs) are sophisticated software that allow patient information (medical history, vitals, prescriptions, laboratory results, X-rays, scans, consultations, and discharge notes) to be integrated onto a single platform which can be accessed by HCPs either on-site or remotely.[4,5] HIS can be developed in collaboration with one or several of the available platforms such as epic systems, patient keeper, and team viewer, but most large-scale institutions prefer to develop their own software as per the convenience and skill of their employee profile. Mobile Apps linked to the HIS database allow access to patient information on the go. Special Apps such as the mobile information management (MIM) have also been developed for processing of medical imaging scans.[6] Mobile MIM, manufactured by Cleveland-based MIM Software Inc., allows the physician to measure distance on the image and image intensity values and display measurement lines, annotations, and regions of interest. This software allows remote viewing of X-rays and imaging scans when radiology workstations are unavailable.[7] It uses a HIPAA compliant server that allows HCPs to store, share, and remotely view medical images. The Ministry of Health and Family Welfare has notified EHR Standards Version 2016 for India in December 2016 (whilst the earlier version of EHR Standards was notified in September 2013) with an intent to bring standardization and homogeneity, interoperability in capture, storage, transmission, and use of healthcare information across various health IT systems.

Communication and Consultation

More than 80% students in several surveys report using mobile devices as the primary means of communication with colleagues and describe texting as a far more efficient way of communication as compared to telephonic conversations and meetings. The push-mail feature in most mobile devices nowadays notifies users of any new correspondence and allows them to respond to it at the touch of a button.[1]

Reference and Information Gathering

Mobile devices are indispensable tools for HCPs to access medical literature.[1] Several acclaimed medical journals, such as the *New England Journal of Medicine, The Lancet*, and *BMJ (British Medical Journal)*, now offer their mobile App version through which scientific literature can be accessed on mobile devices.[8] Search engines and research databases, such as PubMed/MEDLINE, also provide easy access to voluminous amounts of medical literature.[5]

Drug References

Drug reference applications provide information including: Drug names, indications, dosages, pharmacology, interactions, contraindications, cost, formulary status, identification guides, and dose by weight calculators.[4,5] The most commonly encountered drug reference Apps include Epocrates, Skyscape RxDrugs/Omnio, Micromedex, FDA (Food and Drug Administration) Drugs, DrugDoses.net, etc.[5,9-16]

Patient Management

Clinical Decision-making

Mobile devices are easy accesses to evidence-based medical information allowing more sound decision-making at the point of care. The Manhattan Research/Physician Channel Adoption Study studied the increasing reliance of HCPs for information and reported that up to 64% spend double the

time online researching information than they do reviewing print resources.[17]

Many software Apps are useful in making bedside decisions.[5] Some of these Apps are: Johns Hopkins Antibiotic Guide (JHABx), Dynamed, UpToDate, 5-Minute Clinical Consult (5MCC), 5-Minute Infectious Diseases Consult (5MIDC), Sanford Guide to Antimicrobial Therapy (SG), ePocrates ID, Infectious Disease Notes (ID Notes), Pocket Medicine Infectious Diseases (PMID), and IDdx.[5,9] Diagnosaurus, a differential diagnosis App, suggests alternative diagnoses ensuring that they are also covered. Laboratory test Apps such as Pocket Lab Values, Lab Pro Values, Palm LabDX, Normal Lab Values, Lab Unit Converter, Labs 360, Davis's Laboratory and Diagnostic Tests, and Pocket Guide to Diagnostic Tests[5,9] provide information about reference values and interpretation, causes for abnormal values, and laboratory unit conversions **(Table 2)**.[2,5] Mobile Apps are also helpful in conducting simple examinations for visual acuity or color blindness as well as blood pressure or glucose level.[4,5,8] The iPhone iSeismometer App can be used to measure tremor frequency and the iMurmur App can help in learning 20 types of heart murmurs, allowing a physician to match and identify what she or he hears.[4] Many Apps are available to follow pregnancy due dates by using a patient's sonogram and last menstrual period, such as "Perfect OB Wheel".[4]

Several Apps provide current treatment guidelines such as the National Comprehensive Cancer Network guidelines for cancer care available through the Epocrates App, and the American College of Chest Physicians antithrombotic therapy guidelines available via the CHEST App.[7] Other mobile Apps, such as medical calculators, can be used to calculate body mass index (BMI), body surface area (BSA), proper drug doses,[5,10] and clinical scores or indices typically utilizing complex formulas that require several input parameters.[5] Some of the popular calculator Apps are: EpocratesMedMath, MedCalc, Mediquations, Calculate, Medical Calculator, Archimedes, uBurnLite, Softforce's Antibiotic Dosage Calculator, and PaedsED.[7,9] Others that are available are: Vancomycin ClinCalc Full, Softforces's Antibiotic Dosage Calculator, and MedCalc 3000 Pharmacology.[8]

Patient Monitoring

Mobile device Apps can be used for public health surveillance as well as aid in community data collection.[18] Garment-attachable sensors that communicate with mobile devices can be used to remotely monitor chronically ill elderly patients.[10] An intensive care unit clinical monitoring system was developed with features such as alarms and triage, based on vitals of the patient.[5] The iWander App was designed to track patients of Alzheimer's disease using a global positioning system (GPS) device that can be connected to smartphones.[10] Rehabilitation progress in such patients can also be tracked using mobile Apps such as remote electrocardiography (ECG) monitoring which can be connected via Bluetooth to a single-lead ECG device.[10] Although useful, the limitations of these Apps include inability of the patient to use technologies like GPS.[10]

Mobile Apps supplementary to medical devices are also being developed.[8] For instance, the iStethoscope App uses the microphone function of the mobile device to auscultate and record breath sounds.[8] The MobiSante corporation was also the first FDA-approved software that can potentially be used as a mobile echocardiogram machine when connected to an ultrasound probe.

TABLE 2: Various Apps available for use in health care.

Information management: Time management		***Patient management and monitoring***	
• Evernote	• Note-taking and organization	• Diagnosaurus	• Differential diagnosis
• Notability	• Note-taking and organization	• Pocket LabValues	• Laboratory reference
• iAnnotate	• PDF viewer	• Lab ProValues	• Laboratory reference
GoodReader Box	• PDF viewer	• Archimedes	• Medical calculator
• Dropbox	• Cloud storage and file sharing	• MedCalc	• Medical calculator
• Google Drive	• Cloud storage and file sharing	• Mediquations	• Medical calculator
	• Cloud storage and file sharing	• Calculate	• Medical calculator
		• AHRQ ePSS	• Screening and prevention tool
Reference and Information gathering			
• Epocrates		• Drug and medical reference	
• Dynamed		• Drug and medical reference	
• Skyscape/Omnio		• Drug and medical reference	
• Micromedex		• Drug reference	
• Dynamed		• Medical reference	
• UpToDate		• Medical reference	
• Medscape		• Medical reference	
• Johns Hopkins Antibiotic Guide		• Medical reference	
• *Sanford Guide to Antimicrobial Therapy*		• Medical reference	
• *Medpage Today*		• Medical news	

Source: Ventola CL. Mobile devices and Apps for health care professionals: uses and benefits. Journal for Formulary Management 2014;39(5):356-64.

Medical Education and Training

Mobile devices have gained enormous popularity among medical trainees at all levels. Students have become increasingly reliant on mobile applications owing to quick, easy access to vast amounts of information. Resources frequently tapped by medical students are online textbooks, lectures, medical podcasts, medical calculators, and search engines.[1] Mobile Apps also provide information on academic activities such as continuing medical education (CME) keeping HCPs updated on the most recent evidence-based advances and practice guidelines.[4,5,10] In the COVID (corona virus disease) era, we have seen mobile devices emerge as an indispensable teaching tool with the ease and safety of being able to take classes, seminars, and other academic activities from our homes. Moreover, with the development of advanced software strategies, life-support training has significantly improved with Applaudable outputs from trainees in the field.[10] One such tool is Xlung which is an internet-based simulator software that helps medical trainees to understand patient–ventilator interaction and respiratory mechanics in a dynamic and interactive way with the use of real-time situations. It is available on subscription as a mobile App as well as website.

BENEFITS PROVIDED BY MOBILE DEVICES AND APPS FOR HEALTHCARE PROFESSIONALS

Mobile Apps have proved to be an indispensable aid to HCPs, in today's fast paced and precision demanding healthcare setting. These software allow for efficient and accurate decision-making as well as improve data management and accessibility.[1,5,6,19,20] These advantages have been seen to reflect positively on patient care and outcomes, as evidenced by a reduction in adverse events and hospital length of stay.[6,19]

Some of the benefits of these Apps include:

- *Convenience*: Mobile Apps provide fast, flexible, and portable access to a vast array of multimedia resources and communication platforms.
- *Better decision-making*: Rapid and precise decision-making with evidence-based backing, along with an insight into alternative diagnoses and clinical algorithms, hence reducing human error.
- *Improved accuracy*: Advanced diagnostic coding and comprehensive databases lead to increased medication safety and timely documentation of adverse effects and medical errors.
- *Increased efficiency*: Mobile Apps save time as well as the resources that go into reviewing vast amounts of print literature by providing precise, hands-on solutions to clinical problems that HCPs may encounter during their practice.
- *Enhanced productivity*: Analysis of surveys shows that mobile Apps in health care increase productivity and streamline workflow while additionally encouraging digitalization of prescriptions and clinical notes.

CONCLUSION

Future trends in the use of technology in health care are beginning to emerge. Future applications will be operating on even larger databases, facilitating better diagnosis, and care. Mobile devices and Apps with their quick access to enormous amounts of information are reliable tools for students who require on-the-go companion. However, concerns regarding the increasing dependence of HCPs on these software have emerged that include questionable reliability of information as well as issues such as confidentiality of medical records, interpersonal relationships between doctors and patients, medicolegal and ethical implications as well as reluctance of older HCPs to incorporate technology into their practice. These hurdles can be overcome once the application developers acquire adequate and accurate information, expand their databases, and make their user interface simpler to use for all age groups.

REFERENCES

1. Wallace S, Clark M, White J. 'It's on my iPhone': attitudes to the use of mobile computing devices in medical education, a mixed-methods study. BMJ Open. 2012;2(4):e001099.
2. Ventola, C Lee. Mobile devices and Apps for health care professionals: uses and benefits." P & T: a peer-reviewed Journal for Formulary Management. 2014;39(5):356-64.
3. https://support.box.com/hc/en-us/articles/360044194833-Box-HIPAA-and-HITECH-Overview-and-FAQ
4. Kiser K. 25 ways to use your smartphone. Physicians share their favorite uses and Apps. Minn Med. 2011;94(4):22-9.
5. Mosa ASM, Yoo I, Sheets L. A systematic review of healthcare applications for smartphones. BMC Med Inform Decis Mak. 2012;12:67.
6. Mickan S, Tilson JK, Atherton H, Roberts NW, Heneghan C. Evidence of effectiveness of health care professionals using handheld computers: a scoping review of systematic reviews. J Med Internet Res. 2013;15(10):e212.
7. O'Neill KM, Holmer H, Greenberg SL, Meara JG. Applying surgical Apps: Smartphone and tablet Apps prove useful in clinical practice. Bull Am Coll Surg. 2013;98(11):10-8.
8. Yoo JH. The meaning of information technology (IT) mobile devices to me, the infectious disease physician. Infect Chemother. 2013;45(2):244-51.
9. Aungst TD. Medical applications for pharmacists using mobile devices. Ann Pharmacother. 2013;47(7-8):1088-95.
10. Ozdalga E, Ozdalga A, Ahuja N. The smartphone in medicine: a review of current and potential use among physicians and students. J Med Internet Res. 2012;14(5):e128.
11. Chase J. IPads and other drugs. Medical Marketing & Media: The Interactive Guide. 2013:10-11.
12. Moodley A, Mangino J, Goff D. Review of infectious diseases applications for iPhone/iPad and Android: from pocket to patient. Clin Infect Dis. 2013;57:1145-54.

13. Payne KFB, Wharrad H, Watts K. Smartphone and medical related App use among medical students and junior doctors in the United Kingdom (UK): a regional survey. BMC Med Inform Decis Mak. 2012;12:121.
14. Apple Inc. (2014). Apple store sales top $10 billion in 2013. [online] Available from https://www.apple.com/newsroom/2014/01/07App-Store-Sales-Top-10-Billion-in-2013/ [Last accessed February, 2022].
15. Lewis T. (2013). Apple launches dedicated 'Apps for Healthcare Professionals' collection. [online] Available from http://www.imedicalapps.com/2013/02/apple-apps-healthcare-professionals-collection [Last accessed February, 2022].
16. Dolan B. (2011). Apple helps MDs cut thru medical Apps clutter. [online] Available from http://mobihealthnews.com/13254/apple-helps-mds-cut-thru-medical-apps-clutter [Last accessed February, 2022].
17. Murfin M. Know your Apps: an evidence-based approach to the evaluation of mobile clinical applications. J Physician Assist Educ. 2013;24(3):38-40.
18. Boulos MNK, Wheeler S, Tavares C, Jones R. How smartphones are changing the face of mobile and participatory healthcare: an overview, with example from eCAALYX. Biomed Eng Online. 2011;10:24.
19. Divall P, Camosso-Stefinovic J, Baker R. The use of personal digital assistants in clinical decision making by health care professionals: a systematic review. Health Informatics J. 2013;19(1):16-28.
20. Van Velsen L, Beaujean DJ, van Gemert-Pijnen JE. Why mobile health app overload drives us crazy, and how to restore the sanity. BMC Med Inform Decis Mak. 2013;13:23.

CHAPTER 101

Use of Electronic Record and Hybrid Integration of Electronic Intensive Care Unit in Critical Care Practice

Sai Praveen Haranath, Priyanka H Chhabra, Pradeep Rangappa

INTRODUCTION

The safety of air travel has evolved over the years with the combined global experience of various components of the industry. Safety has been the first priority and the various accidents and near-misses have educated aviation science and saved countless passengers. Health care is no different when it comes to the need for safety. Various models have shown the Swiss cheese effect for errors, and the Institute of Medicine Report has revealed the magnitude and gravity of the problem. In this context, the introduction of smart health records has played a role in ensuring a standardized approach to modern medical care.[1] The current advances in clinical decision-making and automated early warning systems are making their presence felt with studies showing their value. There are many examples of artificial intelligence (AI) guiding care including automated radiology systems, drug dose and interaction checkers, therapeutic duplication alerts for medications as well as methods to prevent unnecessary laboratory and imaging testing.[2] The future will be safer, cost effective, and patient friendly as AI assistants become ubiquitous.[2]

ELECTRONIC MEDICAL RECORD

A subset of these advances is the electronic medical record (EMR). Historically, these have been typed documents that can be stored and retrieved for posterity and linked to an individual patient record. They are useful for the outpatient, inpatient, emergency as well as prehospital ambulance, and home care. Documents can include progress reports, consultation notes, imaging reports, notes by the multidisciplinary team including pharmacy, dietary department, physiotherapy, occupational therapy, respiratory therapy, and social work. Imaging and laboratory reports can be directly imported into the medical record and be displayed graphically and sequentially. Trends, alerts, and clinical implications of values can be integrated into the electronic record.

TABLE 1: Electronic medical record features.

	Simple	***Complex***	***Future***
Cost	Low	High	May be low
Sample features	Text based	Automated decision alerts	Integrate with devices and make changes to plan of care
Benefits	Easy to deploy	Decrease errors	Automate tasks
Risks	Errors can occur	Too much information	If using artificial intelligence (AI) needs to be explainable

As shown in **Table 1**, the EMR can be simple or complex but the true utility is probably in legibility and secure access.[3] If we are to look at key features of electronic records, the cost may need to be reviewed. The maintenance expense for software upgrades and wide deployment is often significant and in less-developed economies without institutional support may be prohibitive. The features can be quite robust including automated clinical decision alerts. The future is exciting and may include automated titration of medications from an EMR perhaps. A simpler example was recently shown in managing hyperoxygenation of ventilated patients. In a pilot study,[4] ventilated patients were randomized to respiratory therapist (RT)-driven titration after an electronic alert versus usual physician order-directed care. An automated surveillance system using a hyperoxemia identification algorithm triggered an electronic alert to an RT's pager. Of the 195 subjects in the randomized controlled, 86 were in the intervention arm. The alert accuracy was 78%, and RTs responded 64% of the time. During mechanical ventilation, exposure to hyperoxemia significantly decreased in the intervention group (median 13.5 hours vs. 18.8 hours).

The software used to develop EMR systems has included legacy UNIX (UNiplexed Information Computing System) based languages as well as modern versions. Many are open source and widely deployed as in the Veterans Affairs (VA)

system. In the pandemic, many rapidly deployed versions have come through, and the NETCCN (National Emergency Tele-Critical Care Network) project[5] in the US is an example. In India, many entrepreneurs and startups have created innovative solutions.

As the general documentation guidelines in India are variable, depending on the setting the complexity of the EMR will need to also adapt. Most locations at this time have flowcharts that contain details of vitals, medications, laboratory work, and a simple plan of care. These paper records can be converted to electronic formats. Data entry can be through a COW (Cart On Wheels) or perhaps directly into a desktop. Physician and nurse as well as paramedical staff will also often document on paper and slowly these will be entered into electronic records as adoption increases.

ELECTRONIC INTENSIVE CARE UNIT IN CRITICAL CARE PRACTICE

One subset of importance gaining traction in India is the electronic intensive care unit (eICU) or remote critical care. In simple terms, this is critical care delivery using telemedicine capability. The technology includes audio and video communication and access and integration with a standard EMR. The key, however, is access to trained critical care doctors and nurses who can provide expert advice to locations where there is a lack of intensivists.

The models include simple consultative advice to full spectrum care directing complex ventilator management of acute respiratory distress syndrome (ARDS) for example. Some systems also use pharmacists, RTs, and administrative staff to enhance care delivered remotely. Anecdotal uses of the eICU to guide various emergencies include pneumothorax management, thrombolysis of myocardial infarction detected on an electrocardiogram (ECG) reviewed remotely, trauma care direction, stroke detection, and even remote guidance for bronchoscopy or echocardiography.

Collaborative networks of critical care units can promote quality improvement across an entire system. Proposed advantages include helping more patients, resource efficiency, and common measurement systems for audit and feedback or benchmarking.[6] A detailed overview of eICU usage in the COVID (coronavirus disease) pandemic was described last year and had examples of situations where tele-intensive care can be helpful.[7] The specific case of using remote technology for neurologic consultation and emergency advice has been described in India.[8] A recent article in the Indian Journal of Critical Care Medicine (IJCCM) also detailed the need for tele-ICU service.[9] Another example of the role played by telemedicine in critical care was well described from Karnataka.[10]

HYBRID INTEGRATION OF MEDICAL RECORDS

Manual record keeping is often laborious, illegible, and prone to errors.[11] Medical records are frequently lost or are incomplete predisposing to medicolegal problems. On the other hand, EMRs are standardized, easy to access, and flexible. They often decrease clinician workload by reducing the need for paper handling and storage. There is often reduction in medication errors and avoids unnecessary investigations. Hence, it improves the overall quality of care.[12] However, it is more time consuming as keyboard/mouse input is slow. Also, drawing diagrams or figures of patient's condition is quite difficult in electronic record system. Hence, a hybrid system consisting of both electronic and paper records offers the best advantages of both the systems.[13]

Hybrid integration in critical care practice has various advantages over manual data entry. They are as follows:

- *Enhanced quality of patient care*: It reduces chances of medication errors,[14] and improves sharing of patient information, laboratory test results, and investigations such as X-rays and CT (computed tomography) reports amongst caregivers. It is especially beneficial in emergency situations in reproducing the patient's history and relevant health information. Therefore, it improves the overall quality of care.[14]
- *Improved efficiency of health care*: Making the entire patient information available online helps to understand the patient's clinical condition and progress in a better way.
- *More convenient care*: EHR health alerts serve as a reminder for the clinician for ordering diagnostic tests, thereby minimizing diagnostic errors.[14] Patients also need not carry their copies of documents such as prior health history and laboratory investigations. It can also reduce the overall cost of medical care.[15,16]

Hybrid Electronic Medical Records and Patient Safety

Safeguarding a patient's medical record is one of the biggest challenges in maintaining an EMR. Maintaining privacy, security, and confidentiality are common issues in the EHR. There are two ways of ensuring safety and security in the EHR—physical and technical safeguards. Physical safeguards prevent manhandling by people who are unauthorized to access the health data. Technical safeguards include virus checking systems, firewalls, encryption, cloud computing, antivirus software, and measures used in authenticating information.[17] Application of user name and password or digital signatures provides an effective authentication in EHRs. Two-factor authentication and use of mobile phone or online one-time passwords are often used.

DATA PROTECTION: INDIAN SCENARIO

India now has a framework for health information protection as well as digitization of all aspects of health care. As noted verbatim on the main website, the vision is "to create a national digital health ecosystem that supports universal health coverage in an efficient, accessible, inclusive, affordable, timely, and safe manner, that provides a wide-range of data, information, and infrastructure services, duly leveraging open, interoperable, standards-based digital systems, and ensures the security, confidentiality, and privacy of health-related personal information." The process has been spearheaded by the National Health Authority. The National Digital Health Mission (NDHM) is the country's most ambitious health data digitization drive till date. The proposed legal framework for the future of health data privacy is based on the draft Digital Information Security in Healthcare Act (DISHA) and the Personal Data Protection Bill which along with the Information Technology Act provide general data protection. The Ayushman Bharat Digital Mission (ABDM) aims to develop the backbone necessary to support the integrated digital health infrastructure of the country. It aims to bridge the existing gap amongst different stakeholders of healthcare ecosystem through digital highways. It has a comprehensive approach to personal health records and a unique health identification system called ABHA (Ayushman Bharat Health Account) to access personal health records.[12,17]

CONCLUSION

Electronic medical records and remote electronic intensive care are revolutionary advances that can save lives. As in aviation, automation and system redundancy improve safety. The need for information technology experts and computer technicians as well as overcoming the natural inertia of legacy healthcare systems are challenges to widespread deployment and usage. Integration with billing systems, voice-based transcription, templated notes, and clinical decision support are some of the several ways to integrate the EMR into daily practice. The force multiplier effect of the eICU to allow access to advanced critical care expertise cannot be underestimated. The business case for these technologies is still evolving in India but the COVID pandemic has shown us the varied benefits of collaborative care at all levels. The hope is that critical care can be delivered at the last mile in person as efforts by various organizations to train healthcare teams in evidence-based intensive care progress. Resource-limited settings need customized approaches given issues of manpower availability, power supply, outdated equipment, and lack of bandwidth.[3] Until then and perhaps even after that, remote critical care using a hybrid or integrated EMR can bridge the gap.

REFERENCES

1. Tian S, Yang W, Le Grange JM, Wang P, Huang W, Ye Z. Smart healthcare: making medical care more intelligent. J Glob Health. 2019;3(3):62-5.
2. Tanner C, Gans D, White J, Nath R, Pohl J. Electronic health records and patient safety: co-occurrence of early EHR implementation with patient safety practices in primary care settings. Appl Clin Inform. 2015;6(1):136-47.
3. Millard PS, Bru J, Berger CA. Open-source point-of-care electronic medical records for use in resource-limited settings: systematic review and questionnaire surveys. BMJ Open. 2012;2(4):e000690.
4. Pannu SR, Holets S, Li M, Marquez A, Kashyap R, Brock G, et al. Electronic Medical Record-Based Pager Notification Reduces Excess Oxygen Exposure in Mechanically Ventilated Subjects. Respir Care. 2021;66(3):434-41.
5. https://www.tatrc.org/netccn/overview.html [accessed March 21,2022]
6. Watson SR, Scales DC. Improving intensive care unit quality using collaborative networks. Crit Care Clin. 2013;29:77-89.
7. Haranath SP, Udayasankaran JG. Tele-intensive care unit networks: A viable means for augmenting critical care capacity in India for the COVID pandemic and beyond. Apollo Med. 2020;17(3):209-16. Also available from: https://www.apollomedicine.org/text.asp?2020/17/3/209/295129 [Last accessed March, 2022].
8. Haranath SP, Ganapathy K, Kesavarapu SR, Kuragayala SD. eNeuroIntensive Care in India: The Need of the Hour. Neurol India. 2021;69(2):245-51. Also available from: https://www.neurologyindia.com/text.asp?2021/69/2/245/314591 [Last accessed March, 2022].
9. Ramakrishnan N, Vijayaraghavan BKT, Venkataraman R. Breaking Barriers to Reach Farther: A Call for Urgent Action on Tele-ICU Services. Indian J Crit Care Med. 2020;24(6):393-7.
10. Rangappa P, Rao K, Chandra T, Karanth S, Chacko J. Telemedicine, tele-rounds, and tele-intensive care unit in the COVID-19 pandemic. Indian J Med Spec. 2021;12:4-10. Also available from: http://www.ijms.in/text.asp?2021/12/1/4/306114 [Last accessed March, 2022].
11. Allortoac NL, Wise R. Development and evaluation of an integrated electronic data management system in a South African metropolitan critical care service. South Afr J Anaesth Analg. 2015;21(6):1-5.
12. Manca DP. Do electronic medical records improve quality of care? Can Fam Physician. 2015;61(10):846-7.
13. Terajima K, Negishi N, Maruyama K, Hasegawa H, Akazawa K. A Hybrid Electronic Health Record System Integrating Electronic and Paper-based Records. EJBI. 2018;14(1):58-66.
14. Campanella P, Lovato E, Marone C, Fallacara L, Mancuso A, Ricciardi W, et al. The impact of electronic health records on healthcare quality: a systematic review and meta-analysis. Eur J Public Health. 2015;26(1):60-4.
15. Yoshida Y, Imai T, Ohe K. The trends in EMR and CPOE adoption in Japan under the national strategy. Int J Med Inform. 2013;82:1004-11.
16. Paré G, Raymond L, de Guinea AO, Poba-Nzaou P, Trudel MC, Marsan J, et al. Barriers to organizational adoption of EMR systems in family physician practices: a mixed-methods study in Canada. Int J Med Inform. 2014;83(8):548-58.
17. Lemke J. Storage and security of personal health information. OOHNA J. 2013;32(1):25-6.

SECTION

18

Radiology

CHAPTER 102

Role of Interventional Radiologist in Critical Care Setting

Rozil Gandhi, Ankur Bhavsar, Gopal Raval

INTRODUCTION

Radiology is an integral part of the intensive care unit (ICU). Intensivists are now trained in doing many of diagnostic and therapeutic procedures in an ICU with the help of ultrasound (USG). Over the years, radiology in ICU is evolving. It is not limited to USG, but many therapeutic interventions are becoming lifesaving for critically ill patients [like mechanical thrombectomy (MET) for acute ischemic stroke, CT (computed tomography)-guided aspiration of deep-seated abscess, etc.]. In many situations, doing an invasive procedure or surgery may not be feasible, where CT- or ultrasonography-guided intervention might save the life.

Interventional radiology (IR), the subspecialty in radiology, provides a gamut of minimally invasive procedures that augur very well with the critically ill patients. The intensive care physicians by default accept IR procedures easily rather than invasive and high-risk surgeries, being concerned about their patient demographics. Procedures being image-guided are "smaller, faster, safer, better," mostly under local anesthesia, thus obviating the anesthesia risk. Many procedures like venous access, drain insertions, etc., are done bedside under USG guidance. Vascular procedures are generally done under fluoroscopy guidance in an angiography suite. Interventional radiologists are many a times called to perform a high-risk procedure in hemodynamically unstable patients and thereby saving their life.

SCOPE OF INTERVENTIONAL RADIOLOGY

Many of the ICU patients are too unstable to be shifted to the operation theater (OR) or too unstable to tolerate major surgery and anesthesia for source control (sepsis) or bleeding control [trauma/postpartum hemorrhage (PPH)/occult bleeding]. Such patients can be managed with the help of an interventional radiologist with minimum hemodynamic disturbances or shifting to OR. The following procedures are considered:

- Vascular access
- *Sepsis control—aspirations/drain insertions/percutaneous nephrostomy—bedside under USG guidance*:
  - Liver abscess
  - Postoperative collections
  - Loculated pleural effusions
  - Pelvic abscess
- *Bleeder embolizations*:
  - Bronchial artery (BA)/pulmonary artery embolization for hemoptysis
  - Gastrointestinal (GI) bleeding
  - Post-traumatic—hepatic/splenic/pelvic bleeders
  - Oral bleeding in advanced malignancy
  - Variceal embolization and TIPSS (transjugular intrahepatic portosystemic shunt) in refractory variceal bleeding.
- *Recanalizations*:
  - Deep vein thrombosis (DVT) and pulmonary embolism (PE)
  - Mesenteric artery and venous thrombosis
  - Stroke
  - Acute limb ischemia.

Vascular Access

Implantable or intravascular access devices (IVADs) are essential in the appropriate treatment of patients with a wide range of disease processes in a critical care unit. Central venous catheters (CVCs) are necessary for short-term or long-term management with the following advantages:

- For patients who are unable to maintain sustainable peripheral intravenous access.
- For the administration of drugs toxic to the peripheral veins.
- For patients who require frequent blood draws and for apheresis or dialysis.

Tunneled catheters are used for long-term while nontunneled catheters are used for short-term therapies (<2 weeks). Typically, these procedures are performed by vascular and interventional radiologists under USG or combined USG and fluoroguidance.[1]

Nontunneled, double-lumen hemodialysis catheters (10–13.5 French) provide adequate flow for centrifuge-based and filter-based apheresis systems. Nontunneled catheters are designed to be temporary in nature and thus can be placed even in the setting of systemic infections.

Tunneled Central Venous Catheters

Tunneled cuffed venous catheters (TCVCs) are indicated for access required for >3 weeks' duration in chronic kidney disease patients with long-term dialysis or hematologic malignancies who require stem cell transplantation or long-term therapeutic apheresis. Infection rates are significantly lower for tunneled versus nontunneled catheters because of the presence of polyester cuff which allows the incorporation of catheter in the subcutaneous plane and acts as a barrier against bacteria. Most TCVCs are double-lumen catheters derived from polyurethane or silicone. These materials have high elasticity. In particular, polyurethane catheters have sufficient rigidity to withstand the high flow rates (30–400 mL/min) necessary for treatment. Absolute contraindications for placement are patients with active systemic infection or uncorrectable coagulopathy **(Figs. 1A to C)**.[2]

Percutaneous Drainage

Percutaneous abscess drainage (PAD)/therapeutic aspirations/intercostal drain insertions have been proven to be a safe, effective, and widely used technique for treatment of patients with abdominal, thoracic, and musculoskeletal collections.[3]

Indications

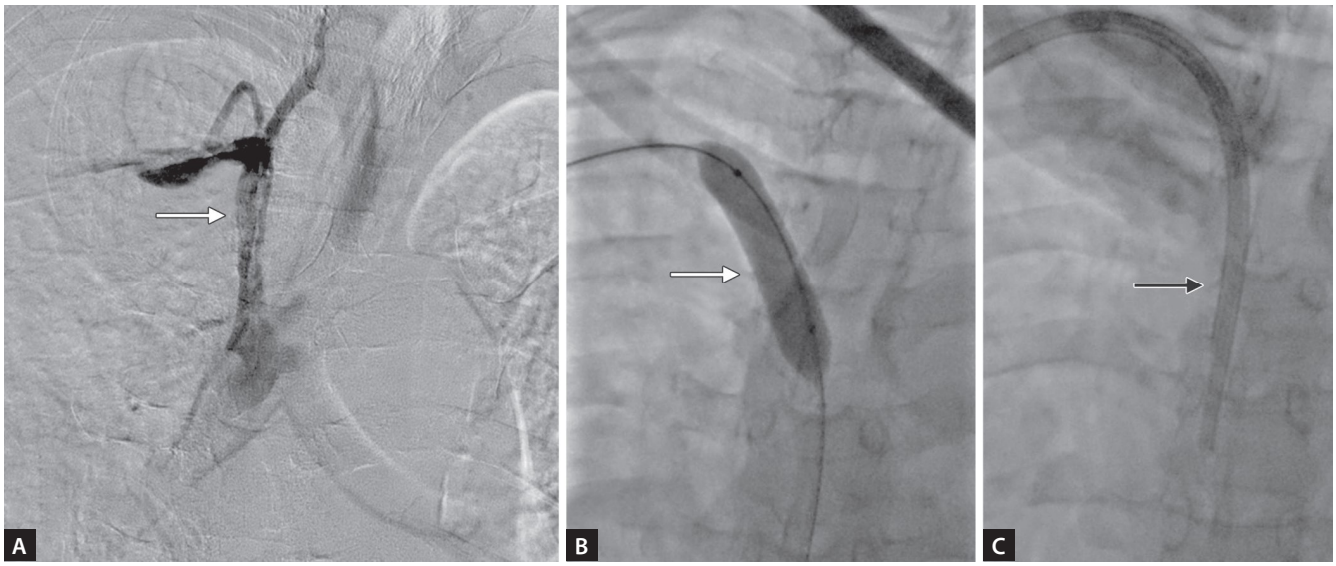
- Liver abscess (ruptured and unruptured)
- Postoperative abdominal collections (bowel, biliary, pancreatic surgeries, etc.)
- Splenic abscess
- Ruptured diverticular abscesses/bowel perforations
- Percutaneous cholecystostomy
- Walled-off pancreatic necrosis and collections in acute pancreatitis
- Pleural effusions
- Musculoskeletal abscesses
- Pharyngeal abscesses, etc.

Advantages

- Image guidance for precision
- Performed under local anesthesia or conscious sedation
- 14–28F over the wire drains available which can be inserted using the Seldinger technique
- Most of the abscesses amenable percutaneously
- Sometimes gives time to the patient by improving him/her clinically and then taking the patient for therapeutic surgery.

Sepsis management through source control is a very important aspect in critical care medicine for effective patient treatment. The mortality of undrained abdominal abscesses may be as high as 35%.

Majority of these drainage procedures are done bedside under USG guidance which obviates the need to shift the high-risk patient. Sometimes, a CT scan is also used for



Figs. 1A to C: A 45-year-old female patient with end-stage renal disease presented with an occluded superficial arteriovenous (AV) fistula. Doppler showed partially occluded right subclavian vein, completely occluded bilateral internal jugular veins, left subclavian vein, and both common femoral veins. Serum potassium levels were 7. The patient was admitted in the nephrology and critical care unit and was in urgent need for dialysis. (A) Venogram through ultrasound-guided access of right subclavian vein showing severe stenosis (white arrow) of subclavian and innominate veins; (B) Dilatation of right subclavian and innominate veins with 10-mm high-pressure balloon (white arrow) was done; (C) Proper placement of tunneled permanent catheter (black arrow) for dialysis after adequate dilatation of the veins. Successful dialysis was done after the procedure.

inserting deeper drains in the abdomen for which patients need to be shifted **(Figs. 2A and B)**.[4]

Embolization for Bleeders

Indications

- Oral bleed in head and neck malignancies
- Hemoptysis—bronchial artery embolization (BAE)
- Pulmonary artery aneurysms—mycotic/post-COVID
- Nonvariceal bowel bleed/peptic or gastric ulcer bleed
- Variceal bleeding—TIPSS or BRTO (balloon-occluded retrograde transvenous obliteration)
- Retroperitoneal bleed
- Postoperative bleeds
- Traumatic liver or splenic or renal injury and bleeds
- Pseudoaneurysms due to pancreatitis
- Musculoskeletal bleeds after femoral surgeries
- Hemarthrosis after total knee replacement (TKR).

Advantages

- Minimally invasive
- Highly successful
- Performed under local anesthesia
- Image-guided and with high precision.

Bleeding from any site in the body is an emergency medical condition that leads to hemorrhagic shock or circulatory instability if left untreated.

Acute Gastrointestinal Bleed

Acute GI bleeding can lead to significant morbidity and mortality without appropriate treatment. Computerized tomography angiography (CTA) is used to localize the bleeds and evaluate the vascular anatomy prior to the embolization procedure. Majority of GI bleeding is attempted to be controlled by endoscopy which claims to staunch 90% of them. However, torrential bleeding which leads to poor visualization, highly unstable patient, small bowel bleeds, recurrent ulcer bleeds, tumor bleeds, etc., cannot be treated with endoscopy. IR plays a major role in such bleeds by transcatheter embolization procedures and with the help of newer microcatheters and embolizing agents, IR achieves high success rates and minimal complications such as bowel infarction, etc. **(Figs. 3A and B)**.[5-7]

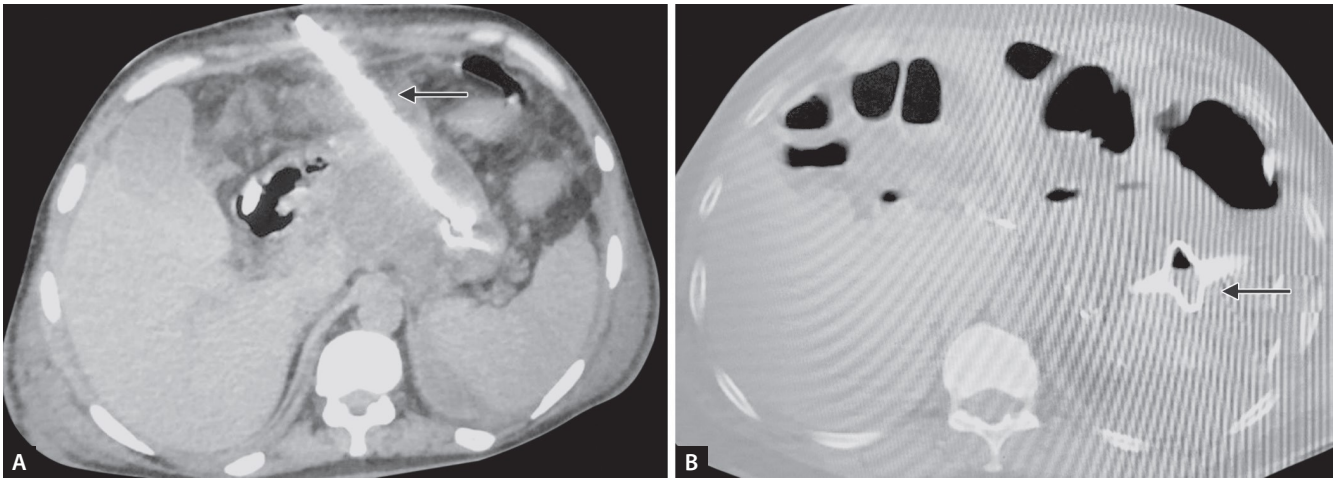
Acute Pancreatitis

Approximately 20% of patients with acute pancreatitis will develop complications that require intervention. These can be classified into vascular and nonvascular complications:

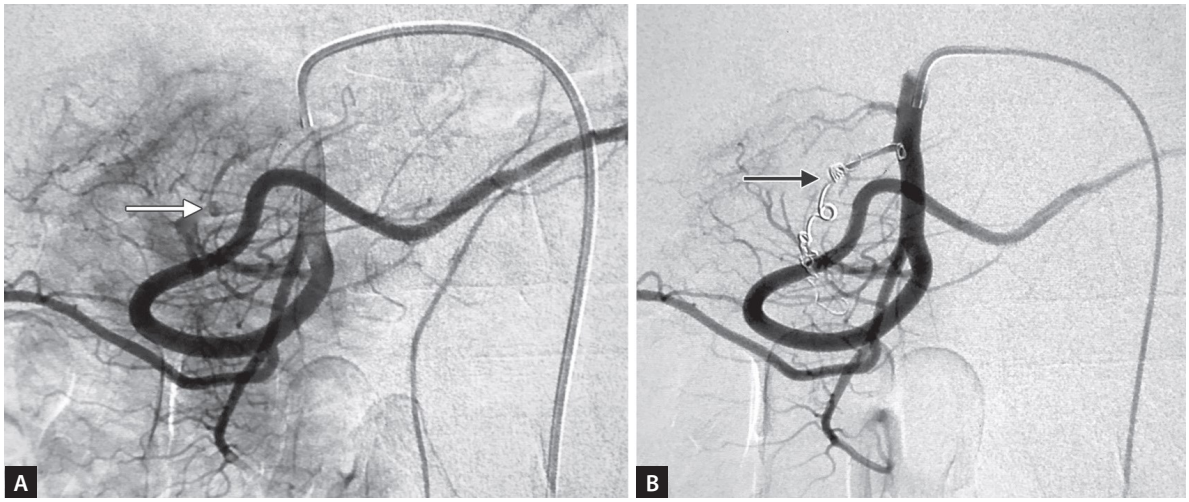
- Nonvascular complications include collections and bowel complications.
- Vascular complications include peripancreatic arterial and venous pseudoaneurysms, venous thrombosis, and arteriovenous malformations (AVMs) **(Figs. 11A to E)**.[7,8]

Hemoptysis

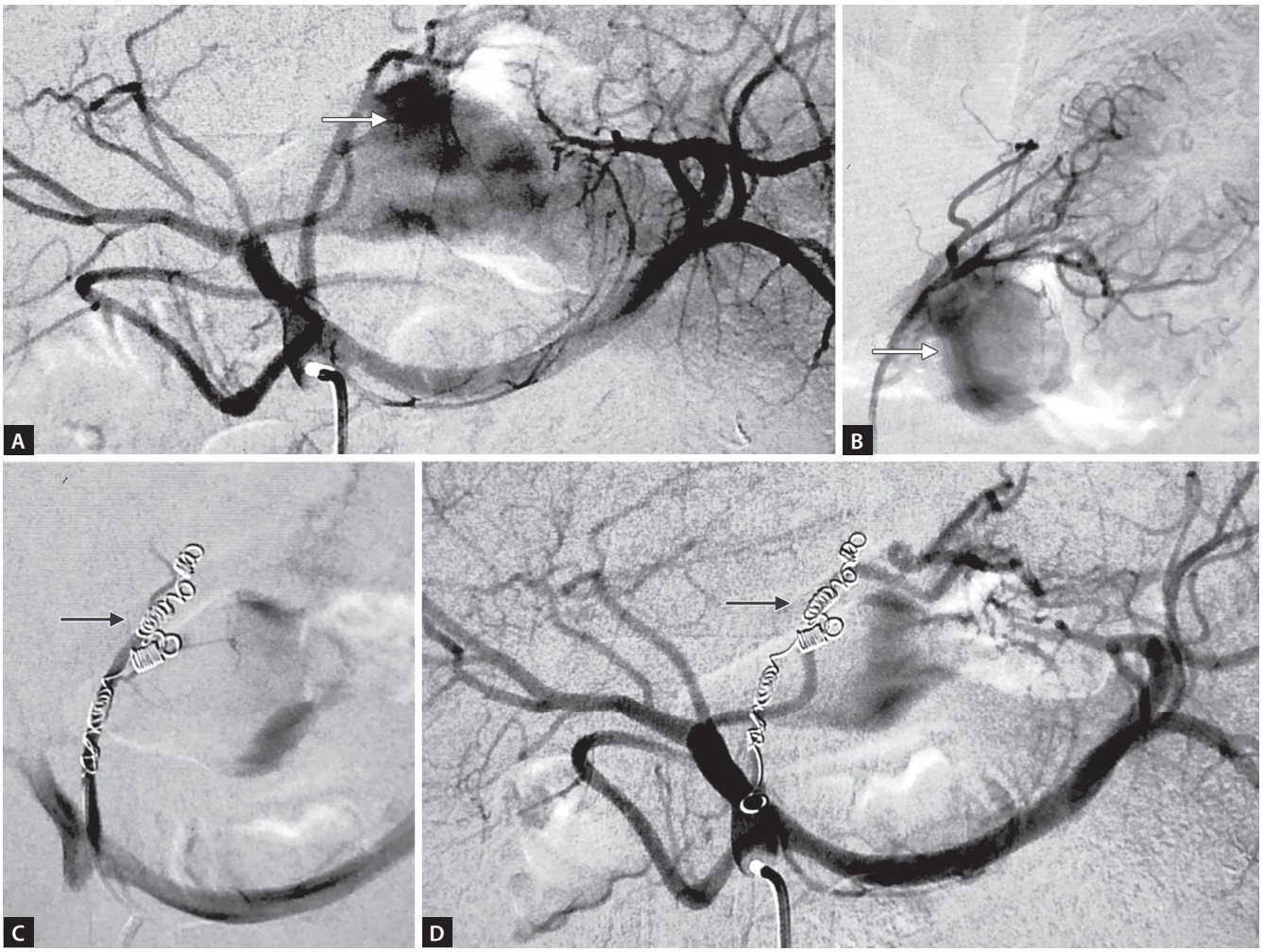
Hemoptysis is a life-threatening pulmonary emergency with high mortality, is symptomatic of an underlying severe pulmonary disease, and requires immediate diagnosis and treatment. Evaluation is done by careful history-taking (history of prior Koch's/COVID), conventional chest X-ray, and contrast-enhanced multislice computed tomography (MSCT) with CTA; in some cases, bronchoscopy provides information regarding the underlying pulmonary disease, bleeding site, the vascular anatomy of the BAs, and extrabronchial branches as well a basis for planning of endovascular intervention. Therapeutically, BAE is a safe, minimally invasive, and effective technique in the hands of an experienced interventionist with profound knowledge of the BA anatomy and possible pitfalls as well as experience with first-line therapy of recurrent and massive hemoptysis



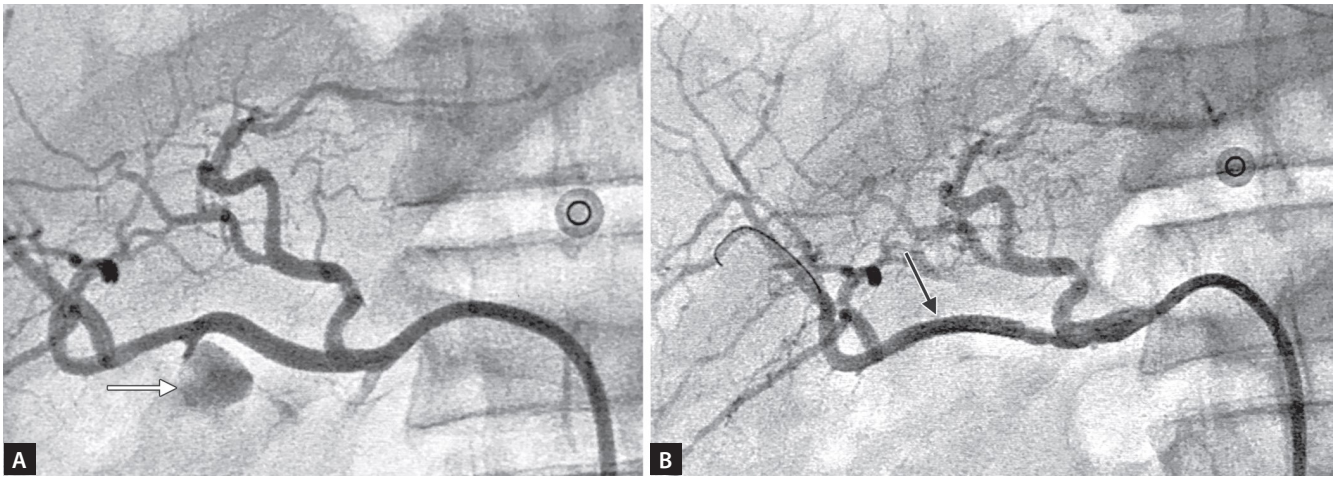
Figs. 2A and B: (A) 14F Malecot drain (black arrow) inserted percutaneously under USG/CT guidance in the peripancreatic collection with the tip adequately confirmed within the collection on CT; (B) 28F large-bore Malecot (black arrow) over the wire drain placed in the peripancreatic collection under CT guidance.



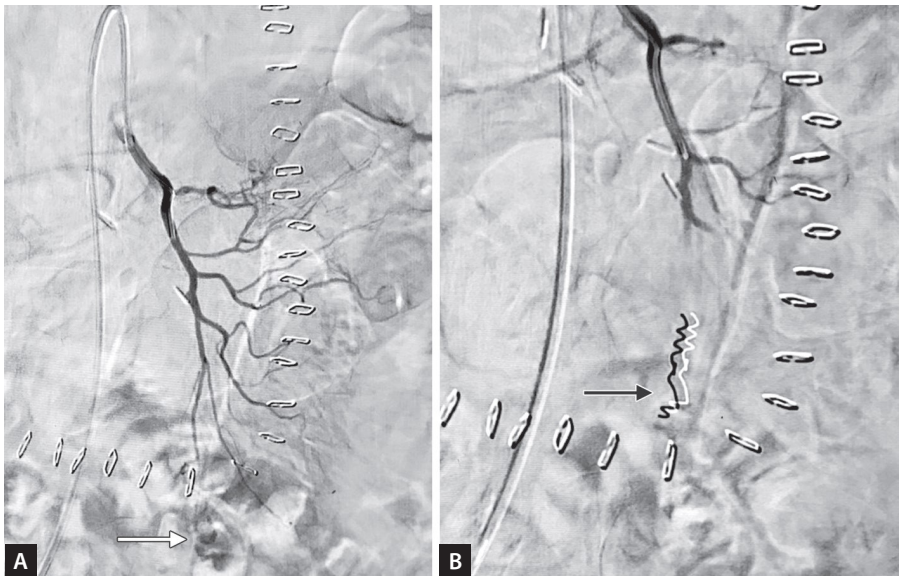
Figs. 3A and B: Patient with duodenal ulcer bleed (confirmed on endoscopy) with hemodynamic instability. (A) Catheter placed in the gastroduodenal artery (GDA) showing tiny active arterial contrast leak (white arrow) from one of its branches; (B) GDA gram showing no active contrast leak with successful embolization of bleeding vessel by coils (black arrow).



Figs. 4A to D: Patient with left gastric artery pseudoaneurysm and hemoperitoneum on CT scan of abdomen with hemodynamic instability. (A) Celiac artery angiogram showing a large pseudoaneurysm (white arrow) arising from the left gastric artery; (B) Superselective cannulation of the left gastric artery with microcatheter showing the filling of pseudoaneurysm (white arrow); ; (C) Placement of occluding coils (black arrow) with nonfilling of pseudoaneurysm; (D) Celiac angiogram showing coiled and occluded left gastric artery (black arrow) with normal filling of hepatic and splenic arteries.



Figs. 5A and B: Patient with acute hematemesis on eighth day after Whipple surgery. (A) Common hepatic angiogram showing pseudoaneurysm arising at the level of gastroduodenal artery stump (white arrow); (B) Poststent-graft insertion (black arrow), angiogram showing complete exclusion of pseudoaneurysm with normal filling of all hepatic artery branches.



Figs. 6A and B: Patient with blunt abdominal trauma postsurgical evacuation of hemoperitoneum. Bleeding and hemoglobin fall 5 days after surgery. CT scan showed pseudoaneurysm arising from the ileal branch of the superior mesenteric artery and large hematoma. (A) Superior mesenteric artery angiogram showing active contrast leak (white arrow) from a tiny ileal branch; (B) Postembolization with coils (black arrow), angiogram showing no active bleed.

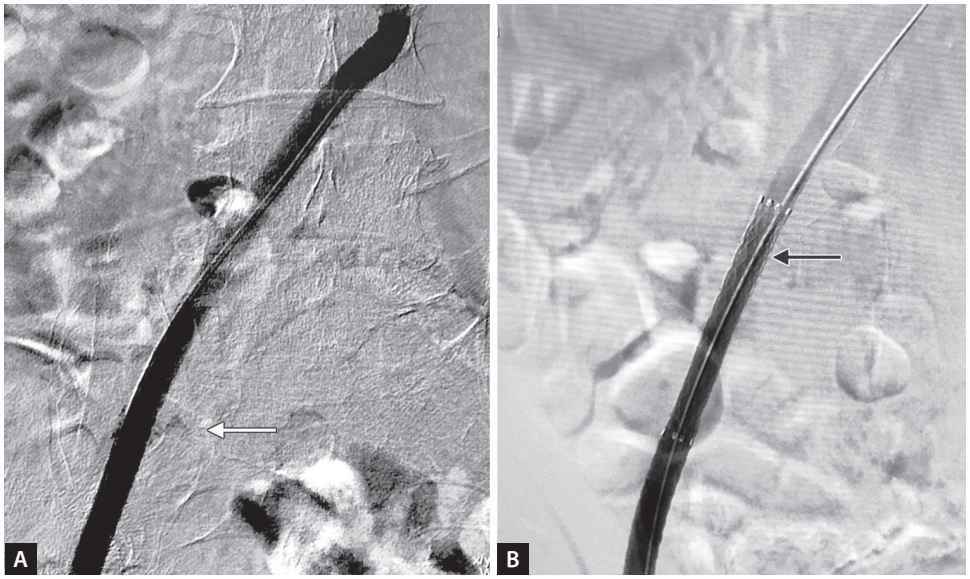
or as an intervention prior to elective surgery. Recurrent episodes of hemoptysis are not uncommon and require a prompt repeat BAE after exclusion of extrabronchial systemic and pulmonary artery bleeding sources **(Figs. 13A and B)**.[9,10]

Oral Bleed

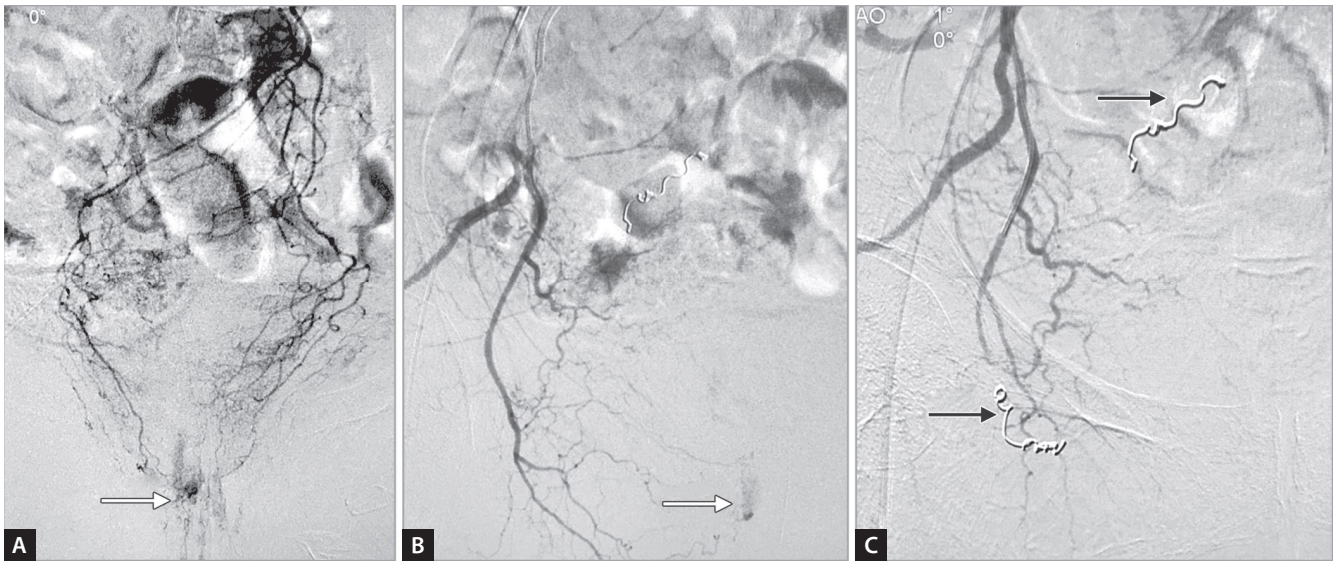
Massive oral bleed requiring critical care units is generally found in postsurgical or radiotherapy patients with head and neck malignancy, epistaxis, high-flow AVM of mandible/maxilla or palate, and postsurgery bleeds. Therapeutic transcatheter embolization is the procedure of choice in these kinds of patients, where the role of surgery is limited or negligible. Embolization of tumor-feeding branches is done in cases of malignancies; bleeding vessel embolization is done in pseudoaneurysm of external carotid branches or covered stent-graft insertion is done in carotid blowout patients **(Figs. 16A to D)**.[11]

Trauma

Endovascular transcatheter embolization is an established life-saving procedure to stop bleeding from solid organs or extremities. The procedure is done through a minimally invasive technique under angiographic control with less disruption of normal tissues. The embolizing agents work by creating a mechanical occlusion by placing coils, vascular



Figs. 7A and B: Patient with aortofemoral bypass presented with large melena and hypotension. CT scan showed active bleed from graft into the ileal loop suggestive of vascular and bowel communication. The patient was 21 days postsurgery. (A) Digital subtraction angiogram showing active contrast leak (white arrow) suggestive of active bleed from the aortofemoral graft site; (B) Postcovered stent-graft insertion (black arrow), gram revealing no active bleed.



Figs. 8A to C: Patient with active fresh per rectal bleeding with hemoglobin fall and hemodynamic instability. (A) Inferior mesenteric angiogram showing active bleed (white arrow) from the right rectal wall; (B) Right internal iliac artery angiogram showing active bleed (white arrow) from the inferior rectal artery; (C) Postembolization of both superior and inferior rectal arteries with coils (black arrow), no active bleed is noted.

plugs, polyvinyl alcohol particles, gelfoam or n-butyl cyanoacrylate (NBCA) in the bleeding vessels. The choice of the embolic agent is governed by anatomy and location of the bleeding vessel. If the vessel is very important like carotid or aorta, covered stent-grafts are used.

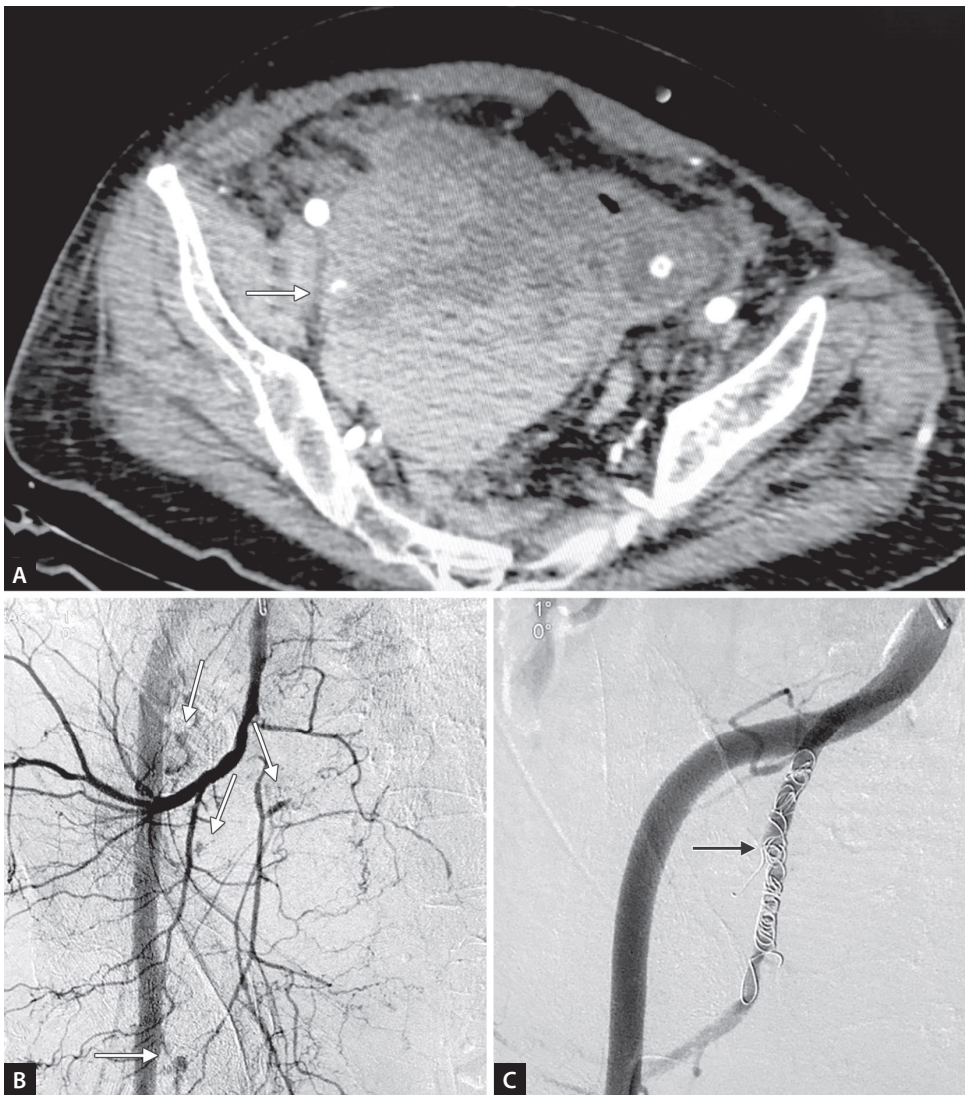
Multidetector computed tomography (MDCT) angiography or arterial phase diagnoses the active bleed or pseudoaneurysm in all the cases prior to taking up the patient for embolization. Embolization is used for liver, spleen, renal, mesenteric, thoracic, carotid, pelvic bone, and femur injuries **(Figs. 18A and B)**.[12]

Pulmonary Embolism

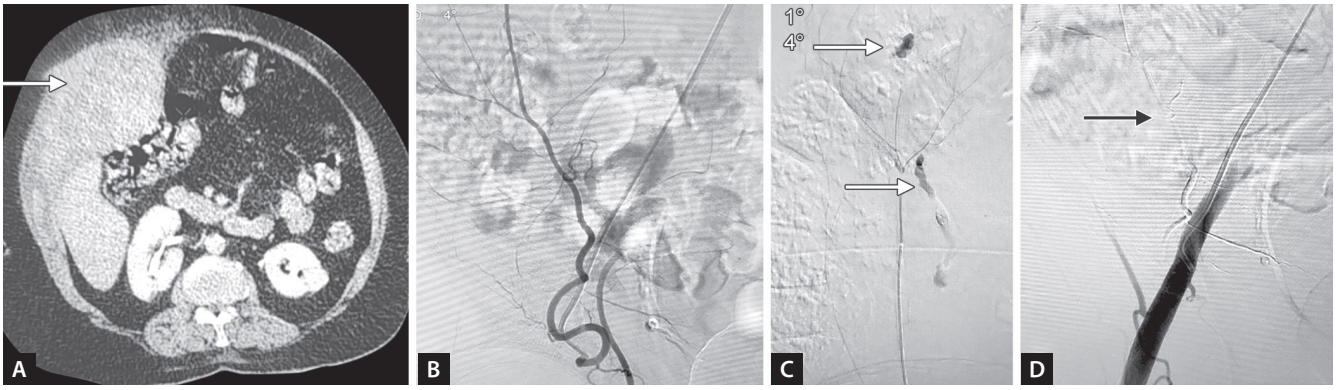
Pulmonary embolism is one of the most common causes of cardiovascular death worldwide, especially if not diagnosed early.

Pulmonary embolisms are categorized into three main risk categories:

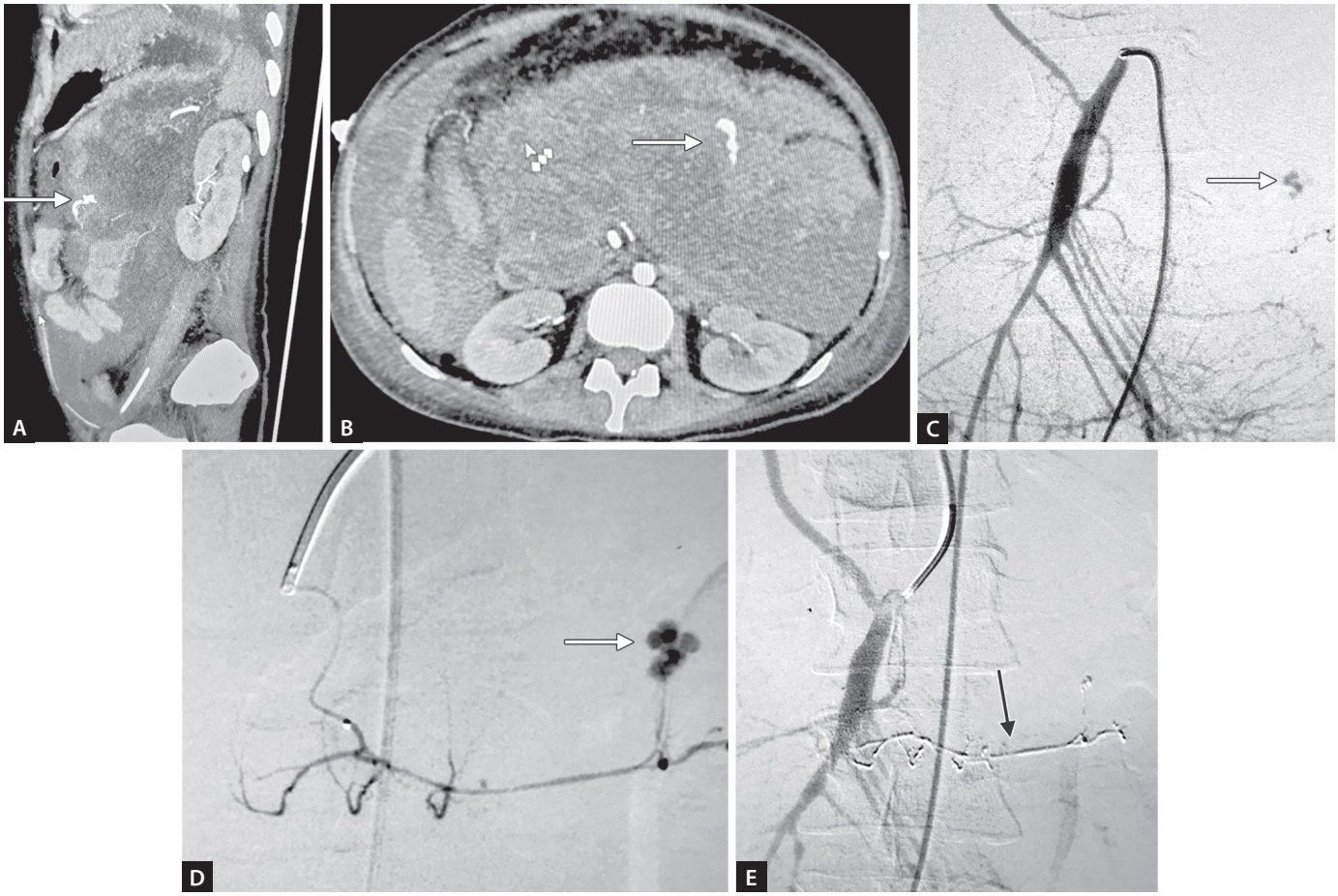
1. Low risk
2. Intermediate (submassive)
3. Intermediate-high:
   a. Intermediate-low risk
   b. High risk (massive)



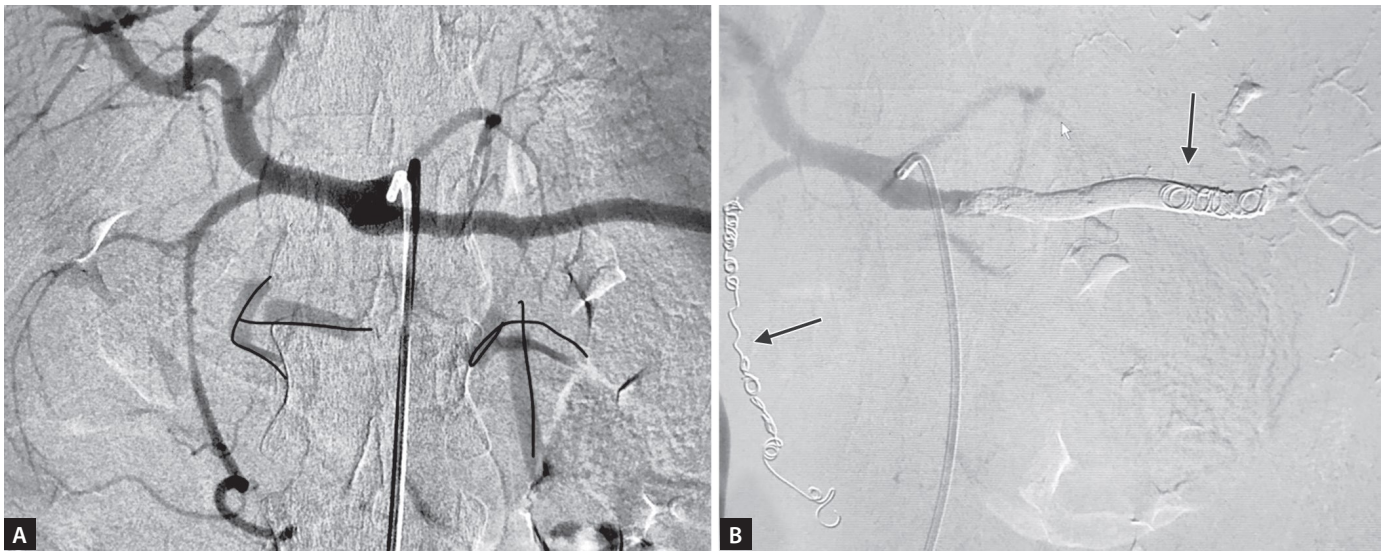
Figs. 9A to C: A 60-year-old male COVID-positive patient with hemoperitoneum and hemoglobin fall with CT scan showing multiple bleeders in the right pelvis. (A) Axial CT angiography image showing active contrast ooze (white arrow) and hemoperitoneum; (B) Right internal iliac artery angiography image showing multiple, tiny contrast leaks from distal aspects of many branches (white arrows); (C) Postembolization of the right internal iliac artery with coils (black arrow), no active bleed is noted.



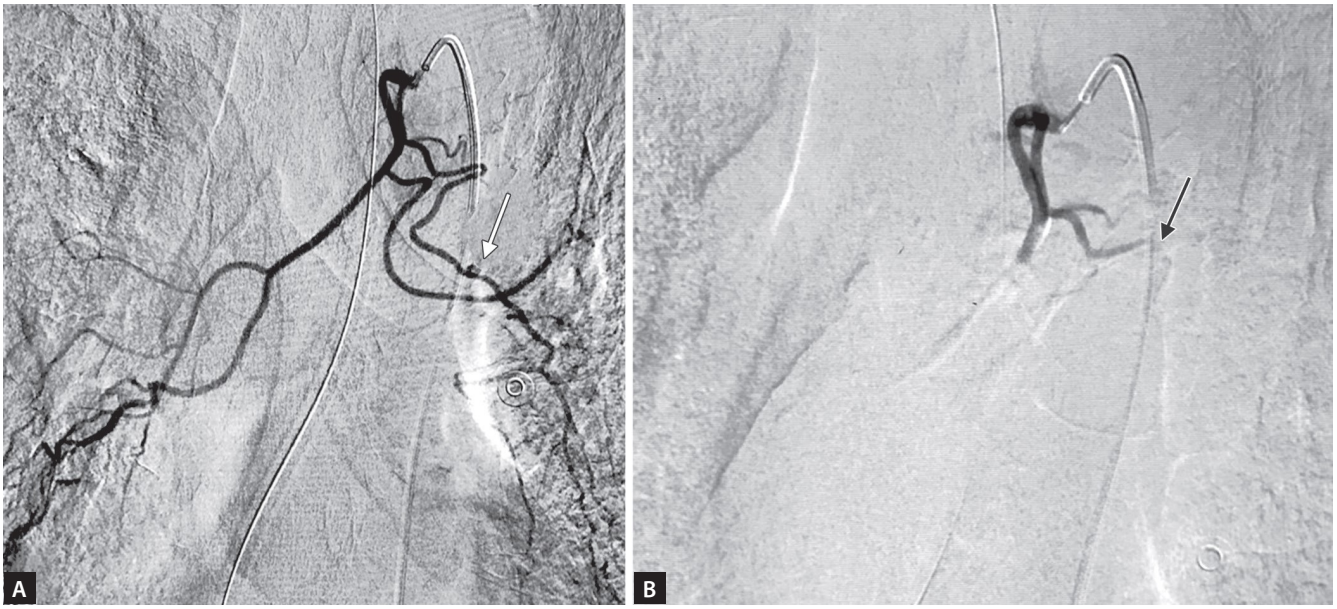
Figs. 10A to D: A 45-year-old male COVID-positive patient with abdominal pain and swelling associated with hemoglobin fall with CT scan showing right rectus sheath hematoma. (A) Axial CT angiography image showing large rectus sheath hematoma (white arrow); (B) Digital subtraction angiogram image of the right inferior epigastric artery; (C) Superselective angiogram with microcatheter in the right inferior epigastric artery showing multiple areas of active bleed (white arrows); (D) Postembolization with N-butyl-cyanoacrylate (NBCA; black arrow), angiogram showing no active bleed and no filling of the right inferior epigastric artery.



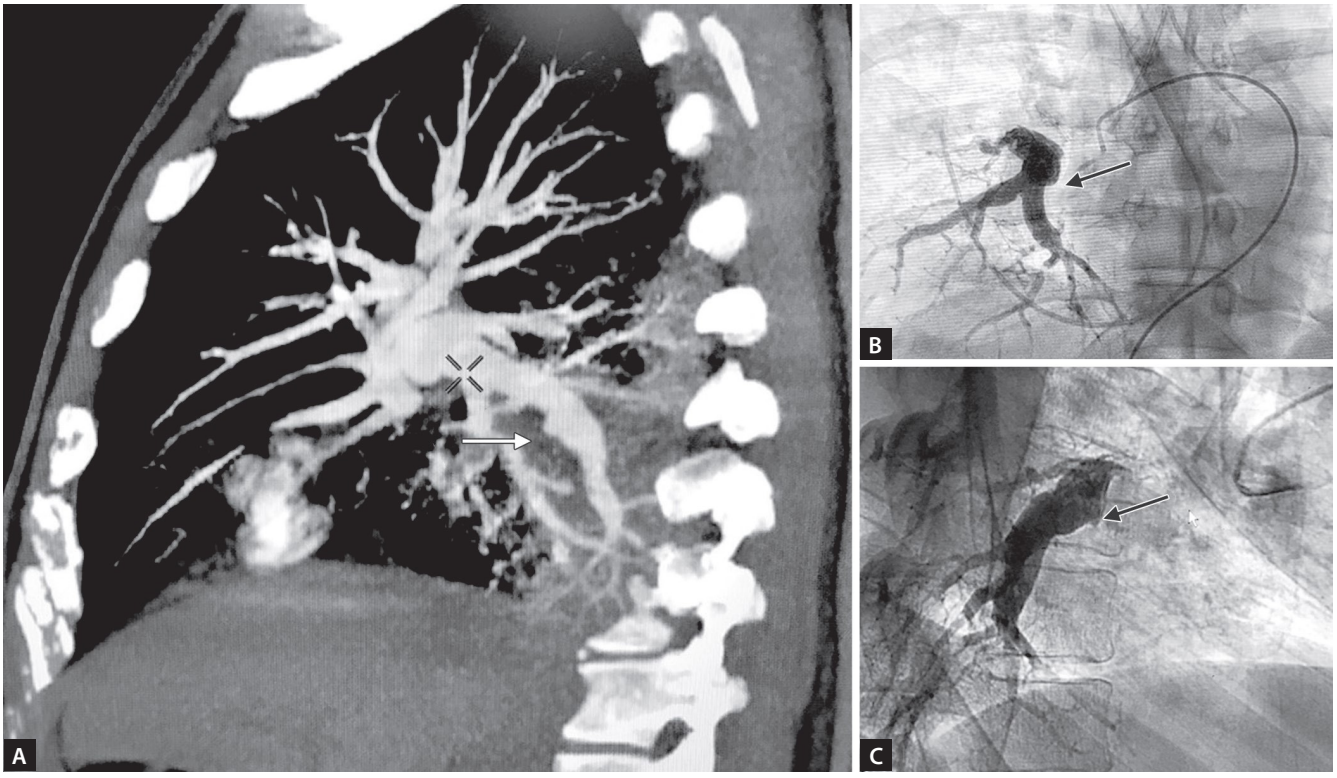
Figs. 11A to E: A 26-year-old female with acute pancreatitis in the fourth week developed severe pain and hypotension. CT scan showed large peripancreatic collection with blood inside and active contrast ooze. (A and B) Sagittal and axial images, respectively, showing active contrast leak (white arrow) in the large peripancreatic collection; (C) Superior mesenteric artery (SMA) angiogram showing active bleed (white arrow) from the first jejunal branch; (D) Superselective cannulation of the first jejunal branch confirming the source of active bleed (white arrow); (E) Postembolization with N-butyl cyanoacrylate (NBCA; black arrow), SMA gram showing no active bleed.



Figs. 12A and B: Acute pancreatitis with hemoperitoneum. CT scan showed gastroduodenal artery (GDA) and splenic artery pseudoaneurysm. (A) Celiac angiogram showing pseudoaneurysm (pencil arrow) arising from mid-GDA and mid-splenic artery; (B) Celiac angiogram after embolization with coils (black arrow) in GDA and coils–N-butyl-cyanoacrylate mixture (black arrow) in splenic artery showing no filling of either GDA or splenic artery.



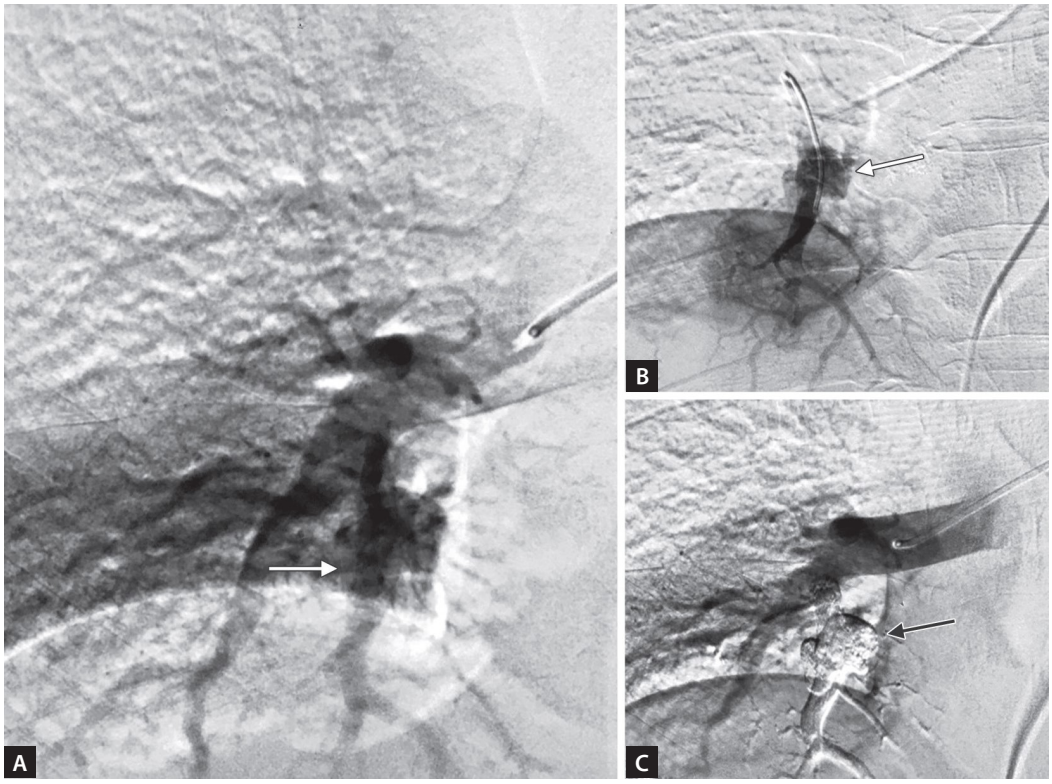
Figs. 13A and B: Patient with massive hemoptysis. (A) DSA showing common bronchial artery with pseudoaneurysm (white arrow) arising from the left bronchial branch; (B) Postembolization, gram revealing filling of pseudoaneurysm and both bronchials (black arrow).



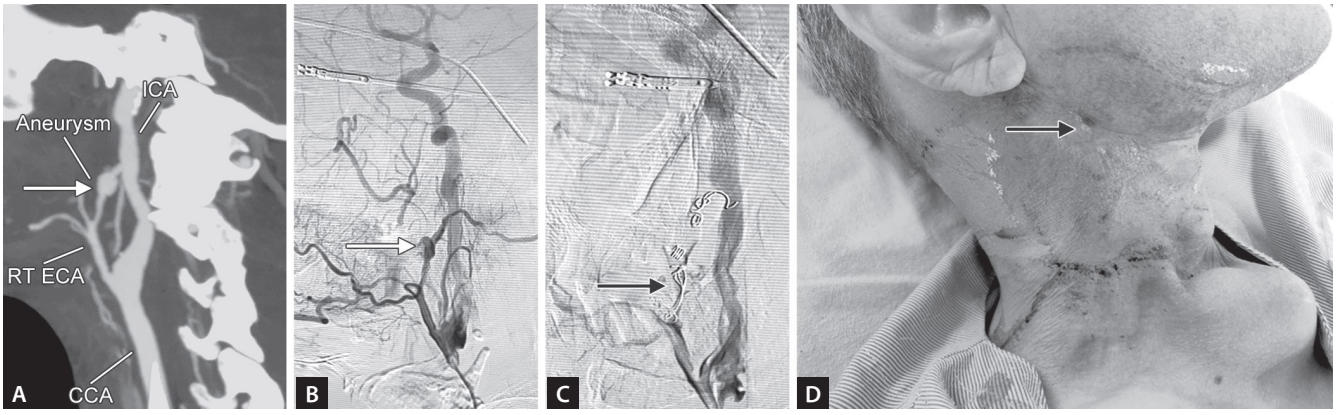
Figs. 14A to C: Patient with massive hemoptysis. History of COVID and admission for the same before 1 month. (A) CT pulmonary angiography image showing aneurysm (white arrow) with surrounding consolidation of posterobasal branch of the right descending pulmonary artery; (B and C) Anteroposterior and lateral views after N-butyl-cyanoacrylate (NBCA) cast formation inside the bleeder branch as well as occluded pseudoaneurysm (black arrow).

Echocardiography and CT pulmonary angiography are the main diagnostic investigations to look for hemodynamic assessment and clot burden.

Massive PE has high mortality rates; hence, IR procedures are performed in emergency. Massive PE is defined by hemodynamic instability with signs of hypotension (systolic pressure < 90 mm Hg) or shock, whereas submassive PE presents with signs of right ventricular dysfunction (RVD) or myocardial necrosis without hemodynamic instability. In the setting of acute PE, RVD is a poor prognostic indicator.



Figs. 15A to C: Patient with massive hemoptysis. History of COVID and admission for the same before 21 days. (A) Digital subtraction angiogram (DSA) showing pseudoaneurysm (white arrow) arising from the medial basal branch of the right descending pulmonary artery; (B) Superselective cannulation of the bleeder branch with microcatheter showing the pseudoaneurysm (white arrow); (C) Postembolization with N-butyl-cyanoacrylate (NBCA; black arrow), no contrast filling of pseudoaneurysm as well as medial basal branch is noted.

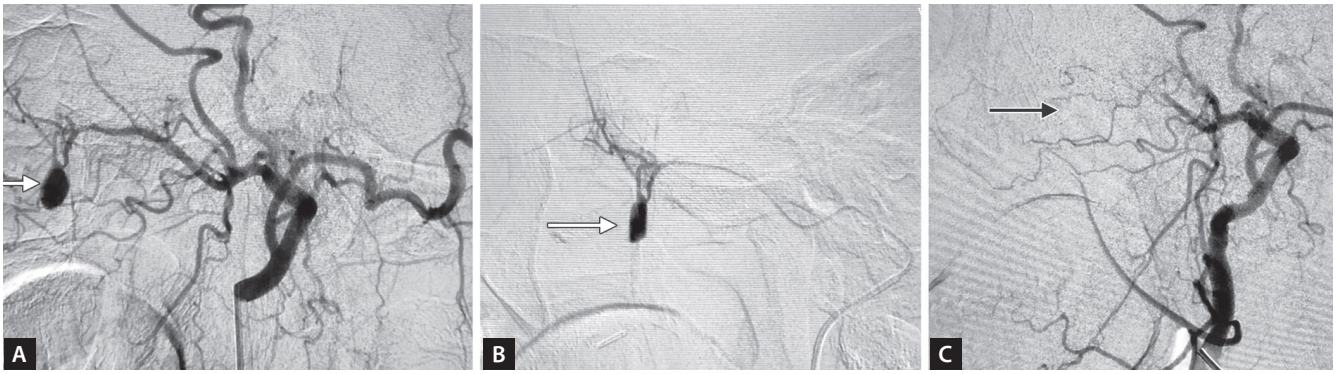


Figs. 16A to D: A 57-year-old male postsurgery/chemotherapy/radiotherapy for right head and neck malignancy. He is presented in emergency with active fresh pulsatile bleed from a neck wound. (A) CT angiography image showing pseudoaneurysm (white arrow) arising from the occipital branch; (B) Digital subtraction angiogram (DSA) confirming the pseudoaneurysm (white arrow); (C) DSA after coiling (black arrow) showing no filling of pseudoaneurysm as well as the occipital branch; (D) Clinical wound picture with area of bleed (black arrow).

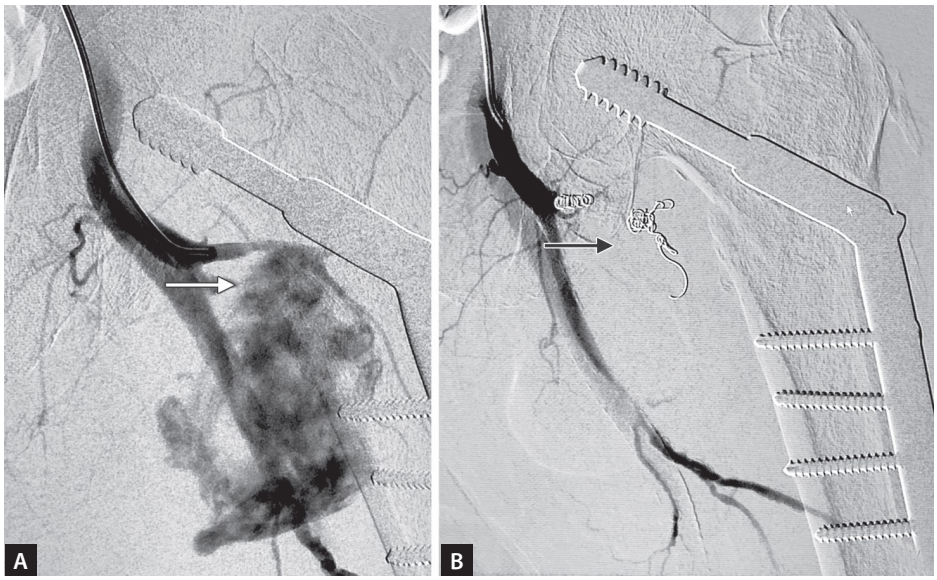
Surgical embolectomy is highly risky, whereas catheter-directed thrombolysis (CDT) + endovascular thrombectomy is less risky and minimally invasive in which thrombus is aspirated and a multiholed catheter is placed in the pulmonary arteries and thrombolytic infusion is started which helps in achieving faster recanalization times. Trials like ULTIMA, SEATTLE II, and PERFECT registry established the role of CDT in massive PE **(Figs. 20A and B)**.[13]

Stroke

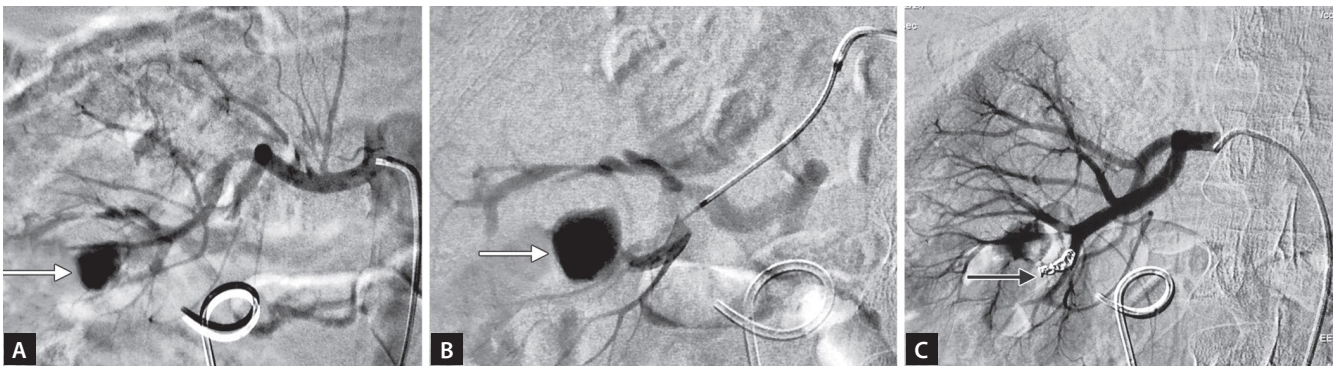
Management of acute stroke has evolved significantly over the last few decades. It started with the introduction of intravenous recombinant tissue plasminogen activator (IV rt-PA) in studies demonstrating improved clinical outcomes in patients treated within 3 hours of stroke ictus. Despite the clinical benefits of IV rt-PA, recanalization rates, ranging between 4.4% for distal internal carotid artery



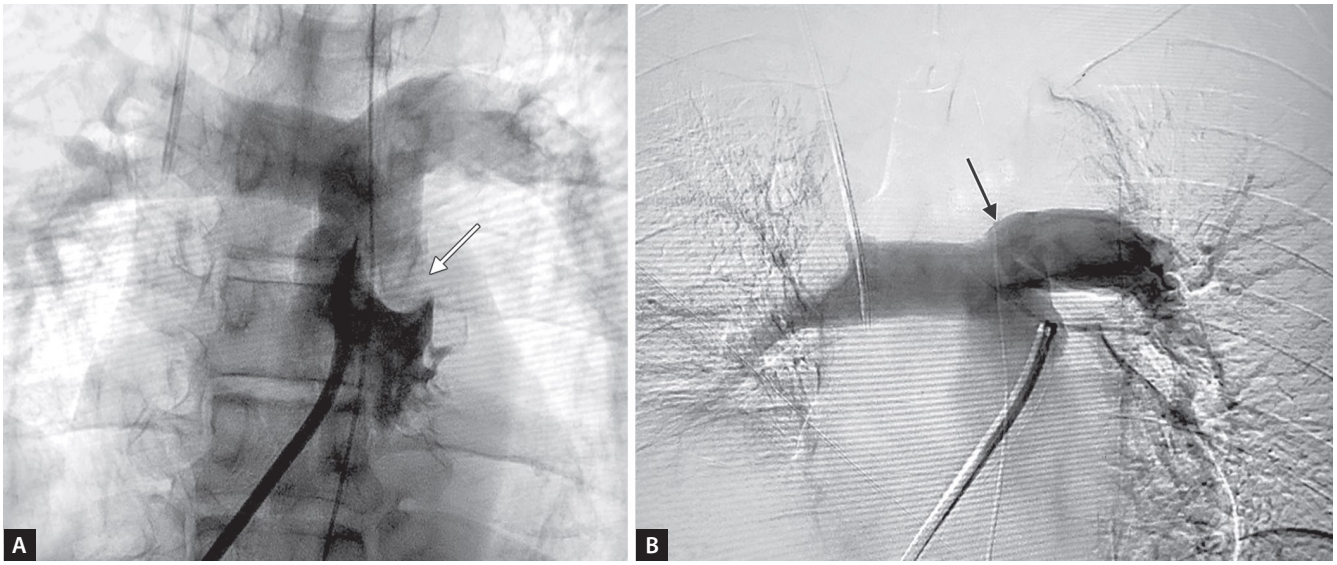
Figs. 17A to C: 11 days postcommando surgery for right buccal malignancy. The patient presented with multiple episodes of fresh bleed from the suture site. (A) Lateral digital subtraction angiogram image of the right external carotid artery showing pseudoaneurysm (white arrow) arising from the internal maxillary artery; (B) Superselective cannulation with a microcatheter confirming the pseudoaneurysm (white arrow); (C) Postembolization, no filling of pseudoaneurysm (black arrow) is noted on the right external carotid gram.



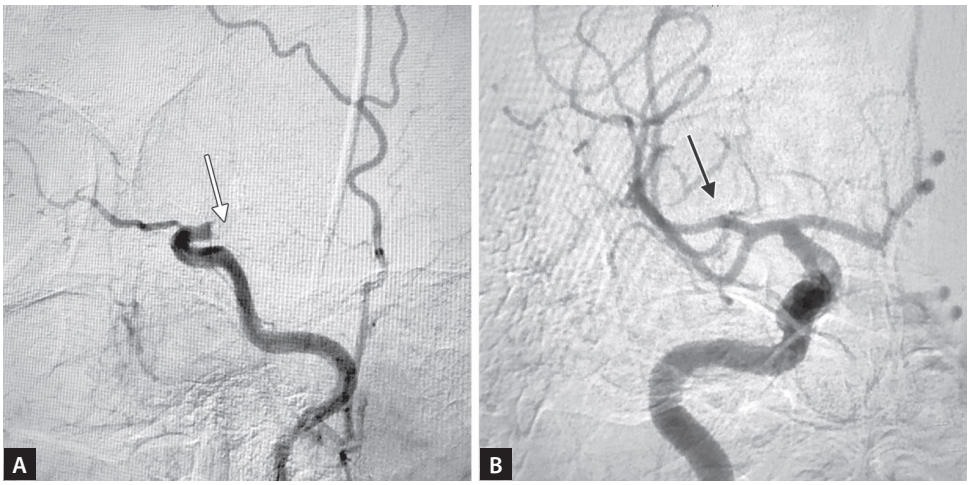
Figs. 18A and B: Patient with large left thigh hematoma after orthopedic surgery for traumatic left femur fracture. (A) DSA showing large pseudoaneurysm (white arrow) arising from the left profunda femoris artery; (B) Postcoiling (black arrow), angiogram showing no filling of pseudoaneurysm with patent rest of the branches of the left profunda femoris artery and patent superficial femoral artery.



Figs. 19A to C: Patient with recurrent hematuria, hemoglobin fall, urinary retention, and severe lower abdominal pain. There is a history of right percutaneous nephrolithotomy (PCNL) before 45 days. (A) Right renal angiogram showing large pseudoaneurysm (white arrow) arising from the lower polar branch; (B) Superselective cannulation of branch feeding the pseudoaneurysm (white arrow) with microcatheter; (C) Post-coiling (black arrow) of bleeder branch, renal angiogram shows no filling of pseudoaneurysm.



Figs. 20A and B: Patient in intensive care unit (ICU) after neurosurgery before 10 days. Acute hypotension with echocardiography findings of right ventricular dysfunction (RVD). Clinical diagnosis of large pulmonary thromboembolism confirmed on computed tomography (CT) pulmonary angiography. Doppler showed right lower limb deep venous thrombosis. With a deteriorating clinical condition, catheter-directed thrombolysis (CDT) was attempted. (A) Angiogram from common pulmonary artery showing large thrombus in the main trunk (white arrow) as well as in both the pulmonary arteries with poor distal filling; ; (B) Post-CDT, clearing of a large amount of thrombus from the main trunk (black arrow) with good filling of distal bilateral pulmonary arterial branches correlating with good clinical improvement after 24 hours.



Figs. 21A and B: A 45-year-old male smoker presented with acute left-sided stroke in emergency with a 3-hour history (window period). Computerized Tomography angiography confirmed the right middle cerebral artery (MCA) occlusion. (A) Lateral digital subtraction angiogram (DSA) image showing complete occlusion of right MCA (white arrow); (B) After mechanical thrombectomy (MET), anteroposterior view showing complete filling of both anterior cerebral artery (ACA) and MCA (black arrow) and brisk distal flow.

(ICA) occlusion, 4% for basilar artery occlusions, and 30% for middle cerebral artery (MCA) M1 and M2 segment occlusions, were not good. Many studies have shown the importance of vascular recanalization for better clinical outcomes. So newer endovascular devices were developed. The MERCI trial achieved 46–48% rates of revascularization in arterial occlusion resistant to IV rt-PA.

The five studies, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), Endovascular Revascularization with Solitaire Device versus Best Medical Therapy in Anterior Circulation Stroke within 8 hour (REVASCAT), Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE), Solitaire TM FR as Primary Treatment for Acute Ischemic Stroke (SWIFT PRIME), and Extending the Time for Thrombolysis in Emergency Neurological Deficits with Intra-Arterial Therapy (EXTEND IA) have demonstrated the critical role of selecting patients by advanced neuroimaging, the superior recanalization capacity of stent retrievers, and the effects of minimization of work processes, thus keeping MET as a first option in patients with stroke presented within the window period. The option of MET is consistent in all the trials though imaging, intervention times, and revascularization rates are different **(Figs. 21A and B)**.[14]

Mesenteric Artery Thrombosis

Mesenteric artery thrombosis is an important cause of acute abdomen with most patients presenting with severe abdominal pain, which persists for >2–3 hours and also tenderness and signs of peritonitis if presented late. Nonspecific symptoms are diarrhea, nausea, and vomiting which are seen early. Occult blood may be present in stools. Sometimes, patients present with chronic abdominal pain followed by sudden increase which is seen as acute on chronic mesenteric ischemia.

CT has emerged as the primary and accurate diagnostic modality for acute abdominal disorders. Vascular pathology is correctly addressed and detailed information is available on CT; however, the bowel vitality can only be accurately diagnosed on laparotomy or laparoscopy. The treatment flowchart for mesenteric arterial ischemia involves endovascular first approach followed by surgical resection.

Endovascular first approach (in order to restore vessel patency to revitalize more length of bowel) consists of:

- Aspiration thrombectomy
- Catheter-directed thrombolysis
- Superior mesenteric artery (SMA) stenting

With this approach, patients are saved from repeated surgeries as cutoff margins are well formed and longer length of bowel is preserved, thus improving survival rates **(Figs. 22A and B)**.[15,16]

Mesenteric Venous Thrombosis

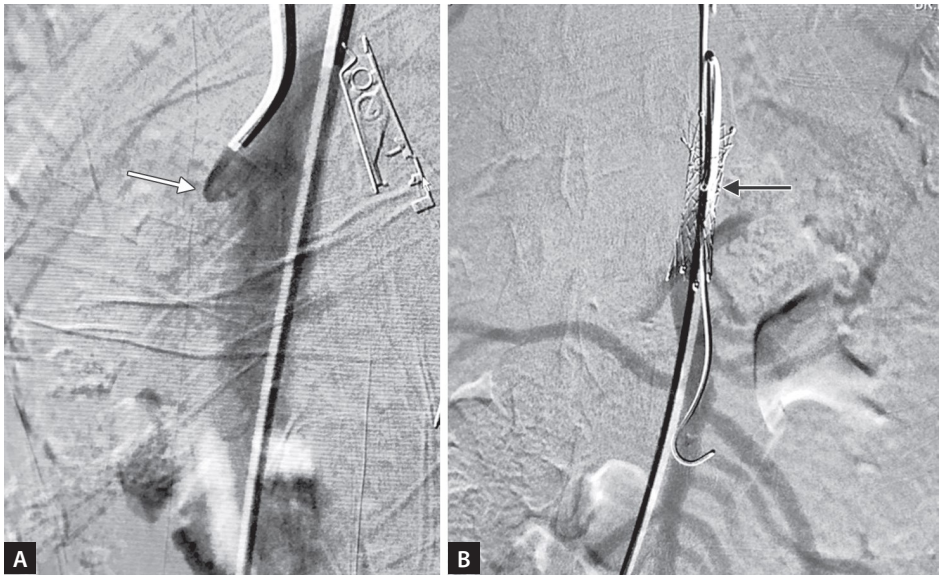
With the advent of MDCT, mesenteric venous thrombosis is increasingly recognized as a cause of mesenteric ischemia, presenting with abdominal pain. Prothrombotic state, hematological malignancy, and local abdominal inflammatory conditions are common predisposing conditions. Over the last decade, *JAK2* (Janus kinase 2) mutation has emerged as an accurate biomarker for diagnosis of myeloproliferative neoplasm, an important cause for mesenteric venous thrombosis. Anticoagulation is the treatment of choice for acute mesenteric venous thrombosis. CDT through the transjugular route and TIPSS are other treatment options reserved for patients not responding to anticoagulation (worsening pain even after 48–72 hours after initiation of anticoagulation) or in severely morbid cases, where early recovery is required to prevent mortality. Surgery is performed on patients with signs of peritonitis or CT suggestive of bowel perforation or gangrene.[17]

CEREBRAL VENOUS SINUS THROMBOSIS

Cerebral sinus venous thrombosis (CSVT) is a rare form of venous thromboembolism (VTE). CSVT represents almost 0.5–3% of all the types of stroke, affecting predominantly younger people, with an estimated incidence for adults of 3–4 per million, and for children 7 per million.

Cerebral sinus venous thrombosis is more common in women with a 3:1 ratio. It is also more common in the puerperium period.

Treatment strategies are aimed to control or resolve the underlying pathology, controlling intracerebral hemorrhage (ICH), and treatment of seizures or focal deficits caused by cerebral edema or infarction. Anticoagulation is used almost universally and in selected morbid cases, endovascular techniques have been employed to remove or dissolve the clot.



Figs. 22A and B: A 50-year-old male smoker presented with acute abdominal pain and distension. Computerized tomography angiography showed acute superior mesenteric artery (SMA) thrombosis with bowel ischemia and no infarct. (A) Lateral digital subtraction angiogram (DSA) abdominal image showing complete occlusion of SMA (white arrow); (B) After SMA stenting, anteroposterior view showing complete patency of stent (black arrow) with good filling of all its branches.

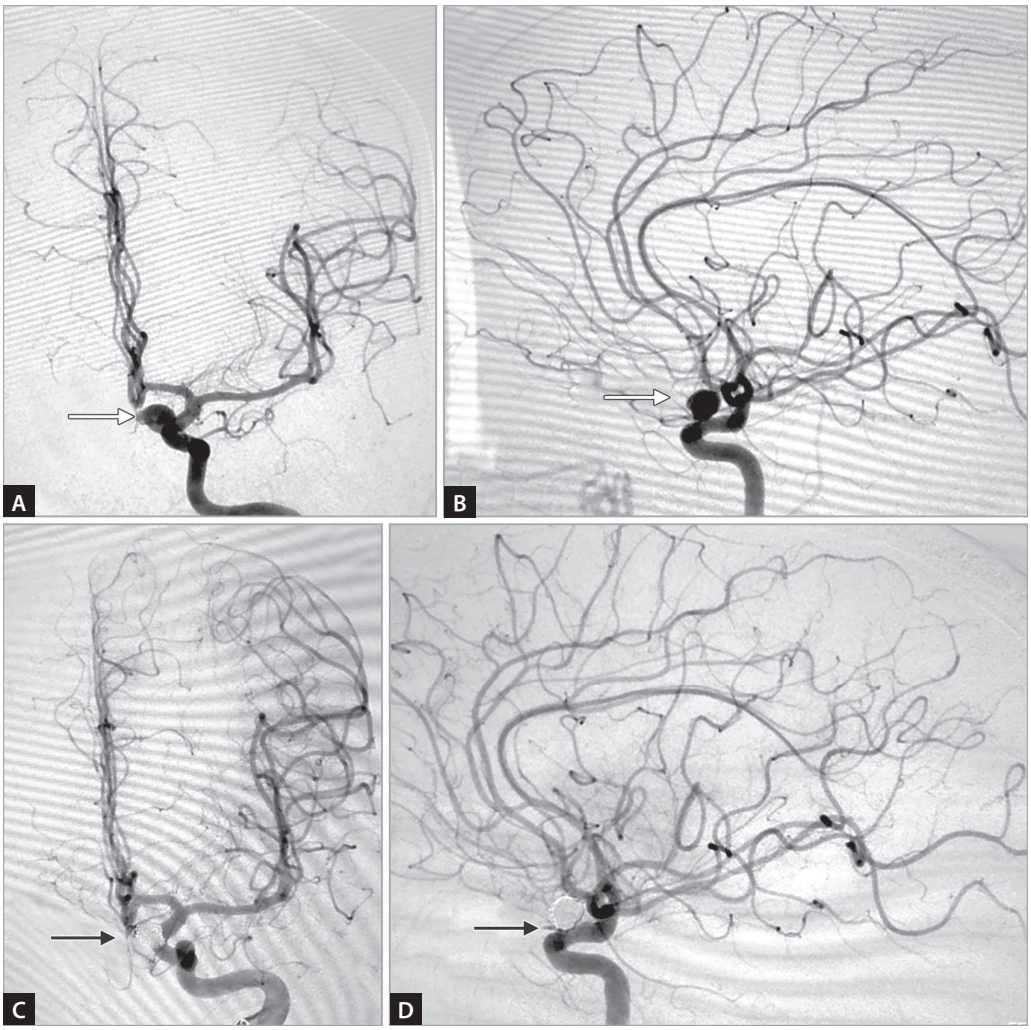
Endovascular thrombolysis or MET improves recovery time. Local fibrinolytic treatment restores blood flow more quickly and efficiently than heparin but carries the risk of hemorrhage.[18]

ANEURYSMAL SUBARACHNOID HEMORRHAGE

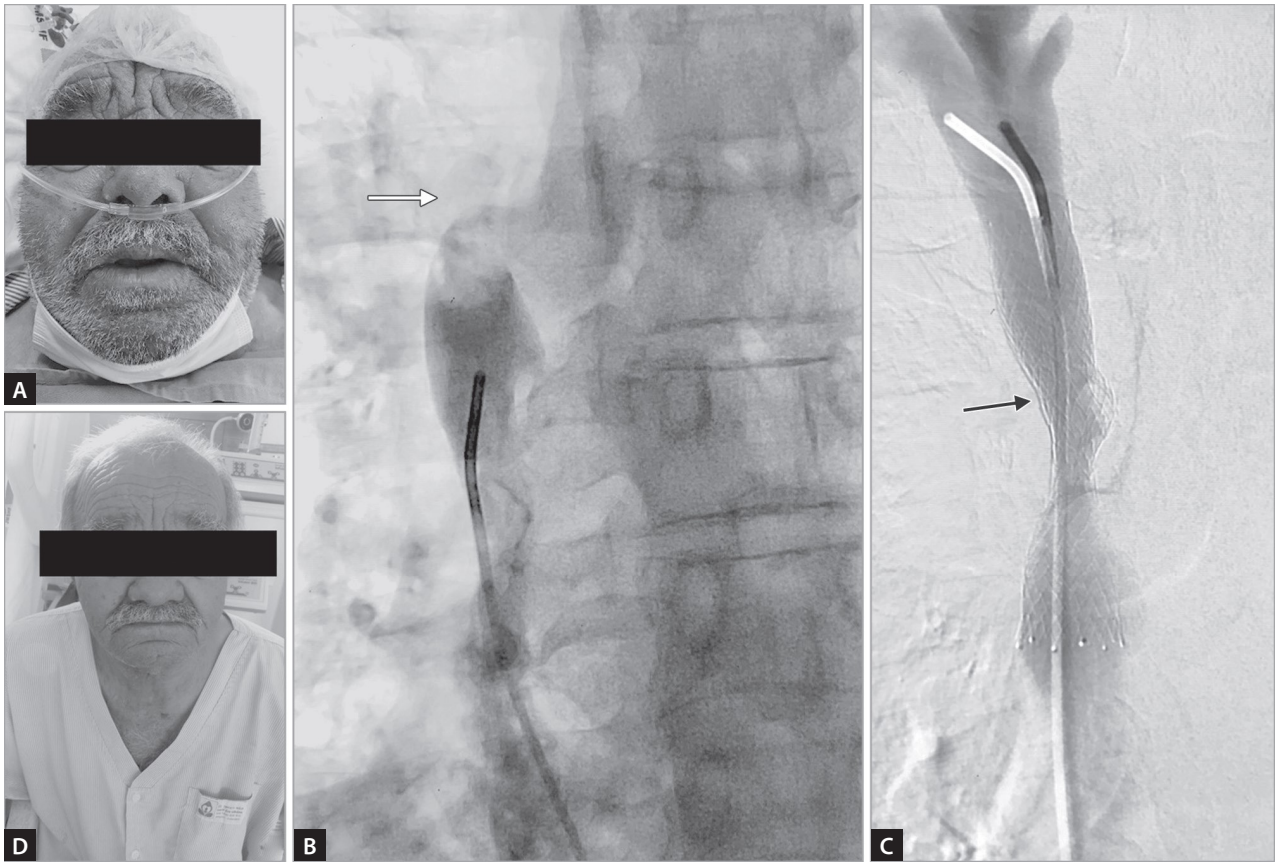
Aneurysmal subarachnoid hemorrhage (SAH) is a worldwide health burden with high fatality and permanent disability rates. The overall prognosis depends on the volume of the initial bleed, rebleeding, and degree of delayed cerebral ischemia (DCI). The important risk factors for the development of cerebral aneurysms are hypertension, smoking, chronic alcohol use, family history of intracranial aneurysms in first-degree relatives, and female sex.[19]

An untreated ruptured aneurysm is at high risk of rebleeding which can occur early or after several days. Risk increases over time and without intervention the cumulative risk at 4 weeks is 40%. Rebleeding has poor prognosis and high morbidity and mortality. In the ISAT trial, 59% of patients who suffered an early rebleed died. It is therefore important to occlude the aneurysm promptly.[20]

Treatment strategy is to occlude the aneurysms through endovascular or surgical technique and medical management of subarachnoid hemorrhage. Endovascular occlusion of intracranial aneurysms with detachable coils/balloon-assisted coiling/stent-assisted coiling or flow diverter insertions has been employed in thousands of patients since introduction of coils in the early 1990s, and in many centers it equals or bests placement of a neurosurgical clip as the first treatment option. Endovascular treatment is very effective for prevention of early recurrences of bleeding, and this technique has a low risk of procedural complications. Also, chemical angioplasty through injection of vasodilators catheter directed in the carotids are done in patients with severe vasospasm to prevent strokes **(Figs. 23A to D)**.[21]



Figs. 23A to D: A 57-year-old female with no comorbidities except hypertension presented with severe headache. CT scan showed subarachnoid hemorrhage grade III. Angiography showed left internal carotid artery (ICA) aneurysm. (A and B) Anteroposterior (AP) and lateral digital subtraction angiogram (DSA) images, respectively, showing large superomedially projecting left ICA aneurysm (white arrow); (C and D) AP and lateral DSA images, respectively, showing complete exclusion of aneurysm after coiling (black arrow).



Figs. 24A to D: A 65-year-old male chronic smoker presented with severe breathlessness and orthopnea. It is a known case of advanced carcinoma of the right lung. (A) Edematous face suggestive of superior vena cava (SVC) syndrome; (B) Occluded SVC on angiographic anteroposterior (AP) view (white arrow); (C) Post-SVC stenting, very good flow across the stent (black arrow); (D) Poststenting, clinical image after 24 hours showing significant improvement with no oxygen requirement.

CONTRAST-INDUCED NEPHROPATHY

Lifesaving vascular procedures such as embolizations and recanalizations cannot be done without iodinated–nonionic contrast media. Also, adequate diagnostic evaluation of the patient in a critical care unit needs a contrast CT scan. These patients being highly comorbid have a high risk of contrast-induced renal damage.

Contrast-induced nephropathy (CIN) is defined as impairment of renal function gauged as either a 25% rise in serum creatinine from baseline or an increase of 0.5 mg/dL in absolute serum creatinine value within 48–72 hours following intravenous contrast administration. However, CIN can occur up to 7 days after contrast administration. Serum creatinine levels increase between 2 and 5 days and usually return to baseline in 14 days. Estimated glomerular filtration rate (eGFR) is an important factor in prognosticating and risk stratifying for CIN. Periprocedural hydration is the best and the only preventive management to avoid CIN. Multiple studies have shown that bicarbonate, n-acetyl cysteine, rosuvastatin, and fenoldopam do not help in preventing CIN. Periprocedural hydration is started with 0.9% normal saline IV infusion at a rate of 1 mL/kg/h for 6–12 hours before the procedure and continuing after the procedure.

Contrast-induced nephropathy resolves itself within 7–14 days after contrast administration. Residual renal impairment is seen in <30% patients. Dialysis is required in <1% of the cases, with a slightly raised incidence either in patients who having an underlying renal impairment (3.1%) and or very high in patients suffering from uncontrolled diabetes or renal failure.[22]

CONCLUSION

Interventional radiology is a rapidly evolving branch and in the field of critical care, it may be of great help. It reduces significant morbidity, reduces the risk involved in conventional procedure, is of shorter duration, and requires minimum anesthesia and sedation.

REFERENCES

1. Lorenz JM. Unconventional venous access techniques. Semin Intervent Radiol. 2006;23(3):279-86.
2. Lee KA, Ramaswamy RS. Intravascular access devices from an interventional radiology perspective: indications, implantation techniques, and optimizing patency. Transfusion. 2018;58(Suppl 1):549-57.
3. Jaffe TA, Nelson RC. Image-guided percutaneous drainage: a review. Abdom Radiol (NY). 2016;41(4):629-36.

4. Priyadarshi RN, Prakash V, Anand U, Kumar P, Jha AK, Kumar R. Ultrasound-guided percutaneous catheter drainage of various types of ruptured amebic liver abscess: a report of 117 cases from a highly endemic zone of India. Abdom Radiol (NY). 2019;44(3):877-85.
5. Takeuchi N, Emori M, Yoshitani M, Soneda J, Takada M, Nomura Y. Gastrointestinal bleeding successfully treated using interventional radiology. Gastroenterology Res. 2017;10(4):259-67.
6. Morgan TG, Carlsson T, Loveday E, Collin N, Collin G, Mezes P, et al. Needle or knife? The role of interventional radiology in managing uncontrolled gastrointestinal bleeding. Int J Gastrointest Interv. 2021;10:17-22.
7. Ramaswamy RS, Choi HW, Mouser HC, Narsinh KH, McCammack KC, Treesit T, et al. Role of interventional radiology in the management of acute gastrointestinal bleeding. World J Radiol. 2014;6(4):82-92.
8. Salahia G, Chin SC, Zealley I, White RD. The role of interventional radiology in the management of pancreatic pathologies. J Gastrointestinal Abdominal Radiol. 2020;3:99-114.
9. Ittrich H, Klose H, Adam G. Radiologic management of haemoptysis: diagnostic and interventional bronchial arterial embolisation. Rofo. 2015;187(4):248-59.
10. Larici AR, Franchi P, Occhipinti M, Contegiacomo A, del Ciello A, Calandriello L, et al. Diagnosis and management of hemoptysis. Diagn Interv Radiol. 2014;20(4):299-309.
11. Storck K, Kreiser K, Hauber J, Buchberger AM, Staudenmaier R, Kreutzer K, et al. Management and prevention of acute bleedings in the head and neck area with interventional radiology. Head Face Med. 2016;12:6.
12. Lopera JE. Embolization in trauma: principles and techniques. Semin Intervent Radiol. 2010;27(1):14-28.
13. Zarghouni M, Charles HW, Maldonado TS, Deipolyi AR. Catheter-directed interventions for pulmonary embolism. Cardiovasc Diagn Ther. 2016;6(6):651-61.
14. Palaniswami M, Yan B. Mechanical thrombectomy is now the gold standard for acute ischemic stroke: implications for routine clinical practice. Interv Neurol. 2015;4(1-2): 18-29.
15. Schoots IG, Levi MM, Reekers JA, Lameris JS, van Gulik TM. Thrombolytic therapy for acute superior mesenteric artery occlusion. J Vasc Interv Radiol. 2005;16(3):317-29.
16. Okamura S, Fujiwara H, Sonoyama T, Ochiai T, Ikoma H, Kubota T, et al. Management of acute superior mesenteric artery occlusion by thrombolytic therapy. Case Rep Gastroenterol. 2009;3(3):300-5.
17. Hmoud B, Singal AK, Kamath PS. Mesenteric venous thrombosis. J Clin Exp Hepatol. 2014;4(3):257-63.
18. Alvis-Miranda HR, Castellar-Leones SM, Alcala-Cerra G, Moscote-Salazar LR. Cerebral sinus venous thrombosis. J Neurosci Rural Pract. 2013;4(4):427-38.
19. D'Souza S. Aneurysmal Subarachnoid Hemorrhage. J Neurosurg Anesthesiol. 2015;27(3):222-40.
20. Anxionnat R, Tonnelet R, Derelle AL, Liao L, Barbier C, Bracard S. Endovascular treatment of ruptured intracranial aneurysms: Indications, techniques and results. Diagn Interv Imaging. 2015;96(7-8):667-75.
21. Sluzewski M, van Rooij WJ, Rinkel GJ, Wijnalda D. Endovascular treatment of ruptured intracranial aneurysms with detachable coils: long-term clinical and serial angiographic results. Radiology. 2003;227(3):720-4.
22. Modi K, Padala SA, Gupta M. Contrast-induced nephropathy. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022.

CHAPTER 103

Contrast Nephropathy: What is New?

Balasubramanian S, Prakash KC

INTRODUCTION

Contrast nephropathy (CN),as a clinical entity of importance, has been recognized since the 1950s after it was first reported by Bartels et al.[1] Much of the available literature published since then has discussed about its prevalence, risk factors, preventive strategies, and outcomes. Controversies continue to exist regarding the actual prevalence and various risk-preventive strategies. Recent years have seen emergence of a new terminology—contrast-associated nephropathy (CA-AKI) to replace the existing contrast-induced nephropathy. With the availability of propensity score adjusted models, recent studies have shown that the actual risk and incidence of CN seem to be overrated. This chapter intends to identify the risk factors of clinical significance and discusses the changing concepts of preventive strategies and the recent advances in the pathophysiology of CN. While indiscriminate use of contrast procedures should be discouraged, it should not be avoided in critically ill patients in the intensive care, when it is absolutely indicated as a lifesaving procedure, because of unfounded fear of CN.

INCIDENCE AND RISK FACTORS

The Kidney Disease Improving Global Outcomes (KDIGO) working group proposed the term "contrast-induced acute kidney injury" and has defined it based on a plasma creatinine level that has increased by 1.5 times or more over the baseline value within 7 days after exposure to contrast medium or a plasma creatinine level that has increased by at least 0.3 mg/dL (26.5 μmol/L) over the baseline value within 48 hours after exposure to contrast medium, or a urinary volume of <0.5 mL/kg of body weight/hour that persists for at least 6 hours after exposure.

This definition is problematic because it does not exclude the influence of other coincident causes of AKI with a casual association of intravenous (IV) contrast. Many of the published studies do not have proper controlled groups of patients with and without contrast exposure, because it may not be feasible to perform high-quality studies, due to many reasons. The effect of other confounding factors could incorrectly implicate the CM as the cause of AKI and overrating the incidence of contrast-induced nephropathy.[2,3] Based on the findings of recent large, well-controlled, observational studies,[3-6] that a substantial proportion of AKI occurring after IV CM administration is not attributable to CM, the American College of Radiology (ACR) committee on drugs and contrast has coined two terminologies—contrast-associated nephropathy and contrast-induced nephropathy.[7]

Contrast-associated acute kidney injury (CA-AKI) is defined as AKI occurring within 48 hours after the administration of CM, which encompasses all associated causes of AKI with casual association of the CM administration. Over the years, various risk factors like preexisting renal disease, diabetes, concomitant use of nephrotoxic drugs, associated comorbidities which cause renal hypoperfusion like congestive cardiac failure, cirrhosis of liver, and hypovolemia due to various causes have been described to be associated with AKI.

Contrast-induced acute kidney injury is the subset of CA-AKI that can be causally linked to CM administration.

A large retrospective study involving 985,737 patients who underwent percutaneous coronary intervention showed that the incidence of CN was strongly associated with the severity of baseline chronic kidney diseases (CKDs).[8] The risk of CN increases with each stepwise increase in stage of CKD. For patients with glomerular filtration rate (GFR) ≥ 60 mL/min/1.73 m^2, the incidence of CN was 5.2%, and dialysis was rarely required in these cases (0.07%). In contrast, in patients with GFR ≤ 30 mL/min/1.73 m^2 the incidence of CN was as high as 26.6%, of which 4.3% required dialysis.[8]

Multiple other patient-related risk factors mentioned above have been associated with CA-AKI, but pre-existing estimated GFR (eGFR) < 30 mL/min/1.73 m^2 has undoubtedly been the only primary risk factor linked to CI-AKI.[8] McDonald et al. performed propensity score analyses in specific cohorts with high AKI risk and these studies did not show an increased risk for AKI after CM exposure, even after risk stratification by eGFR.[9,10]

As far as the procedure-related risk of CA-AKI and CI-AKI is concerned, the osmolality and the volume of the CM are the two important factors to be considered for discussion. There are three types of IV contrast based on their osmolality: iso-osmolar contrast media (IOCM) (approximately 290 mOsm/kg closer to the serum osmolality), low-osmolar contrast media (LOCM) (approximately 600 mOsm/kg, which is still more than the serum osmolality), and high-osmolar contrast media (HOCM; >1,500 mOsm/kg). Most modern iodinated CM are classified as LOCM.[7] Based on results of a 2015 systematic review and meta-analysis, there is no clinically significant difference in CN between LOCM and IOCM.[11]

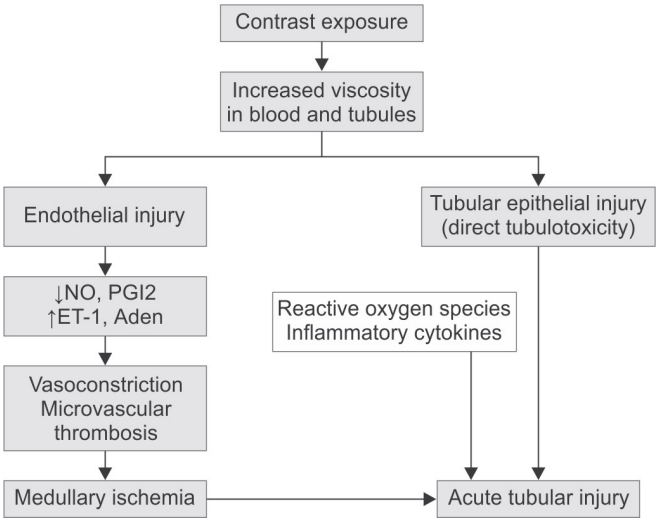
PATHOGENESIS (FLOWCHART 1)

Pathogenesis of CN includes direct tubulotoxicity, hemodynamically mediated vasoconstriction due to endothelial injury causing medullary ischemia, inflammation, release of reactive oxygen species (ROS), and all of these causing acute tubular injury. Dipeptidase-1 (DPEP-1) has been identified as the receptor for tubular reabsorption of contrast, and inhibition of DPEP-1 could be a new therapeutic target for prevention and treatment.[12]

Preventive Strategies

- Avoidance of contrast procedure and consider alternative imaging modalities like magnetic resonance angiography (MRA), carbon dioxide (CO_2) angiography, intravascular ultrasound, etc.
- Selection of LOCM/IOCM.
- Drugs to counteract the effect of vasoconstriction, ROS, and hypertonicity:
  - *Periprocedural IV hydration using 0.9% saline*: Many studies have shown that IV hydration, in variable doses and duration, significantly reduces the risk of CN. But this has been of concern in patients with cardiac failure or severe left ventricular dysfunction. Various studies on these groups of patients have showed significant reduction of CN, with judicious IV hydration done with monitoring of central venous pressure (CVP)[13] and left ventricular end-diastolic pressure (POSEIDON study).[14] The RenalGuard system is a dedicated device that aims to maintain high urine output (>300 mL/h sustained for 6 hours) with combined hydration and furosemide diuresis.[15] This system is currently being evaluated by a series of clinical trials, which have shown reduction in CN.[16,17]

Flowchart 1: Pathogenesis of contrast nephropathy.



(NO: nitric oxide; PGI2: prostaglandins; ET-1: endothelin-1; Aden: Adenosine)

Intravenous sodium bicarbonate and oral/IV N-acetylcysteine (NAC) have been used as antioxidants to counteract ROS. In addition, NAC has been shown to induce nitric oxide (NO) in the endothelium. However, studies have shown conflicting evidence in reducing CN. The Prevention of Serious Adverse Events Following Angiography (PRESERVE) study, which was a prospective randomized control trial including 5,177 patients at high risk for renal complications, showed that IV infusion of 1.26% sodium bicarbonate was not superior to IV infusion of 0.9% sodium chloride [9.5 vs. 8.3%, odds ratio (OR), 1.16; 95% confidence interval (CI), 0.96–1.41; $p = 0.13$]. This study also showed that 1,200 mg of oral NAC was not superior to oral placebo (9.1 vs. 8.7%, odds ratio (OR), 1.16; 95% CI, 0.96–1.41; $p = 0.13$) in the prevention of CN.[18]

Another prospective trial that included 2,308 patients at risk for CN, with two groups, one on 1,200 mg of oral NAC group and the other on oral placebo, showed same incidence of CN (12.7 vs. 12.7%, OR, 1.00; 95% CI, 0.81–1.25; $p = 0.97$).[19] These data do not support the use of NAC or sodium bicarbonate for the prevention of CN.

- Statins have also been used for their anti-inflammatory and antioxidant properties, with conflicting results in various trials.[20,21]
- Minimizing the volume of CM:
  - *Coronary sinus aspiration of contrast*: When performing a coronary angiogram, a part of the volume of IV contrast opacifies the coronaries and the rest of the contrast refluxes back into the coronary sinus and systemic circulation. This novel technique is used to aspirate the latter volume of contrast to reduce systemic exposure. Another contrast-modulating device called AVERT system has also been used to achieve the same. These techniques have been shown in studies that the volume of contrast exposure was significantly reduced but did not show clinical benefits in reducing the incidence of CN.[22,23] Properly designed high-quality studies with a larger number of patients may be needed to establish evidence for the clinical benefits.

CONCLUSION

With the emerging evidence, CM causes AKI undoubtedly in patients with pre-existing reduced eGFR < 30 mL/min/1.73^2 and may be in patients with eGFR between 30 and 45 mL/min. AKI occurring in patients with all other traditionally known risk factors who undergo intravascular contrast procedure may be misattributed to the CM, hence overrating the risk. While intravascular contrast procedures should be avoided wherever possible, it should not be denied in cases where the risk of avoiding it outweighs the risk of CN.

REFERENCES

1. Bartels ED, Brun GC, Gammeltoft A, Gjørup PA. Acute anuria following intravenous pyelography in a patient with myelomatosis. Acta Med Scand. 1954;150(4):297-302.
2. Davenport MS, Cohan RH, Ellis JH. Contrast media controversies in 2015: imaging patients with renal impairment or risk of contrast reaction. AJR Am J Roentgenol. 2015;204(6):1174-81.
3. Dekkers IA, van der Molen AJ. Propensity score matching as a substitute for randomized controlled trials on acute kidney injury after contrast media administration: a systematic review. Am J Roentgenol. 2018;211(4):822-6.
4. Davenport MS, Khalatbari S, Dillman JR, Cohan RH, Caoili EM, Ellis JM. Contrast material-induced nephrotoxicity and intravenous low-osmolality iodinated contrast material. Radiology. 2013;267(1):94-105.
5. McDonald RJ, McDonald JS, Bida JP, Carter RE, Fleming CJ, Misra S, et al. Intravenous contrast material-induced nephropathy: causal or coincident phenomenon? Radiology. 2013;267(1):106-18.
6. McDonald JS, McDonald RJ, Carter RE, Katzberg RW, Kallmes DF, Williamson EE. Risk of intravenous contrast material-mediated acute kidney injury: a propensity score-matched study stratified by baseline-estimated glomerular filtration rate. Radiology. 2014;271(1):65-73.
7. American College of Radiology. (2021). Manual on Contrast Media. [online] Available from https://www.acr.org/Clinical-Resources/Contrast-Manual [Last accessed March, 2022].
8. Tsai TT, Patel UD, Chang TI, Kennedy KF, Masoudi FA, Matheny ME, et al. Contemporary incidence, predictors, and outcomes of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the NCDR Cath-PCI registry. JACC Cardiovasc Interv. 2014;7(1):1-9.
9. McDonald JS, McDonald RJ, Williamson EE, Kallmes DF, Kashani K. Post-contrast acute kidney injury in intensive care unit patients: a propensity score-adjusted study. Intensive Care Med. 2017;43(6):774-84.
10. McDonald JS, McDonald RJ, Williamson EE, Kallmes DF. Is intravenous administration of iodixanol associated with increased risk of acute kidney injury, dialysis, or mortality? A propensity score-adjusted study. Radiology. 2017;285(2):414-24.
11. Eng J, Subramaniam RM, Wilson RF, Turban S, Choi MJ, Zhang A, et al.; Rockville (MD): Agency for Healthcare Research and Quality (US). Contrast-induced nephropathy: comparative effects of different contrast media [Internet]. 2015;15(16)-EHC022-EF.
12. Zhang F, Lu Z, Wang F. Advances in the pathogenesis and prevention of contrast-induced nephropathy. Life Sci. 2020;259:118379.
13. Qian G, Fu Z, Guo J, Cao F, Chen Y. Prevention of contrast-induced nephropathy by central venous pressure-guided fluid administration in chronic kidney disease and congestive heart failure patients. JACC Cardiovasc Interv. 2016;9(1):89-96.
14. Brar SS, Aharonian V, Mansukhani P, Moore N, Shen AYJ, Jorgensen M, et al. Hemodynamic-guided fluid administration for the prevention of contrast-induced acute kidney injury: the POSEIDON randomised controlled trial. Lancet. 2014;383(9931):1814-23.
15. Putzu A, Berto MB, Belletti A, Pasotti E, Cassina T, Moccetti T, et.al. Prevention of contrast-induced acute kidney injury by furosemide with matched hydration in patients undergoing interventional procedures: a systematic review and meta-analysis of randomized trials. JACC Cardiovasc Interv. 2017;10(4):355-63.
16. Briguori C, Visconti G, Focaccio A, Airoldi F, Valgimigli M, Sangiorgi GM, et al. Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II). RenalGuard System in high-risk patients for contrast-induced acute kidney injury. Circulation. 2011;124(11):1260-9.
17. Barbanti M, Gulino S, Capranzano P, Immè S, Sgroi C, Tamburino C, et al. Acute Kidney Injury with the RenalGuard System in patients undergoing Transcatheter Aortic Valve Replacement: The PROTECT-TAVI Trial (PROphylactic effecT of furosEmide-induced diuresis with matched isotonic intravenous hydraTion in Transcatheter Aortic Valve Implantation). JACC Cardiovasc Interv. 2015;8(12):1595-604.
18. Weisbord SD, Gallagher M, Jneid H, Garcia S, Cass A, Thwin SS, et al. Outcomes after angiography with sodium bicarbonate and acetylcysteine. N Engl J Med. 2018;378(7):603-14.
19. ACT Investigators. Acetylcysteine for prevention of renal outcomes in patients undergoing coronary and peripheral vascular angiography: main results from the randomized acetylcysteine for contrast-induced nephropathy trial. Circulation. 2011;124(11):1250-9.
20. Jo SH, Koo BK, Park JS, Kang HJ, Cho YS, Kim YJ, et al. Prevention of radiocontrast medium-induced nephropathy using short-term high-dose simvastatin in patients with renal insufficiency undergoing coronary angiography (PROMISS) trial—a randomized controlled study. Am Heart J. 2008;155(3):499.e1-8.
21. Leoncini M, Toso A, Maioli M, Tropeano F, Badia T, Villani S, et al. Early high-dose rosuvastatin and cardioprotection in the protective effect of rosuvastatin and antiplatelet therapy on contrast-induced acute kidney injury and myocardial damage in patients with acute coronary syndrome (PRATO-ACS) study. Am Heart J. 2014;168(5):792-7.
22. Diab OA, Helmy M, Gomaa Y, El-Shalakany R. Efficacy and safety of coronary sinus aspiration during coronary angiography to attenuate the risk of contrast-induced acute kidney injury in predisposed patients. Circ Cardiovasc Interv. 2017;10(1):e004348.
23. Mehran R, Faggioni M, Chandrasekhar J, Angiolillo DJ, Bertolet B, Jobe RL, et al. Effect of a contrast modulation system on contrast media use and the rate of acute kidney injury after coronary angiography. JACC Cardiovasc Interv. 2018;11(16):1601-10.

104

CHAPTER

How to Avoid Catastrophe in Radioimaging?

Amrish Patel, Digvijaysinh Jadeja, Tejas Karmata

INTRODUCTION

Catastrophe means a sudden disaster that causes great suffering or damage.

In medical services, various areas in patient treatment are likely to be associated with development of catastrophe. Procedures for investigation or therapeutic purpose along with radiology are associated with this.

Catastrophe in imaging like X-ray, ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) may occur in hospital room, intensive care unit (ICU), operation theater, or during transport from any hospital facilities to radiology department or from hospital to private radiology center. This directly affects patient outcome and mortality.

Catastrophe includes radiology—guided-procedure related catastrophe:

- Catastrophe while transportation of patient.
- In-department catastrophe.

IMAGING-GUIDED PROCEDURES IN INTENSIVE CARE UNIT

- Ultrasound-guided central venous access.
- Ultrasound-guided arterial line access—radial and femoral.
- Ultrasound-guided pleural fluid tapping, intercostal chest drain (ICD) insertion.
- Ultrasound-guided ascites tapping.
- Ultrasound-guided percutaneous tracheostomy.

Complication of Imaging-guided Procedures

- Not able to visualize vessel or misdiagnosed the vessel–arterial puncture–hematoma.
- During pleural fluid tapping iatrogenic pneumo-/hemothorax.
- During ascitic fluid tapping, there may be vital organ injury.
- Esophageal injury, vessel injury during tracheostomy.

HOW TO AVOID CATASTROPHE IN IMAGING-GUIDED PROCEDURES IN INTENSIVE CARE UNIT

- Take proper written consents of procedure in local language as well as in English.
- We should explain probable complications of procedures.
- Look for contraindication like abnormal coagulation profile.
- Proper position of patient is mandatory to avoid complication.
- In case the patient is irritable or noncooperative, then we should use sedative and paralytic agent with all preparation of airway protection/intubation.
- Use proper dose of local anesthetic agent with optimum time for its effect before skin puncture.
- Take all aseptic/antiseptic precautions before needle puncture to prevent procedure-related infection.
- Proper trained nursing staff and assistant who are trained to assist procedures.
- Proper selection of probe of ultrasound and aseptic measures for different procedures and imaging.
- Continuous vitals monitoring should be carried out during and after procedure.

Performing Biopsy

Nowadays, biopsy from the body part is a very less invasive procedure so if possible this can be done under radiology guidance, either ultrasound or CT scan guidance.

Similar to other procedures proper consent and explanation to patient, comfortable position, checking for contraindication are prerequisites for this. During procedure, proper monitoring of patient is required and also check for likely complication before shifting the patient to the department.

Likely complications—extravasation of contrast, contrast-induced nephropathy.

X-ray-related Catastrophe

- During handling of X-ray plates and affected body part, one should handle the injured part carefully with required stabilization; it may need more than two trained assistants.
- During X-ray of chest for ventilated patient, one must look for endotracheal (ET) tube position and avoiding accidental extubation.
- Patient should not cough during mobilization for X-ray of chest to prevent barotrauma.
- During abdominal X-ray in case of pelvic and abdomen trauma, one should be careful and avoid abdominal/pelvic drain displacement.

Computed Tomography Scan-related Catastrophe

- Department must have one crash cart with automatic external defibrillator (AED) and all airway protection equipment.
- It should be checked 8 hourly.

Department must be ready for any procedure-related complication and must protocolize the complication management including presence of constant consultant/staff for emergency procedures.

Contrast-induced Catastrophe and its Prevention[1]

Contrast-induced side effects include a mild inconvenience like itching, to a life-threatening emergency.

Hypersensitivity reactions, thyroid dysfunction, and contrast-induced nephropathy are the most important adverse effects of contrast media.

Radiographic Contrast Media-induced Hypersensitivity Reactions

A patient with previous allergic reactions to contrast media has increased risk of adverse reactions to contrast agents. Preprocedure steroid and diphenhydramine reduce the chance of allergic response to contrast which includes anaphylaxis or life-threatening emergency.

Hydrocortisone (200 mg intravenously, 1 hour before contrast injection) and diphenhydramine (50 mg intravenously/intramuscularly/orally, 1 hour before contrast injection) are used.

- *Mild hypersensitivity reactions:* Immediate skin rashes, flushing or urticaria pruritus, rhinorrhea, nausea, brief retching and/or vomiting, diaphoresis, coughing, and dizziness.
- *Moderate-to-severe reactions:* Persistent vomiting, diffuse urticaria, headache, facial edema, laryngeal edema, mild bronchospasm or dyspnea, palpitations, tachycardia or bradycardia, abdominal cramps, angioedema, coronary artery spasm, hypertension, or hypotension.

  Life-threatening cardiac arrhythmias (i.e., ventricular tachycardia), overt bronchospasm, laryngeal edema, cardiac failure, loss of consciousness, pulmonary edema, seizures, syncope. Mortality is less than one death per 100,000 patients.

Asthma, history of multiple allergies, and therapy with beta blockers increase the risk of bronchospasm.

Infusion of the contrast media should be stopped as soon as allergic reaction occurs, and treatment with antihistamine should start immediately.

Adrenaline, intravenous (IV) fluids, and oxygen should be started in case of bronchospasm, wheezing, laryngospasm, and stridor or hypotension in addition to antihistamines with or without hydrocortisone.

Contrast-related Thyroid Disorder

Due to effect of biologically active iodinated present in dye, there is all possibility of either hyperthyroid or hypothyroidism.

Contrast-related Nephropathy

There is a rise in the serum creatinine level from baseline occurred in 5% of patients with normal renal function test. Some patients may require hemodialysis due to severely disturbed renal function test with oliguria.[2]

The treatment of contrast-related nephropathy is the same as of acute kidney injury due to other etiologies.

Side Effects of Radiographic Contrast Media: Pathogenesis, Risk Factors, and Prevention

- To avoid renal catastrophe, one should monitor kidney function test [serum creatinine and glomerular filtration rate (GFR)] once before contrast imaging procedure and then one time a day for next 5 days.
- Following are the nephrotoxic drugs which should be avoided before and after contrast imaging: (1) Aminoglycosides, (2) Vancomycin, (3) Amphotericin B, (4) Metformin, and (5) nonsteroidal anti-inflammatory drugs.
- Either iso-osmolar contrast media (IOCM) or low-osmolar contrast media (LOCM) should be preferred choice of the contrast with lowest possible dose.

Fluid management: At least 500–700 mL of water/liquid before contrast imaging and 2,000–2,500 mL of water/liquid in the next 24 hours postcontrast imaging should be given.

N-acetylcysteine may also be used with an oral dose of 600 mg twice daily on the day before and the day of contrast imaging. IV N-acetylcysteine doses of 150 mg/kg over half an hour before the contrast imaging or 50 mg/kg administered over 4 hours may be used in patients unable to take orally.

TABLE 1: Risk factors for the development of contrast-induced nephropathy (CIN).

Nonmodifiable risk factors	*Modifiable risk factors*
Advanced age (>65 years)	
Large doses and multiple injections of contrast media preexisting impairment of renal function	Osmolality of contrast media
Route of administration advanced congestive heart failure	Severe dehydration
Diabetes mellitus	Prolonged hypotension
Multiple myeloma	Anemia
Sepsis	Reduction of effective intravascular volume
Compromised left ventricle systolic performance	Concomitant use of nephrotoxic drugs
Renal transplant	Concomitant use of ACEi and/or ARBs

(ACEi: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers)

Catastrophe during Transfer to Radiology

- It is common to shift a critically ill ICU-admitted patient to the radiology department for CT/MRI or image-guided interventions and it is essential for diagnosis and decision-making. It sometimes cannot be postponed till the patient becomes stable.
- Transportation to an imaging facility requires ongoing oxygen support in an unfavorable environment. Failure to prepare both patient and transport team may lead to adverse events. So risk and benefits of transfer to imaging must be assessed during the time of planning which must include:
  - Full assessment of patient condition
  - Assessing advantage of transfer
  - Appropriate support including staff and resources to provide resuscitation and stabilization
  - Checking transport equipment
  - Plan B, if patient is deteriorating during transport, abandon the shifting and go back to ICU.

RISK TO CRITICALLY ILL PATIENT DURING TRANSPORT

- Technical complications—displacement of tracheal tubes, intravascular lines, drains, etc.
- Pathophysiological deterioration = increased intracranial pressure (ICP) from lowering head to recumbent position, oxygen desaturation, hypotension.
- Inadequate cardiovascular and pulmonary function monitoring due to motion, less-sophisticated monitors, ventilators.
- Inadequate therapy due to lack of detailed monitoring.
- Dislocation of fractures, clots, sutures, vascular emboli due to movements during transport.

Critical studies on ICU transport noted incidence of up to one technical and/or clinical adverse event per transport.

PLANNING TRANSFER OF CRITICALLY ILL PATIENT

- Decision to transfer in imaging facility should be made by critical care physician, balancing risk versus benefits.
- Make a final phone call in radiology to ensure readiness to accept patient.
- Take sufficient medicines and fluids as sometimes the length of stay in imaging may increase.
- Check all medical equipment for transfer monitors, syringe pumps, ventilators, defibrillators, and intubation equipment.
- Ensure compatible equipment for MRI, ventilators, monitors, syringe pumps, etc.
- Assign specific roles for members, e.g., one member for respiration support and another for medication deliveries
- Ensure presence or availability for critical care physician.

TRANSFER EQUIPMENT

- Dedicated ICU transfer trolleys mechanically coupled with beds if available is very helpful.
- Contains all necessary equipment such as mounted monitor, ventilator, syringe pump, defibrillator, suction equipment, oxygen cylinder, etc.
- Accurate to monitor—three lead, electrocardiography (ECG), noninvasive and invasive pressures, saturation of peripheral oxygen (SpO_2), end tidal carbon dioxide ($EtCO_2$).
- Memory-capable monitors should be used to document data during transport.
- *Mechanical ventilator*: Use portable ICU ventilators rather than transport ventilator if the patient requires high positive end-expiratory pressure (PEEP) and higher fraction of inspired oxygen (FiO_2) clamping ET tube before disconnecting and changing ventilator.
- Ensure adequacy of oxygen pressure before transport. Keep standby extra O_2 cylinders.
- For critical care purpose, suction machines should be capable at 25 L/min strength.
- Basic emergency drugs needed—epinephrine, norepinephrine, antiarrhythmic, vasopressin, sedatives, narcotics, analgesics, muscle relaxants, dextrose, appropriate IV fluids.
- Endotracheal tube should be secured in position. Monitors and ventilators should be secured with straps on trolley/bed.

TRANSPORT OF PATIENT SHOULD NOT BE UNDERTAKEN IF (CONTRAINDICATION)[3]

- Inability to provide adequate oxygenation and ventilation during transport or at destination.
- Inability to monitor or maintain acceptable hemodynamic parameters during transport/destination.
- Inability to maintain airway control during transport or destination.
- All members of transport team not present.
- Receiving team is not ready.

Performing Biopsy

Contrast-induced complication: Nowadays contrast-related imaging is part of a diagnostic procedure like CT scan of various parts of body and MRI procedure.

Likely complication: Extravasation of contrast, contrast-induced nephropathy.

How to prevent: Take a proper large-bore intracatheter or central catheter. Flush it with saline to check for proper patency.

For preventing kidney injury: Use nonionic contrast material. Check for creatinine value and keep adequate hydration.

CONCLUSION

- Catastrophe in imaging is not uncommon. It should be anticipated in a critically ill patient so that appropriate preventive measures can be taken. However, an institute should have protocols and guidelines for managing sudden unexpected catastrophe in radiology.
- Risk versus benefit should always be compared while transport of a critically ill patient in the radiology department.
- Radiology department should be equipped with all resuscitation facilities for managing any catastrophe with presence of trained staff and specialists.

REFERENCES

1. Andreucci M, Solomon R and Tasanarong A. (2014). Side Effects of Radiographic Contrast Media: Pathogenesis, Risk Factors, and Prevention. [online] Available from: https://www.hindawi.com/journals/bmri/2014/741018/ [Last accessed March, 2022].
2. Mohammed NMA, Mahfouz A, Achkar K, Rafie IM, Hajar R. Contrast-induced Nephropathy. Heart Views.2013;14(3):106-16. Also available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3969626/
3. Dewan S, Chanana P. Transportation of critically ill patients. ICU Protocols. Germany: Springer Science and Business Media LLC; 2020. pp. 285-93.

CHAPTER 105

Bubble Contrast Imaging

Sachin Gupta, Shrikanth Srinivasan, Deeksha Singh Tomar

INTRODUCTION

Bubble contrast imaging is the introduction of a contrast agent comprising a microbubble to the traditional ultrasonography. This technique has been used primarily in echocardiography to enhance the estimations of various measurements. In the intensive care unit (ICU), obtaining good-quality images with traditional transthoracic echocardiography (TTE) is difficult due to various reasons such as patient in supine position, mechanical ventilation, not able to turn the patient for optimizing the image quality, and sometimes the surgical drains/dressings that hamper the ideal window.[1] As per the studies, roughly 25% of ICU patients have suboptimal echocardiographic images. Contrast-enhanced TTE is a safe, noninvasive technique that can easily overcome many of these shortcomings and can be easily performed on the bedside even in unstable patients.[2]

PRINCIPLE OF THE TECHNIQUE

During conventional echocardiography, the cardiac chambers appear black as the echogenic difference between the red blood cells in the blood and the surrounding tissue is less. The microbubbles which are either available commercially or are created at the bedside by agitating saline are basically gas/air-filled bubbles. These bubbles have a very high degree of echogenicity and are reflected by the ultrasound beam and causes a scattering effect. This scatter is due to a very large difference in echogenicity between the gas in the microbubbles and the surrounding tissue.[3] On the ultrasound, the image appears as opacification of the cardiac chamber.

CONTRAST AGENTS

For the conventional bedside contrast echocardiography, saline bubble contrast is the most preferred technique. This is prepared just before the study has to be performed. It is prepared by hand agitation of saline which is flushed between two 10-mL syringes which are connected via a three-way stopcock. One should prefer a luer-lock syringe to avoid accidental splashing of the contrast medium by dislodgment of the syringe due to the pressure created by constant pushing on the syringes. Utmost care should be taken to break any large bubble which is created due to this agitation. Adding 1 mL of patient's blood to 8-mL saline and 0.5 mL of air creates a prolonged and a more pronounced effect.[4]

Besides this, there are three generations of commercially available contrast agents based on the way the air bubble is trapped inside. The first generation of contrast agents had the air bubbles stabilized either by encapsulation or by adherence to microparticles. The second-generation agents replaced air with fluorocarbon gas which had low solubility and stabilized the bubble further. The third-generation agents are not commercially available and are used only for research-based activities.[5,6]

CLINICAL APPLICATIONS

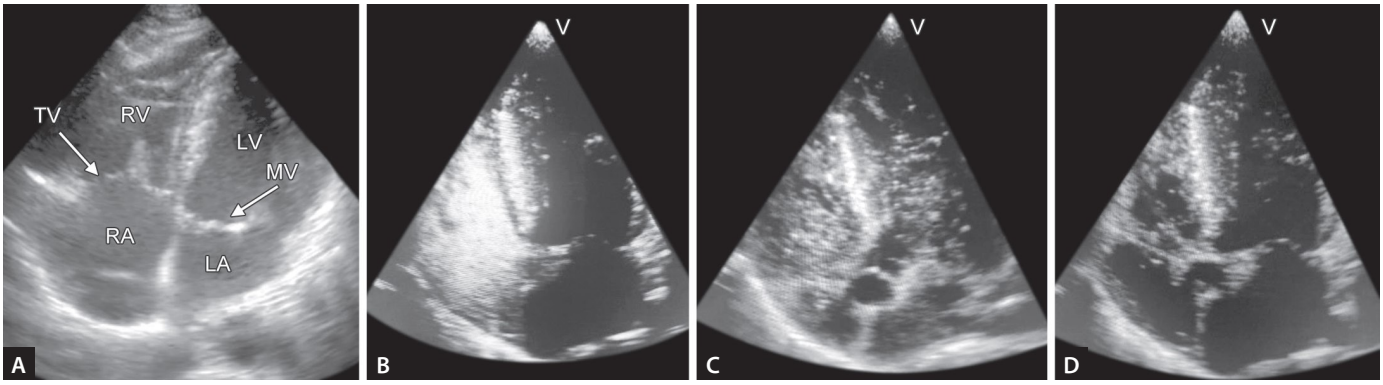
The clinical applications are dependent on the type of contrast agent used.

Agitated Saline Contrast

Detection of Shunts

The most studied application of agitated saline is for detection of right-to-left shunts. After instilling agitated saline intravenously via a large-bore cannula, the right chamber opacification can be seen, and these bubbles then get absorbed into the lungs while passing through the pulmonary circulation **(Figs. 1A to D)**. Hence, there should be no passage of bubbles on the left side of the heart. If the microbubbles gain access to the left chambers of the heart, then it confirms the presence of either an intracardiac or a pulmonary shunt.

The appearance of microbubbles within—three to five beats after right heart opacification confirms the presence of an intracardiac shunt such as atrial septal defect or patent foramen ovale (PFO). Appearance later than five cardiac beats suggests the presence of intrapulmonary arteriovenous



Figs. 1A to D: Agitated saline contrast echocardiography: (A) Normal 4 chamber apical view of the heart; (B) Right chamber opacification after intravenous administration of agitated saline; (C) Few microbubbles seen in left chamber of the heart after 10 beats suggestive of pulmonary shunt; (D) Almost clearing of microbubbles from both right and left chambers of the heart.
(LA: left atrium; LV: left ventricle; MV: mitral valve; RA: right atrium; RV: right ventricle; TV: tricuspid valve)

shunting. The grading of shunt is based on the number of microbubbles passing from the right atrium to the left atrium within three cardiac cycles. Mild shunt is labeled when 3–10 bubbles pass, moderate shunt 10–20 bubbles, and large shunt > 20 bubbles. If the patient is hypoxic, then few bubbles may still appear on the left side of heart due to physiologic intrapulmonary shunting, giving a false-positive result. This phenomenon generally resolves after application of oxygen therapy.[7] Similarly, false-negative results can occur due to inadequate injection volume or inability to increase right atrial pressure greater than left side in case of a PFO.

The sensitivity of detection of shunts can be increased by attempting multiple injections and by techniques such as Valsalva maneuver or coughing.[8] While attempting multiple injections, one should be mindful of breaking the bubbles to very small size.

Pericardiocentesis

The risk of needle being inside the cardiac chamber and not in the pericardium is always present while performing pericardiocentesis. To confirm the position of the needle, agitated saline is injected through the needle. The presence of bubbles inside the pericardial fluid and not in the cardiac chamber confirms the correct placement of the needle.

Doppler Signal Enhancement

Assessment of transvalvular blood flow velocities is a standard procedure during echocardiography. In patients with low-intensity signals, contrast administration augments the Doppler signals and helps in determining the velocities. It is mostly used in patients with aortic stenosis.[9]

Microbubble Contrast Agents

Systolic Function Evaluation

The left ventricular function evaluation is very important for patients getting admitted to the ICU. This is important to differentiate between cardiogenic and septic shock in hemodynamically unstable patients. Acute chest pain accounts for nearly 20–30% of emergency admission.[10] The presence of a regional wall abnormality sometimes is difficult to interpret as ongoing ischemia or residual changes of a previous cardiac event. These changes can also be present in other pathological conditions such as myocarditis, right ventricular dysfunction, presence of pacemaker, or left bundle branch block.

The opacification of the left ventricle after infusion of the contrast agent results in enhanced endocardial border detection. This has shown to improve the sensitivity and specificity of the conventional echocardiography to detect acute coronary syndrome (ACS).[11,12]

Similarly, contrast echocardiography can also be utilized while performing diagnostic or pharmacological stress echocardiography for accurate assessment of a segmental wall motion abnormality.[11]

Left ventricular opacification is also utilized to confirm the presence of suspected apical thrombus. The filling defect is seen in the presence of the thrombus.

Left Ventricular Rupture

Free wall rupture with pseudoaneurysm formation is a dreaded complication of myocardial ischemia and if not dealt timely, it results in high mortality. The extravasation of the contrast in the pseudoaneurysm and not in the pericardial space confirms the diagnosis and these patients require urgent surgical repair of pseudoaneurysm.[13] This helps in preventing the pseudoaneurysm to rupture.

Decompensated Heart Failure

Differentiating between systolic and diastolic failure as the cause of heart failure is important as their treatment is significantly different. By good visualization of endocardium, postcontrast instillation helps in evaluating the systolic function.

Liver Mass

Contrast ultrasound imaging of the liver for focal masses has been used for many years. The contrast ultrasound enhances the liver mass as compared to the adjacent liver parenchyma.[14] The advantages are that these microbubbles are non-nephrotoxic, so they can be used even in patients with renal failure. Second, the imaging is cheaper as compared to computed tomography (CT) or magnetic resonance imaging (MRI) of the liver.

Contrast-guided Intervention

The liver biopsy of a very subtle or a small mass which is barely visible on a conventional ultrasonography can be enhanced after administration of a contrast. The contrast ultrasound provides exact identification of the site of the tumor. This technique can also be used for ablation of small liver mass.[15]

ADVANTAGES OF BUBBLE IMAGING

- There is 73% water content in our body and hence the acoustic image is homogenous. Blood and other surrounding tissues appear similar due to minimal acoustic difference, so it becomes difficult to establish the degree of blood flow. The contrast echocardiography exploits this characteristic.
- Ultrasound examinations are real time and do not involve the risk of radiation exposure.
- The cost implications are much lesser as compared to MRI or CT scan.
- The signals produced by microbubbles are very strong, so the dose required is less as compared to the dose of the contrast agents used for CT or MRI scan.

DISADVANTAGES OF BUBBLE CONTRAST IMAGING

The most important disadvantages are as follows:

- The life of microbubbles in the circulation is very short, so the imaging must be done quickly.
- Increasing the mechanical index of the ultrasound not only results in good-quality image but also increases the microbubble destruction.

CONCLUSION

Contrast ultrasonography is an easily available, inexpensive, and reproducible modality that provides additional information in critically ill patients. It also helps to enhance the quality of the images and helps the clinician in reaching the most probable diagnosis. Agitated saline contrast is the most practiced technique and can be done at the bedside without any complications.

REFERENCES

1. Kornbluth M, Liang DH, Brown P, Gessford E, Schnittger I. Contrast echocardiography is superior to tissue harmonics for assessment of left ventricular function in mechanically ventilated patients. Am Heart J. 2000;140(2):291-6.
2. Reilly JP, Tunick PA, Timmermans RJ, Stein B, Rosenzweig BP, Kronzon I. Contrast echocardiography clarifies uninterpretable wall motion in intensive care unit patients. J Am Coll Cardiol. 2000;35(2):485-90.
3. Soliman OII, De Jong N, Van Der Zwaan HB, Galema TW, Vletter WB, Van Dalen BM. Contrast echocardiography: mechanism of action, safety and clinical applications. Minerva Cardioangiol. 2010;58(3):343-55.
4. Jeon DS, Luo H, Iwami T, Miyamoto T, Brasch AV, Mirocha J, et al. The usefulness of a 10% air-10% blood-80% saline mixture for contrast echocardiography: Doppler measurement of pulmonary artery systolic pressure. J Am Coll Cardiol. 2002;39(1):124-9.
5. de Jong N, Ten Cate FJ. New ultrasound contrast agents and technological innovations. Ultrasonics. 1996;34(2-5):587-90.
6. Seol SH, Lindner JR. A primer on the methods and applications for contrast echocardiography in clinical imaging. J Cardiovasc Ultrasound. 2014;22(3):101-10.
7. Velthuis S, Buscarini E, Gossage JR, Snijder RJ, Mager JJ, Post MC. Clinical implications of pulmonary shunting on saline contrast echocardiography. J Am Soc Echocardiogr. 2015;28(3):255-63.
8. Silvestry FE, Cohen MS, Armsby LB, Burkule NJ, Fleishman CE, Hijazi ZM, et al. Guidelines for the echocardiographic assessment of atrial septal defect and patent foramen ovale: From the American Society of Echocardiography and Society for Cardiac Angiography and Interventions. J Am Soc Echocardiogr. 2015;28(8):910-58.
9. Nakatani S, Imanishi T, Terasawa A, Beppu S, Nagata S, Miyatake K. Clinical application of transpulmonary contrast-enhanced Doppler technique in the assessment of severity of aortic stenosis. J Am Coll Cardiol. 1992;20(4):973-8.
10. Blatchford O, Capewell S, Murray S, Blatchford M. Emergency medical admissions in Glasgow: general practices vary despite adjustment for age, sex, and deprivation. Br J Gen Pract. 1999;49(444):551-4.
11. Dolan MS, Riad K, El-Shafei A, Tamirisa K, Bierig M, St Vrain J, et al. Effect of intravenous contrast for left ventricular opacification and border definition on sensitivity and specificity of dobutamine stress echocardiography compared with coronary angiography in technically difficult patients. Am Heart J. 2001;142(5):908-15.
12. Malm S, Frigstad S, Sagberg E, Larsson H, Skjaerpe T. Accurate and reproducible measurement of left ventricular volume and ejection fraction by contrast echocardiography: a comparison with magnetic resonance imaging. J Am Coll Cardiol. 2004;44(5):1030-5.
13. Main ML, Goldman JH, Grayburn PA. Thinking Outside the "Box"–The Ultrasound Contrast Controversy. J Am Coll Cardiol. 2007;50(25):2434-7.
14. Leen E, Ceccotti P, Kalogeropoulou C, Angerson WJ, Moug SJ, Horgan PG. Prospective multicenter trial evaluating a novel method of characterizing focal liver lesions using contrast-enhanced sonography. AJR Am J Roentgenol. 2006;186(6):1551-9.
15. Kisaka Y, Hirooka M, Kumagi T, Uehara T, Hiasa Y, Kumano S, et al. Usefulness of contrast-enhanced ultrasonography with abdominal virtual ultrasonography in assessing therapeutic response in hepatocellular carcinoma treated with radiofrequency ablation. Liver Int. 2006;26(10):1241-7.

106

CHAPTER

Approach to Undifferentiated Fever in the ICU by POCUS: A New Way?

Pradeep M D'Costa

INTRODUCTION

The term point-of-care (PUO) usually involves cases wherein the duration of febrile illness is more than about 3 weeks or so.

In the critical care unit, cases of fever with such a long duration are unlikely, but on the other hand febrile disease with the exact cause uncertain or requiring further evaluation are quite common and hence the term acute undifferentiated fever is better used for intensive care unit (ICU) patients.

These cases can either present to the ICU with a febrile illness (such as dengue and rickettsial) or develop fever during the course of their stay in hospital. The fever in these groups could be attributed either to pre-existing illnesses (maybe in incubation period at time of presentation) or fever due to illnesses or processes acquired when in hospital [e.g., ventilator-associated pneumonia (VAP)].

Pyrexia can be either due to a prominent easily seen cause (superficial abscess) or quite often difficult to find cause (occult abscesses).

It is in these two sets of patients that I propose to put a new means of approach to these patients. This approach will try to give reasons, means, and ways to approach these cases of undifferentiated fevers in ICU with the use of point-of-care ultrasound (POCUS).

One must remember, for this approach to get best results, it is advisable to combine with a robust clinical examination and a focused laboratory evaluation.

Ultrasound is easily available, easily repeated, cost effective, can be performed at the bedside, and, if required, repeated repetitively!! Thus, increasing its utility manyfold!!

One must keep in mind that sometimes seriously ill patients in ICU may present with hypothermia and not increased temperatures (patients who are at extremes of age, on medications to control fever, have underlying immunocompromising conditions, etc.).

Hence, most of the present approach is with persons with reasonably preserved immune systems.

CLASSIFICATION OF UNDIFFERENTIATED FEVERS IN ICU

- *Hyperpyrexia*: Patients with extremely elevated temperatures many times >41°C usually could be due to drugs [malignant hyperthermia/neuroleptic malignant syndrome (NMS)], heat emergencies or endocrine emergencies, thyrotoxicosis, and pheochromocytoma.
- *Further causes*: May be grouped for simplicity into those being caused by infections and those not related to infections.

  Each of them may be further subdivided for simplification into those which are acquired from the community or those which have been got from the healthcare setting/hospital.
- *Systemic approach*: All possible causes related to infectious agents could be clubbed in a system like manner to simplify things, e.g., gastrointestinal system, respiratory system, blood spread, genitourinary tract, etc.
- Fever due to noninfectious causes can also be simplifies by first an organ-based approach (resp, others), then a look for other miscellaneous causes.

AN APPROACH TO FEVER WITH ULTRASOUND

What I will try an do is show how the POCUS can help our decision making in a case of undifferentiated fever in ICU or new onset fever.

It must be emphasized that the POCUS, if used in addition to good clinical examination and aggressive laboratory evaluation can really make the difference.

For example, if the undifferentiated fever in the critical care setting has got (many a times) high white counts or neutrophilic predominant picture, if the procalcitonin is high, we may be looking for an infective cause.

If all the biomarkers for bacterial sepsis are inconclusive, it could well be a noninfective source that is the culprit (e.g., pulmonary embolism).

I will attempt to simplify the matter by discussing the causes of fever etiology or cause wise as described previously.[1]

HYPERPYREXIA

Thyrotoxicosis

- *Clinical pointers*: Very high fever, tachycardias, arrhythmias, and tremors
- If thyroid function tests are done, may give a clue (many times overlooked in the critical care setting)
- POCUS pick up
- Locate a multinodular goiter
- Locate a diffusely enlarged gland with increased vascularity.

Pheochromocytoma

- *Clinical features*: Fever, tachycardia, blood pressure fluctuations, headaches, and unexplained sweating[2]
- POCUS: May be able to pick up enlarged adrenal glands.

FEVER DUE TO INFECTIOUS CAUSES

Respiratory System

- *Clinical*: The same criteria for community-acquired pneumonia (CAP) and VAP. Cough, fever, fatigue, dyspnea, chest pain, new-onset shadows on imaging, sputum production, and breathlessness.
- *POCUS*:
  - By studying different areas of the lungs we may be able to pick up new consolidations and effusions.
  - Localized B profiling, new onset "C" or consolidation profiling will help localize the disease.
  - Presence of dynamic air bronchogram **(Fig. 1)**, shred sign, and new pleural effusions add the clinical conclusions.
  - Pleural space collections and their qualities can be very well assessed at bedside.
  - A fast assessment of the quantity of pleural fluid as well as the contents can be done at the bedside Relatively clear fluid which is anechoic usually signifies a transudative nature to the fluid. Pleural fluid which shows either the presence of sediments or fibrin strands is many a times exudative in nature **(Fig. 2)**.
  - Similarly loculated pleural based collections can be seen with POCUS.
  - A further confirmatory pleural tap can be done under POCUS guidance at bedside to confirm the diagnosis.[7-10]

Urogenital

- *Clinical*: Urinary symptoms, change in urinary habits of patient, change in color of urine, pain during micturition or straining during micturition, if urine catheters are in situ, turbid urine and abdominal pains may be present.
- *Cystitis*:
  - Bladder wall thickening (thickness > 3.9 mm) can be accurately picked up by bedside ultrasound as well, debris in bladder is easily found by ultrasound.
  - Echogenic renal calculi can be located and obstructions to the urogenital system can be picked up.
  - Varying grades of hydronephrosis are diagnosed at the bedside as well as the color of the fluid **(Fig. 3)**.
  - Similarly perinephric collections, masses can be diagnosed by ultrasound (fluid between the fasciae covering the kidneys) **(Fig. 4)**.
  - In the males, the prostate gland, seminal vesicles can also be visualized well and enlargements, obstructions possible fever foci localized there as well.
  - The female urogenital system can be visualized and intrauterine collections, cervical pathologies, and tubo-ovarian pathologies can be picked up at bedside.
  - Percutaneous drainage of collections can be done safely at bedside.

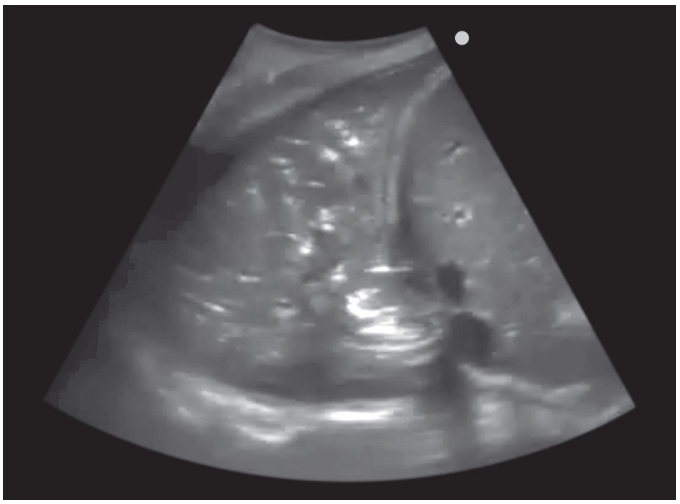


Fig. 1: Dynamic air bronchogram—consolidation.

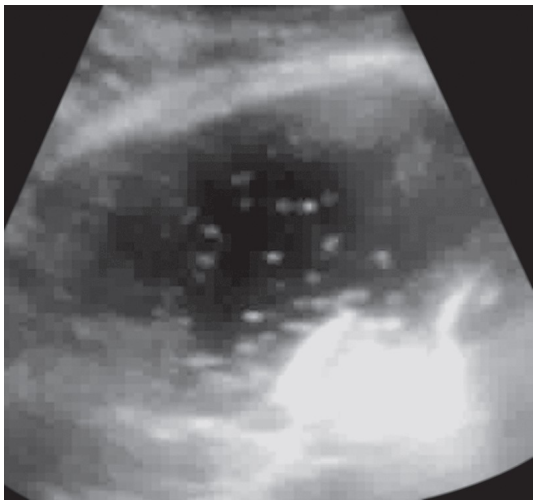


Fig. 2: Pleural effusion with sediments.

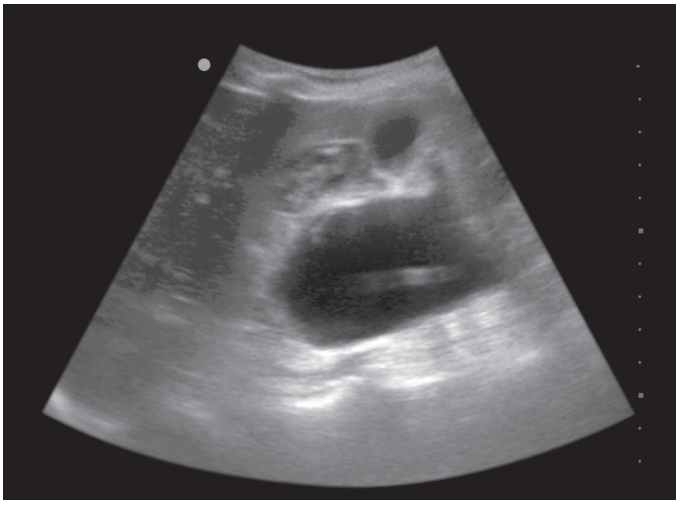


Fig. 3: Gross hydronephrosis with double-J (DJ) stent.

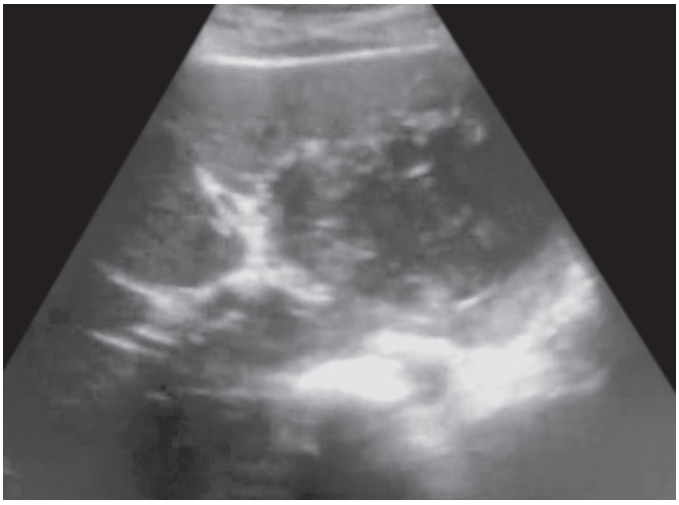


Fig. 5: Liver abscess large.

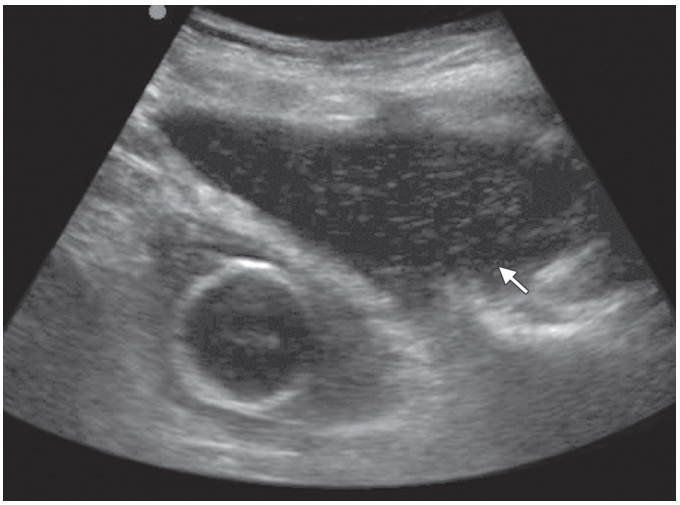


Fig. 4: Collection above bladder.

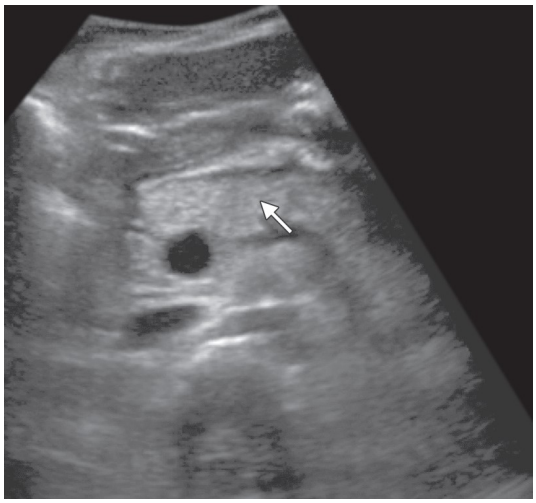


Fig. 6: Pancreas.

Hepatobiliary System

Clinical: Abdominal pain, jaundice, and itching may be present.[5]

Liver

- Occult liver abscesses (multiple hypo, hyper, or mixed echoic lesions) within the substance of the liver can be seen at bedside. Based on the liquefaction, drainage can be done.
- Liver enlargements as seen in a hepatitis process as well as changes in texture of the liver are noted **(Fig. 5)**.[6]
- Dilatation of the hepatobiliary radicals is seen at bedside, and can give many clues to a possible obstructive cause (pancreatic or other).

Gallbladder

- Cholecystitis
- One of the most important features is presence of gallbladder stones and tenderness in the right hypochondral region with probe pressure (sonographic Murphy sign).
- Thickening of the wall of >3 mm and presence of fluid around the gallbladder are other features. The diameter of the common bile duct of >7–8 mm generally indicates obstruction.

Pancreas (Fig. 6)

- The head, neck, body, and tail are visualized at bedside.
- Hypoechoic areas around the pancreas and an inhomogeneous pancreatic echo texture along with a change of normal shape of the pancreas are seen.
- Increase in thickness of head, neck, body, or tail are noted (head > 2.6 cm and body > 2.2 cm).
- Presence of collections in the peripancreatic area is noted (pseudocysts or necrotic collections) and if indicated, drainage procedures can be done with ultrasound guidance.
- Pancreatitis is all easily visualized at bedside.

Intra-abdominal

Clinical

- Distension of abdomen, localized guarding, and raised enzymes.
- Purulent collections, many times subdiaphragmatic are the cause of fever in certain groups and can be seen very well at bedside.
- Bowel pathologies may be picked up but this requires some specializations.
- Dilated bowel loops (normal small intestine up to 3–4 mm and large intestine up to 4–5 mm).
- Five layers of the intestine, i.e., premucosal, mucosal, intramucosal, muscular, and serosal layers can be seen.[13]
- Compressibility is usually reduced, note can be made of collections in the lumen or within the layers, as well as visualization of peristalsis can be done.
- Contrast-enhanced ultrasound helps us to visualize the bowel wall microperfusion.[14]
- Ulcerative colitis and Crohn's disease can be diagnosed.
- Appendicitis (an often fluid-filled cord-like roundish structure with a diameter of >6 mm and lacking peristalsis) as well as diverticular disease (round hypoechoic ring with varying thickness, likened to bubbles along the wall of the bowel) may be identified at bedside **(Fig. 7)**.

Skin and Soft Tissue (Fig. 8)

Clinical

- Redness pain swelling discharge may be present.
- Generalized thickening and increase in echogenicity of the area with hypoechoic strands representing fluid are noted.
- Cellulitis is typically diagnosed by the crazy pavement appearance on ultrasound. This is also known as cobblestone appearance.[11]
- Swelling within the fascial planes can help diagnose fasciitis.

Cardiovascular System

Clinical

- Fever, arrhythmias, clubbing, new onset murmurs splenomegaly as well as culture positivity may be seen.
- Common causes of undifferentiated fever in the critical care setting include infective foci on the valves.
- Endocarditis and mass-like lesions can be reasonably well appreciated by transthoracic echocardiography **(Fig. 9)**.[3]
- Quantification of the possible etiology is possible (e.g., large friable masses likely go in favor of fungal cause, right-sided endocarditis commonly seen in drug abuser, and likely *Staphylococcus* as cause).
- Looking for vegetations, measuring their sizes, attachments, bases, and location can give invaluable clues in approach to such patients.
- We can also assess for valve abscesses and prosthetic valve pathologies at bedside by the use of ultrasound.

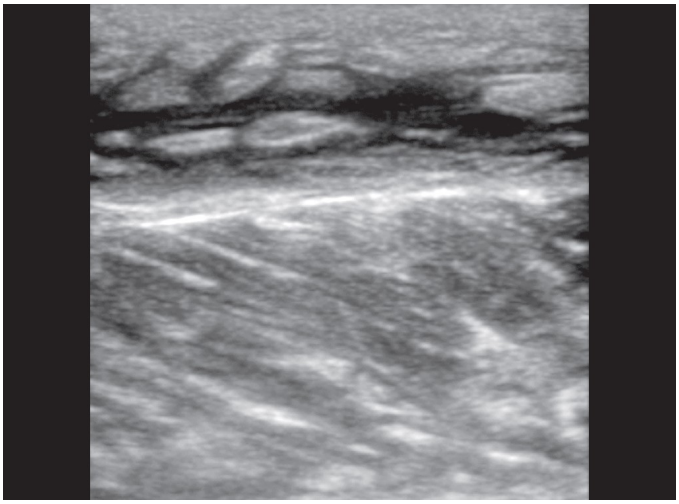


Fig. 8: Skin and soft-tissue edema.

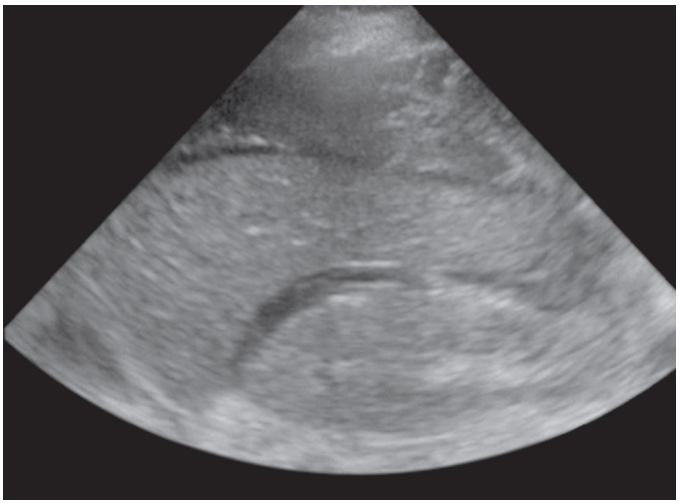


Fig. 7: Perisplenic collection.

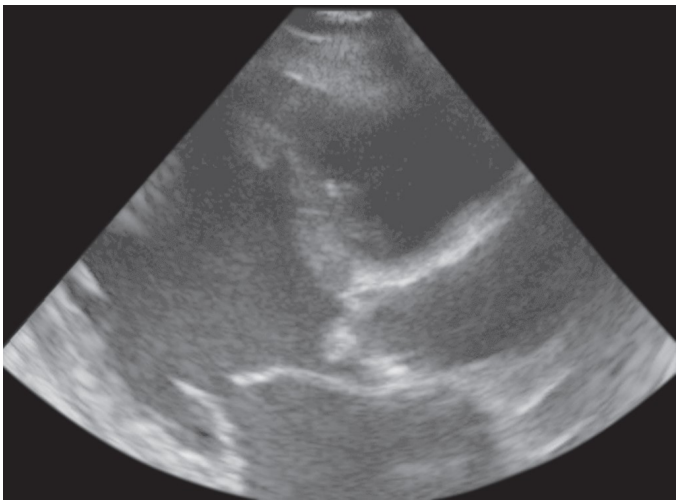


Fig. 9: Aortic valve endocarditis.

- Myxomas in the heart chambers or rarely malignant processes within the heart are seen.
- The myocardium can present with a speckled appearance sometimes leading us to a possible cause of myocarditis.

Pericardium (Fig. 10)

- Clinically beck's triad may be seen.
- The pericardium can also be well seen at the bedside by the use of POCUS.
- We can evaluate for pericardial effusions, and by the appearance of the fluid and make important conclusions about etiology (clear fluid likely transudative, septate effusion likely infective, hazy effusions likely infective or blood).
- Ultrasound can further facilitate a guided diagnostic tap of the fluid for evaluation.

Pulmonary Embolism

Clinical

- Unilateral limb swelling, unexplained dyspnea, and hypoxia may be present.
- Indirect evidence of pulmonary embolism as the cause of fever can be sought at bedside, evidence of enlargement of the right ventricle, right atrium, and the "D" sign, along with the evidence of a thrombus in an extremity vessel make the diagnosis of pulmonary embolism very likely.
- Some observers mention commonly seeing an A profile, sometimes a C profile where a pulmonary infarct is setting in.

Musculoskeletal

Clinical

- Soft tissue swelling pain may be present.
- Collections around long bone fractures and intramuscular hematomas can be seen prominently as many times mixed echogenic collections.

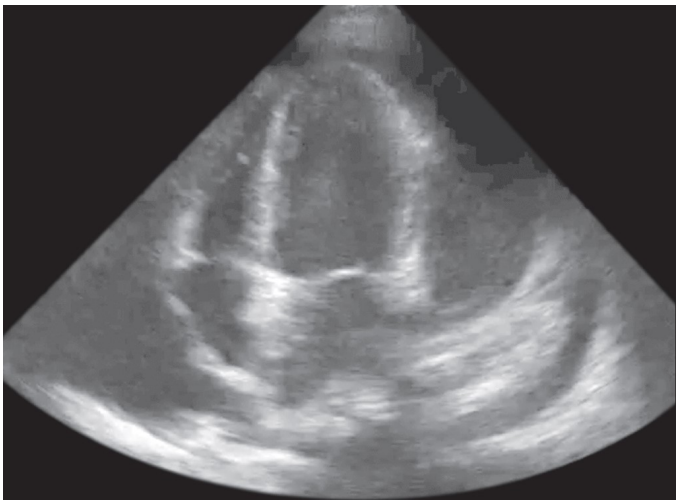


Fig. 10: Pericardial effusion.

- Aspirations may be done safely at bedside under ultrasound guidance.
- Joint effusions, their quantity and volume can be done at bedside, and guided aspirations safely performed.

Paranasal Sinuses

Clinical

- Swelling and tenderness along the sites of the sinuses (mainly maxillary) can be elicited in the conscious patient.
- Many times indwelling nasogastric tubes and recently the scare of rhinocerebral mucormycosis should prompt the physician to make an evaluation of the sinuses as well.
- Complete opacification of the sinuses is called the *complete sinusogram* (vase shaped) and incomplete opacification is called the incomplete sinusogram. These indicate the amount of fluid or secretion filling in the maxillary sinuses.[4]

Perioral

Clinical

- Pain, difficulty in chewing, swallowing, jaw area swelling, and swellings in the soft tissues around the oral cavity may be noted.
- POCUS can help identify fever due to pathologies around perioral area, tooth abscesses can be easily seen at bedside. These are seen as filling defects adjacent to the bone.
- Collections in the subcutaneous areas, their measurements and progressive spread can be closely monitored and seen at bedside (Ludwig's angina).

MISCELLANEOUS CAUSES

- Pancreatitis (described in previous section)
- Acute febrile disease many times due to inflammation may be seen early in the course of pancreatitis.
- The pancreas can be reasonably well examined at the bedside.
- The swelling of the pancreas can be measured by various normograms, as well as search can be done for peripancreatic collections as well as pancreatic pseudocysts.
- If infected necrosis is suspected, an ultrasound-guided aspiration can be easily done under guidance.

THROMBOSIS

- Prominent among noninfectious causes are thrombotic lesions.
- At the bedside, POCUS can identify deep vein thrombosis reasonably accurately.

- The compression test is done to achieve a diagnosis in the extremities.
- Thrombotic foci may be located in both the upper and lower extremity veins as well as the arterial systems **(Fig. 11)**.[11]
- Superficial thrombophlebitis, sometimes also responsible for fever and can be seen as thickened vessel walls on the ultrasound.
- Rarely, we may locate thrombi in the pulmonary vessels, commonly located by using the parasternal short-axis view at pulmonary artery level, where we are able to see the main pulmonary artery and its bifurcation.

MALIGNANCIES

- Fever due to underlying malignant processes many times flummoxes the clinician.
- POCUS can help identify nodes, percutaneous aspirations can be easily performed for identifying etiology.
- Oral malignant processes near mandible or tongue can be seen well, as are some other malignancies like sarcoma.
- Lung masses **(Fig. 12)**, if superficial, can be picked up bedside as also lesions (primary or metastatic) within solid organs such as liver, spleen, kidneys, or others **(Fig. 13)**.

LINE-RELATED SEPSIS (FIG. 14)

Clinical

- Redness, pain discharge, and tenderness around the area of the line.
- This important cause of undifferentiated fever is sometimes overlooked by the clinician.
- Ultrasound evaluation can help in identifying possible infective foci in the line:
  - Soft tissue swellings at port of entry and evidence of edema as seen

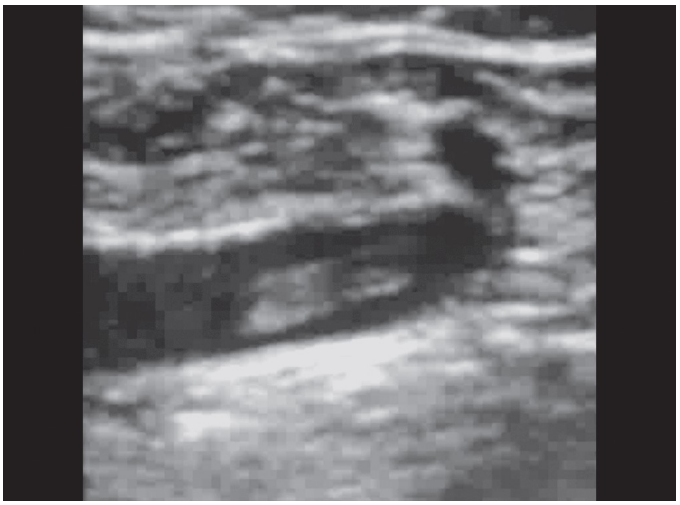


Fig. 11: Free mobile clot in femoral vein.

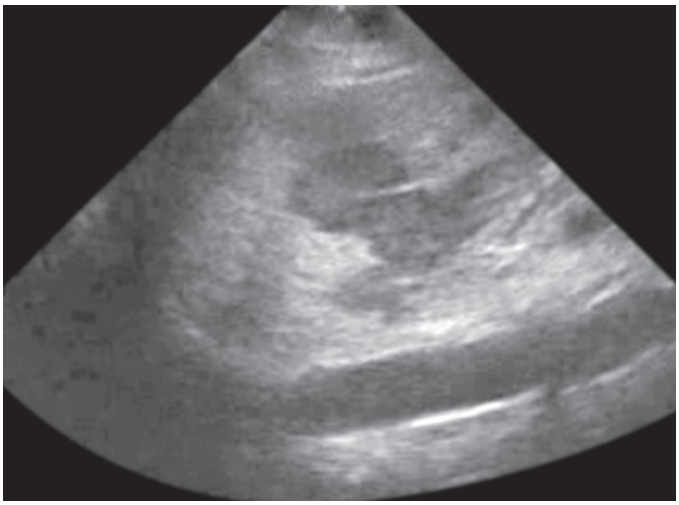


Fig. 13: Metastases in liver.

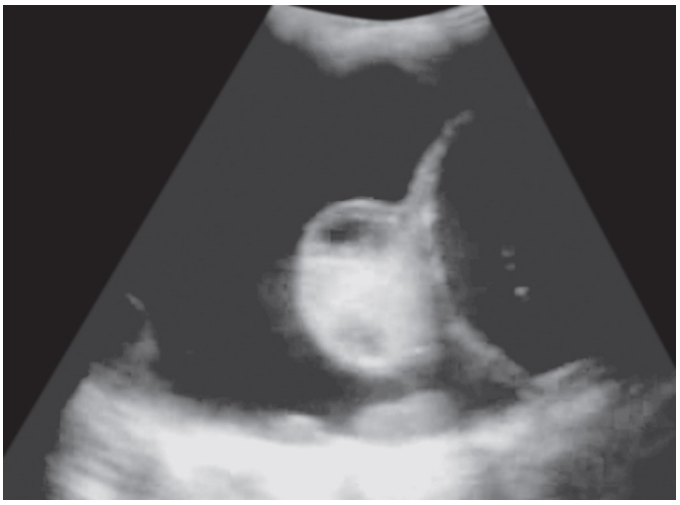


Fig. 12: Mass in lung.

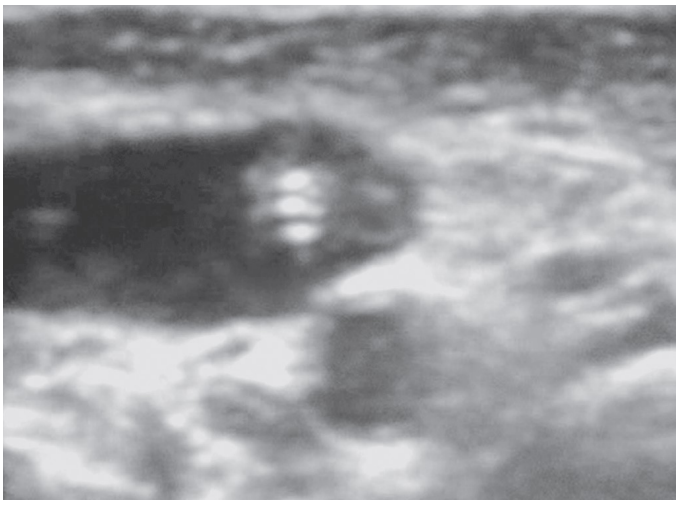


Fig. 14: Line sepsis biofilm.

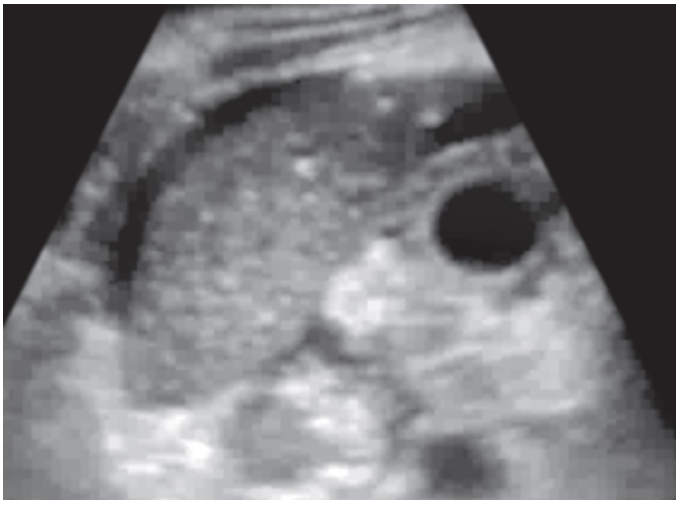


Fig. 15: Dengue, gallbladder, and ascites.

  - By tracing the path of the cannula, we may be able to locate "films" which begin to accumulate around/on the lines.
- These "biofilms" are also likely foci of infection and merit consideration of line removal.

TROPICAL FEVER HELP (FIG. 15)

Clinical

- Febrile illness with associated hepatosplenomegaly, rashes, jaundice, joint swellings, and altered sensorium may be seen.
- Description of the ultrasound features in dengue has been studied.
- Typical among the findings are:
  - Evidence of "leaking" or polyserositis seen as ascites and pleural effusions
  - Thickening of the gallbladder wall (acalculous cholecystitis)[12]
- The appearance of the gallbladder has been described as a cobblestone appearance.
- Some authors have found a correlation between thickened gallbladder wall and low platelet counts.
- However, these findings are not exclusively seen in dengue and may be seen in other diseases as well.

CONCLUSION

- POCUS is an invaluable tool in the bedside assessment of undifferentiated fever in ICU.
- A large number of pathologies can be effectively screened by a thorough examination.
- Clinical examination, robust laboratory interpretation, and evaluation are strongly recommended with ultrasound for better results.
- All infective/inflammatory processes may not present as fever and should be kept in mind.
- Ultrasound cannot rule out drug-related fevers.
- Wise use of the POCUS can indeed improve outcomes.

REFERENCES

1. Niven DJ, Laupland KB. Pyrexia: aetiology in the ICU. Critical Care. 2016;20:247.
2. Robba C, Goffi A, Geeraerts T, Cardim D, Via G, Czosnyka M, et al. Brain ultrasonography: methodology, basic and advanced principles and clinical applications. A narrative review. Intensive Care Med. 2019;45:913-27.
3. Sordelli C, Fele N, Mocerino R, Weisz SH, Ascione L, Caso P, et al. Infective endocarditis: echocardiographic imaging and new imaging modalities. J Cardiovasc Echogr. 2019;29(4):149-55.
4. Neagos A, Dumitru M, Vrinceanu D, Costache A, Marinescu AN, Cergan R. Ultrasonography used in the diagnosis of chronic rhinosinusitis: From experimental imaging to clinical practice. Exp Ther Med. 2021;21(6):611.
5. Yikilmaz A, Taylor GA. Sonographic findings in bacterial meningitis in neonates and young infants. Pediatr Radiol. 2008;38(2):129-37.
6. Vidili G, Sio ID, D'Onofrio M, Mirk P, Bertolotto M, Schiavone C, et al. SIUMB guidelines and recommendations for the correct use of ultrasound in the management of patients with focal liver disease. J Ultrasound. 2019;22(1):41-51.
7. Mongodi S, Via G, Girard M, Rouquette I, Misset B, Braschi A, et al. Lung ultrasound for early diagnosis of ventilator-associated pneumonia. Chest. 2016;149(4):969-80.
8. Zhou J, Song J, Gong S, Hu W, Wang M, Xiao A, et al. Lung Ultrasound combined with procalcitonin for a diagnosis of ventilator-associated pneumonia. Respir Care. 2019;64(5):519-27.
9. D'Amato M, Rea G, Carnevale V, Grimaldi MA, Saponara AR, Rosenthal E, et al. Assessment of thoracic ultrasound in complementary diagnosis and in follow up of community-acquired pneumonia (CAP). BMC Med Imaging. 2017; 17:52.
10. Javaudin F, Marjanovic N, de Carvalho H, Gaborit B, Le Bastard Q, Boucher E, et al. Contribution of lung ultrasound in diagnosis of community-acquired pneumonia in the emergency department: a prospective multicentre study. BMJ Open. 2021;11:e046849.
11. O'Rourke K, Kibbee N, Stubbs A. Ultrasound for the evaluation of skin and soft tissue infections. Mo Med. 2015;112(3): 202-5.
12. Santhosh VR, Patil PG, Srinath MG, Kumar A, Jain A, Archana M. Sonography in the diagnosis and assessment of dengue fever. J Clin Imaging Sci. 2014;4:14.
13. Andrzejewska M, Grzymisławski M. The role of intestinal ultrasound in diagnostics of bowel diseases. Prz Gastroenterol. 2018;13(1):1-5.
14. AlAli M, Jabbour S, Alrajaby S. ACUTE ABDOMEN systemic sonographic approach to acute abdomen in emergency department: a case series. Ultrasound J. 2019;11:22.

SECTION

19

Present and Future Challenges in ICU Organization and Management

CHAPTER 107

Organizational Challenges of Intensive Care Unit in India during the COVID-19 Pandemic: How to Prepare?

Ratender K Singh, Om P Sanjeev, Chandrakanta Singh

INTRODUCTION

The impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on our health infrastructure has been challenging and a wake-up call to speed up the entire process of its transformation for any future pandemics. The state of poor health infrastructure as witnessed during coronavirus disease 2019 (COVID-19) needs to be rejuvenated by appropriate allocation of funds to the tune of at least 5% of gross domestic product (GDP) sustained over decades.[1]

Severe demand–supply imbalance of intensive care units (ICUs) was observed during the COVID-19 pandemic globally. India too suffered as many sick patients could not be provided ICU care primarily due to the poor ICU bed to hospital bed ratio. In a preprint data published in 2020, it was estimated that India has approximately 1.9 million hospital beds, 95,000 ICU beds, and 48,000 ventilators.[2] Other than scarcity of ICU beds, heterogeneous distribution within the country, quality of ICUs, wide variability in payment-based access, vaguely defined qualification, training, and credentialing of ICU doctors/nurses are major challenges that already existed even before the COVID-19 pandemic.

To begin with, the current proportion of ICU to hospital beds must be increased from 10–15% to 30% seeing the current COVID-19 situation and any future similar pandemics to fulfil the unmet demands immediately. Simultaneously tremendous efforts must also be made to improve both the quality and quantity of the human resource for these ICUs to uphold the desired standards of ICU care. Technological advancements in telehealth must be used to its fullest potential for improving the reach and quality for our generations to come.

CHALLENGES AND IMPROVEMENT STRATEGIES FOR INTENSIVE CARE UNIT

Several challenges have been encountered by COVID-ICUs at all fronts, namely infrastructure, manpower, equipment, etc. Major challenges faced by these of COVID-ICUs are detailed in **Table 1**. Possible, achievable, and sustainable reforms are required to meet the future needs of quality-assured and surge-congruent ICUs. A need-based strategic and reorganizational approach is presented here in **Table 1**.

TABLE 1: Challenges and strategies to better prepare intensive care units (ICUs) for future pandemics.

Characteristics	*Challenges faced in COVID-ICUs*	*Strategies to better prepare ICUs for future pandemics*
Initial planning		
• Nomination of team leader/ coordinator • Assessment, planning, teamwork dynamics, accountability, logistics required needs for all aspects of ICU care must be meticulously done • Planning for surge capacity	• Unknown nature of virus, disease, risk of transmission and absence of a definitive treatment instilled fear and misconceptions amongst HCWs • Existing poor and fragmented health infrastructure due to poor investment in health • Scaling up the infrastructure in limited time was challenging • Optimally trained ICU human resource in sufficient numbers was a major limitation • Logistics were based on assumptions about case load and case mix	• Population-based region, city, state, and country-based models of ICUs and their optimal distribution be determined in advance • Mandatory credentialing and certification of all ICUs • Focus on building modular ICUs that are easy to install and scalable in short time • Incorporate expandable spaces in initial design layout for ICUs • Identify in advance expandable pool of hybrid ICUs, trained manpower, and equipment that can be used if needed • Evidence-based triaging be mandated for admissions to ICUs to make best use of scare resources • Advanced planning for surge capacity at all levels

Contd...

Contd...

Characteristics	***Challenges faced in COVID-ICUs***	***Strategies to better prepare ICUs for future pandemics***
Initial planning		
	• Arranging for logistics with simultaneous lockdown was a bottleneck • Pandemic preparedness of hospitals, emergencies, and ICUs was found wanting	• Validated models for predicting case load be made available in time for better planning and implementation • SOPs for pandemics and/or other disasters must be prepared in advance with clear roles and responsibilities
Infrastructure		
Proportion of ICU beds/hospital beds	Gross demand–supply imbalance, more so in the second wave	• Increased allocation of ICU beds to at least 30% of hospital beds • Identify expandable pool of ICU beds both within and outside ICUs
• *Level of ICU care* • *Number of beds/units*	Distinction between the levels of ICU care could be hardly implemented or maintained as "some care was better than no care" for needy patients	Maintaining levels of ICU care is advisable for better allocation of scarce logistics, human resources, and patient needs
Site/location of ICU	• Most current ICUs are not strategically located for dealing with pandemics • Larger emergencies with larger/multiple ICUs at front end of hospital not available at most centers • Often ICUs placed within difficult-to-access complexes located far off from emergency, OTs, and diagnostic blocks, not amenable to structural alterations for preventing cross-contamination in COVID-19	• Creation of large front-end emergency block with larger or multiple ICUs within it as is desired for disasters is needed with separate entry and exit for patients and HCWs and BMW disposal • Diagnostic and therapeutic intervention areas should be in close vicinity to this block
ICU design	• Mostly halls with wall-based head-end panels were prevalent in most ICUs • Partition between patients were either nonexistent or only by curtains in most ICUs • Negative-/positive-pressure isolation rooms were not available at most centers	• Physical partitioning is desirable for optimal IPC measures, provided easy visibility of patients is not hampered from nursing station • Negative- and positive-pressure isolation rooms must be planned and constructed at the initial stages of ICU construction itself for better isolation of infected/contagious or immunosuppressed patients
Zones of ICU	• Because of the fear factor, zone distribution within ICUs was maintained owing to restricted movement • Family support areas were either nonexistent or distantly placed from the ICUs	Conventional zones of ICUs need to be expanded from three to five, namely, grossly contaminated, contaminated, buffer, clean, and HCWs donning/doffing (separate) zones other than family support zones should be more clearly defined and maintained
Environmental requirements	• The set standards of heating ventilation and air-conditioning (HVAC) for ICUs were suboptimal at most centers • The air quality index (AQI) of most COVID-ICUs not known • Tolerance to humidity and temperature differed between patients and HCWs due to wearing of PPE • Poor visibility due to either improper wearing of goggles, poor-quality goggles, and/or poor control of temperature and humidity remained a niggling issue	• HVAC systems of ICU must be in accordance with set standards • Higher rate of air changes of at least six cycles per hour with two cycles from outside fresh air or 15 cycles per hour are preferable • HVAC maintenance and upkeep must be a priority • Doffing areas are hazardous areas for HCWs and should be optimally ventilated and stationed at a distance from the ICUs • Crowding at these areas should be avoided by staggered doffing of HCWs at the end of a shift

Contd...

Contd...

Characteristics	***Challenges faced in COVID-ICUs***	***Strategies to better prepare ICUs for future pandemics***
ICU equipment		
Ventilators, monitors, infusion pumps, USG, X-ray, RRT, drugs, etc.	• Availability of common ICU equipments was initially below par • Pace of installation of invasive ventilators and the training required to run them by less-trained ICU staff proved challenging at most centers • Availability of video laryngoscopes was also an issue initially • Availability of invasive ventilators with capability of NIV mode was also an issue and resulted in much use of single-tube BiPAP devices which were an inferior choice • Helmet–mask interface though preferable for NIV was used minimally due to nonavailability and cost • HFNC though in much demand was initially in limited supply and also costly and on many instances was initiated without due consideration to the amount of oxygen consumed in background of oxygen crunch • Oxygen wastage was an issue at most centers • Difficult-to-maintain supply chain of lifesaving antimicrobials, remdesivir, steroids, tocilizumab, low-molecular-weight heparin, etc. • ABG machines were installed at sites distant from ICU, leading to issues with transportation, sample processing, and reporting of ABG samples at most centers • Dedicated renal replacement therapy (RRT), USG, and X-ray machines were not available at many centers compromising ICU care	• Pooling of lifesaving equipments with advanced surge capacity planning • Have an active biomedical engineering wing for regular upkeep and maintenance of vital equipment • Having a central log of all such vital equipment and their functional status will help quicker relocation and utilization • Equipments with multitasking capabilities should be preferred, like ventilators with both NIV mode and IMV basic modes for ICUs • All ICU equipments should be compatible with available hospital information systems for easier data transfers • Better technologies adopted to improve equipment/patient ratios • Module-based scalable monitoring solutions should be adopted for greater flexibility • Medical equipments with reasonable battery backup are preferable • Appropriate use of antimicrobials and other lifesaving drugs must be promoted, monitored, and audited regularly • Oxygen is a vital resource and its wastage should be avoided
Human resource		
Intensivist or critical care specialist	• Trained intensivists in requisite numbers for full-time coverage were not available • Often, inexperienced ICU physicians were on floor being guided by their more trained seniors via use of varied communication devices for episodic consultations only	• Need to identify trained intensivists within the system and use them more diligently in times of need as they are and will continue to be in short supply • Their expertise should be made readily available to less trained on-floor staff, via intelligent use of telemedicine resources • Identify an expandable pool of specialists from Critical Care Medicine, Emergency Medicine, Anesthesiology, and Pulmonary Medicine • Organize regular academic meetings amongst these specialties as they will be your most valuable resource for ICUs
Resident/junior doctors	• A mix of residents of clinical (ICU and non-ICU) and nonclinical specialties had to be posted for an extended period of time • There were not enough trained ICU residents to provide quality ICU services round the clock	Emergency and ICU rotations should become a regular feature of training for residents across the specialty and subspecialties

Contd...

Contd...

Characteristics	***Challenges faced in COVID-ICUs***	***Strategies to better prepare ICUs for future pandemics***
Human resource		
Nursing	• In public hospitals, 1:1 nursing is not available at most centers • Often the ratio of 1:5–7 was observed even for ventilated patients • Similar to intensivists and resident doctors, a mixed pool of nurses from ICU segment and non-ICU segment were deployed inside ICUs	Policy of rotation of nurses for emergency and ICU training must become mandatory to increase awareness about Airway, Breathing, and Circulation; hemodynamic monitoring and lifesaving emergency, and ICU drugs and equipment
Respiratory therapist/ physiotherapist/nutritionist	Not available at most centers, hence this work was also relegated to nurses and residents; chest and limb physiotherapy were severely compromised, resulting in poor outcomes. Similar difficulties faced with enteral/parenteral nutritional support	Pooling of this manpower will be helpful
Psychological counsellor	Nonavailability led to poor psychological support of all three stakeholders, i.e., patients, their relatives, and healthcare providers	Need to be considered an integral part of the ICU team and used more often
Disaster preparedness		
Fire	• Major fire outbreaks reported at several ICUs in India • Fire safety norms not adhered to or only minimally implemented • Upkeep and maintenance not guaranteed	• Any new, even if it is a temporary ICU needs strict adherence to fire safety norms • Upkeep and maintenance service records mandatory
Interrupted oxygen supply	• Oxygen reserves stretched to the limit in second wave when demands far exceeded the supply • Oxygen cylinder-based supply proved precarious at several ICUs and situation became panicky in several hospitals, as reported in media • Liquid oxygen supply was only available at major hospital ICUs, and they too scrambled to maintain their supply due to overwhelming demand • Clearly demand–supply imbalance was created due to faulty planning and overwhelmed demands • Timely extraordinary efforts by both state and central government averted the inevitable oxygen crisis throughout India	• Oxygen wastage is very common in any hospital setting • Oxygen stewardship programs are needed to increase awareness • Every ICU must try and keep a record of oxygen consumption • Oxygen monitoring nurses can help stem the wastage • Oxygen delivery devices which minimize wastage must be promoted
Major power failure	• Inadequate battery backup of lifesaving equipments during power failure compromised functionality • Lack of generator supply with UPS backup jeopardized safety of equipments at several ICUs	• Backup power should be made mandatory for most of the feasible ICU equipments • At hospital level, there must be a power backup facility in case of failure
Communication systems	• Absence of a centrally located public and staff address system hampered communication between patients and HCWs and amongst HCWs both within and outside COVID-ICUs • This lack of communication made working in COVID-19 hospitals and ICUs a struggle and in times of crisis help was not available as desired	Centralized and state-of-art public address systems should be made mandatory for hospitals, ICUs and Emergencies

Contd...

Contd...

Characteristics	***Challenges faced in COVID-ICUs***	***Strategies to better prepare ICUs for future pandemics***
Disaster preparedness		
Human violence which includes violence by relatives/political activists of patients on HCWs	• Fragmented teams–fragmented communications led to suboptimal care • Owing to safety concerns, families of COVID patients could not be allowed within the ICUs at most centers • Expectantly so, there were unending demands for communication with their loved ones admitted in the ICU through voice and video calls • Customized solutions were adopted at some centers using telemedicine	• Conscious patients allowed to keep their mobiles with them for direct communication with their families • Telemedicine can provide may be the much-needed family access to patients and vice versa
Infection prevention and control (IPC)		
• *Cleaning and disinfection* • *Biomedical waste (BMW) disposal* • *Prevention care bundles for CRBSI/VAP/CAUTI* • *FASTHUGBD* • *Safe injection practices*	• Difficult to maintain the higher and more stringent IPC practices in context of COVID • Limitations of logistics, infrastructure, and HCWs failed to implement even the most basic IPC measures in the COVID-ICUs • Preventive care bundles could be partially implemented that too only by trained ICU staff • Elements of standard ICU care were also only partially implemented • More often than not, all above important aspects remained ignored and/or unmonitored	• Provision of adequate number of trained staff • Additional staff monitoring and auditing these activities • Provision of CCTV surveillance to ensure compliance • Regular training of staff about these aspects of ICU care
Telemedicine		
Tele-ICUs	• Not yet equipped for telemedicine in ICUs • Provision of CCTV surveillance to strengthen the compliance to improve standards of ICU care was requested by government but not complied with at most centers • Piles and piles of paper records were difficult to sustain and maintain • Electronic medical record (EMR) in ICUs hardly available • Difficulties of data compilation, integration, collation, and analysis were hurdles to care and research in COVID-19	• Telehealth surge has been witnessed during COVID-19 and is going to be even more utilized in coming times • Paperless-ICUs are the way ahead • Tele-ICU services can help circumvent many shortcomings noticed in COVID-ICUs • Tele-ICUs can help minimize the risk to HCWs and emphatically utilize the services of senior intensivists • ICU-specific EMRs soon will become a reality in most ICUs • Digital health is coming of age in India with the right push at the right time

(ABG: arterial blood gas; BiPAP: bilevel positive airway pressure; COVID: coronavirus disease; CAUTI: catheter-associated urinary tract infection; CCTV: closed-circuit television; CRBSI: catheter-related bloodstream infection; HFNC: high flow nasal cannula; HCW: healthcare worker; IMV: intermittent mandatory ventilation; NIV: noninvasive ventilation; OT: operation theater; PPE: personal protective equipment; SOP: standard operating procedure; USG: ultrasound; UPS: uninterruptible power supply system; VAP: ventilator-associated pneumonia)

CONCLUSION

Expectations from society for upholding the higher standards of ICU care, despite the overwhelming demands and poor infrastructure, could be fulfilled to some extent. However, bitter lessons learnt by COVID-ICUs should be taken as an opportunity to better ourselves for future needs. Technological advancements in telemedicine have and will continue to lead the way for any future pandemics. Telehealth surge was observed during COVID-19 and is expected to continue rising further as the set standard in health care. The experience gained using telemedicine in COVID-19 needs to be furthered and extended to the non-COVID-ICUs as well to overcome the heterogeneity in delivery of critical care services in India. Health care in India needs structural, organizational, operational, and technological overhaul to meet the rising ICU demands.

REFERENCES

1. World Health Organization. (2003). How much should countries spend on health? [online] Available from https://www.who.int/health_financing/en/how_much_should_dp_03_2.pdf [Last accessed March, 2022].
2. Kapoor G, Hauck S, Sriram A, Joshi J, Schueller E, Frost I, et al. (2020). State-wise estimates of current hospital beds, intensive care unit (ICU) beds and ventilators in India: Are we prepared for a surge in COVID-19 hospitalizations? [online] Available from https://www.medrxiv.org/content/10.1101/2020.06.16.20132787v1 [Last accessed March, 2022].

SUGGESTED READING

1. Arabi YM, Azoulay E, Al-Dorzi HM, Phua J, Salluh J, Binnie A, et al. How the COVID-19 pandemic will change the future of critical care. Intensive Care Med. 2021;47:282-91.
2. https://egazette.nic.in/WriteReadData/2020/219374.pdf.

CHAPTER

108

Managing Change in Intensive Care Unit: Why Won't Doctors Do What They're Told?

Gauri R Gangakhedkar, Jigeeshu V Divatia

INTRODUCTION

Scientific and technological advances have transformed the healthcare sector. Consumerization of healthcare, changing economic and institutional facets, and the widespread permeation of insurance in healthcare have altered both the spectrum and the nature of services provided by the healthcare providers. The healthcare sectors in rapidly growing low- and middle-income countries, which are becoming global centers of technological and organizational innovation, have been particularly impacted by these changes.[1] Incorporation of these advances into healthcare services is not an easy task given the distinct socioeconomic and infrastructural constraints in these countries.

To facilitate the incorporation of the changes brought on by the advances, the concept of professional health managers has become popular. Health managers help organize and provide cost-effective and efficient healthcare, taking the pressure off healthcare workers who are also being increasingly burdened by documentation and administrative tasks as well as participation in management-led quality-improvement initiatives.[2]

Of all the components that make up the healthcare systems, the intensive care units (ICUs) are among the most complex and expensive. The innate complexity of the ICU stems from multiple causative factors such as critically ill patients with acute life-threatening illnesses, high mortality rates, unpredictable outcomes at work, dynamic interdepartmental team structures, and the immense emotional burden to provide clear and honest information to vulnerable patients and their families.[1,3]

Continuous change is integral to the ICU culture; however, acceptance and incorporation of anything new contradict the basic human need for a stable environment.[2] Available literature suggests that doctors rely more on knowledge gained from their past experiences, education, and information from journals than they are at accepting and adhering to new protocols. However, presenting them with evidence to support the need for the change appears to make it easier for doctors to accept new evidence and protocols.[4]

In this chapter, we attempt to highlight factors that affect the acceptance of change and make the acceptance of these changes challenging. We will also attempt to suggest means by which doctors could possibly find it easier to accept and adapt to change easily.[5]

We have identified four major domains which in clinicians might encounter challenges in consolidating changes that emerge with evolving evidence and thus have trouble doing what they are told.

Implementing evidence-based practices (EBPs): EBPs truly form the core of modern medicine. The formal definition for EBP is the conscientious, explicit, and judicious utilization of current evidence to make decisions that improve the care of individual patients. It represents an attempt to accurately understand medical developments, and apply newer principles as they evolve, to provide the best care for the patients.[6]

Evidence-based practice utilization, based on international standards, has been shown to reduce costs, improve patient and family satisfaction, and enhance the quality of patient care.[7] In fact, a review by Pronovost et al. estimated that 167,819 lives can be saved annually, in the United States alone, with the implementation of key EBP-based intervention to target major ICU causes of mortality such as sepsis, adult respiratory distress syndrome (ARDS), and inadequate glycemic control.[8]

Conventionally, clinical decisions are usually based on traditional teaching, intuition, information obtained from peers or colleagues, and information from procedure manuals and application of EBP may appear to de-emphasize the value of these sources. However, it must be remembered that EBP holds no value unless implemented against the backdrop of strong clinical expertise. While EBP allows integration of research evidence with clinical expertise and patient values, its application and adaptation are unlikely to

be effective or sustainable, unless it is applied in the right setting by the right clinicians on the right patients, as is represented in **Figure 1**.[6]

Barriers to implementation of EBP on an individual level include lack of familiarity with EBP, individual flawed perceptions of EBP, or lack of credible information sources of evidence. Jordan et al. found that a significant number of doctors thought that the available information was overwhelming and difficult to synthesize, which suggested an inability to critically appraise, validate, and comprehend the information in order to make a clinical decision.[7]

This is a perception that requires immediate rectification since preappraised literature is available on websites such as the Cochrane database of systematic reviews, UpToDate, The Bottom Line, and the ACP journal club, free of cost or at a small price. The authors thus propose a six-step plan to understand and implement EBP **(Fig. 2)**.

Pharma-funded trials and possible financial incentives evoke a rather skeptical view on available literature. As a clinician, being a skeptic allows you to critique the available evidence and only accept it if a definitive advantage is evident. Unfortunately, this means that sometimes good evidence gets ignored and pathophysiologic reasoning or biologic plausibility is given precedence.[9] On the contrary, trials showing overwhelmingly negative outcomes, such as the ones proving the impact of starches on the kidney, seem to be accepted easily.[10] The only plausible explanation behind this seemingly easy acceptance of negative studies is that when faced with a dilemma, a clinician will always choose the safest alternative for their patient.

Additionally, incorporation of EBM into practice incorporates a commitment to regularly review the available literature to assess validity. This needs to regularly review evidence and the brevity of validity of most of the evidence, be it guidelines or that from other scientific papers that could also be perceived as a deterrent to EBM. Lack of support from management, poor facilitation, lack of authority to change practice, high workload, and inadequate infrastructure were found to be major organizational barriers to the implementation of EBP.

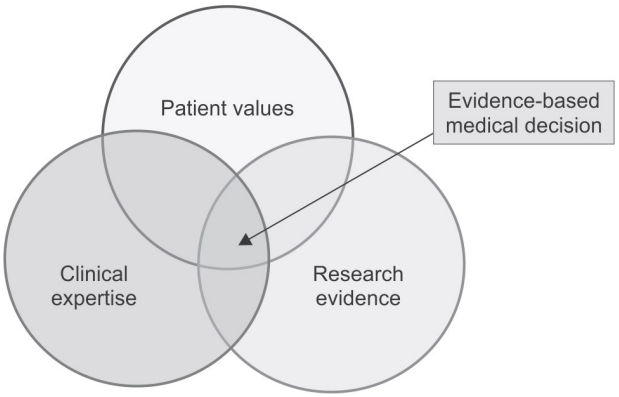


Fig. 1: Evidence-based medical decisions.

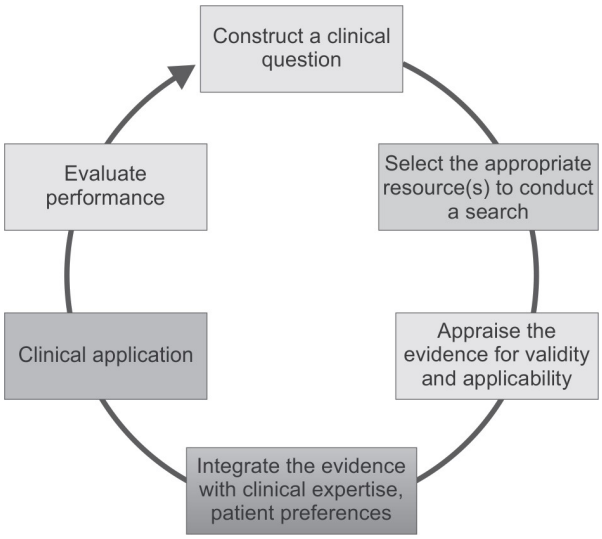


Fig. 2: Six-step plan to implement evidence-based practice (EBP) into clinical practice.

Implementing new protocols: While prima facie, there appears to be no difference between EBP and protocolized care, it must be understood that protocolized care represents an effective way to incorporate EBP into practice, and EBP involves regularly updating the protocols to reflect the latest evidence.

Protocols and checklist consist of simple measures that are "bundled" and have shown improved outcomes. Protocols standardize care of patients with similar diseases and hence increase the consistency of behavior. They allow the nursing and paramedical staff to work with directives in the absence of doctors.[11] Additionally, they reduce the risk of errors by reducing the pressure of performing unfamiliar tasks at critical times and create additional defenses to prevent errors.[12] Multiple studies and reviews have validated the immense contribution that protocols have had in improving outcomes in critically ill patients.[13-15]

Since caring for critically ill patients demands management of multiple severe problems with a slim margin of error, incorporation of protocols has the potential to replace idiosyncratic behaviors. However, they serve as a guide for classical situations, when in reality, clinical practice consists of complex and unpredictable scenarios, for which the approaches may have to be tailored.[4] Furthermore, the evidence proving that protocols are associated with markedly improved outcomes does not assess the impact of individual components on outcomes; the bundle is assessed only in its entirety leading to impact misattribution, where each individual component is credited with having been responsible for the benefit.[16,17]

An observational study conducted in Pennsylvania ICUs showed that the implementation of protocols that are known to improve outcomes was seen in 14–41% of

the ICUs though the protocols were available in 96% of them.[18] The possible reason for this is that implementation of exhaustive checklists may increase the complexity of given tasks, making it difficult to accomplish particularly in high-volume or high-functioning ICUs. Consequently, even in the face of evidence to suggest that protocols and checklists have shown to vastly improve outcomes, one must remember that protocols promote safety, not excellence!

When we consider employing protocols to clinical practice, it becomes important to fit the available resources with the protocol implementation desirable, to prevent protocol misalignment.[17] Maitland et al. found that using "fluid bolus techniques" to resuscitate critically ill children in a resource-poor setting did not lead to the intended benefit, since facilities such as invasive monitoring and mechanical ventilation were not easily available.[18]

Though there is evidence that checklists and protocols are excellent tools to monitor the state of a system, their successful implementation depends on achieving the right balance between standardization and in providing the physicians with some decision-making latitude.[4] In other words, the real challenge is to not allow patient care to become a series tick boxes which treats patients as an abstract image rather than individuals.

Implementing technology: One of the most important challenges that ICU physicians face is the need to continually learn and imbibe evolving healthcare technology in order to undertake their professional tasks, to the best of their competence.[19]

Adopting new technology can be taxing since it entails approval by team members, meeting budgetary requirements, developing the requisite infrastructure, and training of team members. Financial constraints, deficient infrastructure, information technology (IT) workforce shortages, and untrained and reluctant staff members are at the forefront of challenges in implementation of new technology.

Besides these challenges, introduction of any new technology can disrupt the delivery of care and can also lead to new, unforeseen errors which impact the safety and quality of clinical care or even lead to patient harm. Unfamiliarity with the software leading to an increased requirement of time to carry out otherwise simple tasks, administering medications twice, and entering orders for incorrect patients are often seen when the team is new to a technology. In fact, up to 21 studies have identified delay in providing care, due to unavailable or inaccessible software, power failures, or computer viruses preventing access.[20] All of this could give rise to a growing feeling of frustration, a sense of futility, and a convoluted perception that the technology is a waste of time, thus leading to creation of workarounds to avoid using the software.

When the introduction of a new technology is a management initiative, its acceptance becomes easier if it is introduced after looking into the perceived facilitators and barriers to implementation.[21,22] Furthermore, a detailed assessment regarding the actual needs of the center would ensure that the programs are accurately structured to meet the center's needs.[23] This is predominantly true about technologies that have long learning curves and whose functionality is likely to increase over time.

When the team members perceive a technology as having little value or impact, its implementation is met with resistance. All these factors possibly explain why technology initiatives that are led by nurses or physicians, rather than administration' lead to better outcomes.

Providing initial training on a device, availability of technology support staff to assist novices, and the availability of continued guidance along with refresher courses have a significant impact on widespread acceptance.[21] It is these differences in implementation that possibly lead to the same technology to thriving in one institution yet failing in another.

Interpersonal relations/conflicts: The ICU, as a workplace, is dynamic not just because of how rapidly the condition of the patients changes but also because the ICU has multidisciplinary teams whose members work together regularly, disband, and regroup together repeatedly.[23] Multidisciplinary teams where each team member provides a distinct approach and perspective toward a uniform goal, i.e., better patient outcomes, have been the characteristics of critical care. A fundamental component of effective teamwork in the ICU thus becomes fluid leadership, with an identification of common goals. Fluid team leadership involves assessing a given scenario and patient requirements to dictate which team member, with their training and understanding, would be the best to lead the treatment plan at that point.

Unfortunately, this unique structuring could also entail an incomplete grasp of the other team members' background and understanding of the situation. Given the highly volatile environment where stakes and tensions remain high, the changing interpersonal dynamics can make the ICU a place rife with conflicts.

Team conflicts can be classified as task or relationship conflicts. Disagreement about tasks at hand such as team strategy and policy development leads to task conflicts while relationship conflicts consist of disagreements due to differences in personality, personal values, and beliefs.[23] Team conflicts can be used to clarify misunderstandings and disagreements about roles and tasks. Relationship conflicts unlike task conflicts are invariably detrimental to team performance and hence patient outcomes.[23] They lead to situations where actions of the team members are viewed with suspicion. As a consequence, conflicts have

the potential to alter team dynamics and communication, decrease trust and team performance, and lead to poor mental health among professionals.[24] Failure to collaborate and communicate effectively could lead to patient care decisions being taken in isolation and without taking into account the perspectives of all team members.[24]

Conflicts in the ICU have been shown to be strongly associated with burnout syndrome in nurses and physicians. A multicentric study by the European Society of Intensive Care Medicine (ESICM) carried out in 323 ICUs in 24 countries showed that 72% of the respondents reported at least one conflict over one 24-hour period evaluation.[3] While 70% of respondents reported that these conflicts had possibly a harmful effect on the quality of care provided, 44% of respondents reported a possible harmful effect on patient survival.[3]

Understanding the root cause of conflicts and domains of patient care that are affected is crucial. It will help attending physicians, nurse managers, and quality management programs implement appropriate countermeasures more efficiently. Task conflicts provide an excellent opportunity to revisit and review policies to improve outcomes. Team identification, regular debriefings, and policy review meetings can help reduce relationship conflicts. Furthermore, since death of the patients is one of the strongest risk factors leading to team conflicts and physician burnout, it may be advisable to ensure that the same team member is not in charge of several dying patients at the same time. When dealing with patients who are dying, having the entire team formulate an approach to explain the principles of palliative care to the family significantly increases team identification and decreases conflicts while simultaneously improving the quality of care.[3]

MANAGING CHANGE IN INTENSIVE CARE UNIT

Implementing sustainable changes in the ICU practices is not limited to simply introducing amendments but necessitates focused efforts to plan, implement, and evaluate interventions or the so-called Plan-Do-Study-Act (PDSA), as a continuous quality improvement initiative as recommended by the Institute of Healthcare Improvement (IHI).

It would probably help to understand that implementing an effective and sustainable change begins much before the introduction of the idea for the change, i.e., of the PDSA cycle. The planning of the change is indubitably the most important part of the process. It involves understanding the history and evolution of the health sector in that particular region, the functioning and culture of the same, studying potential innovations that could be effective based on the current set of challenges, analysis of infrastructural and managerial policies that influence health system performance, and understanding of health system stewardship.[1] The fundamental components to choosing the right intervention are shown in **Figure 3**.

Forming a core project implementation team that regularly reviews project status and plans next steps, enrolling enthusiastic experts, provides regular updates, use of digital tools such as online forums, applications that show individual contributions, and outcomes in real time, and reinforcing the importance of the initiative by mentors or team, the ICU director, and key unit leadership personnel, holds the key to success.[5,25]

However, this is easier said than done, since ensuring the same requires extensive interdisciplinary leadership and collaboration. Rather than a chain of events, implementing change consists of a never-ending cycle as represented in **Figure 4**.[26]

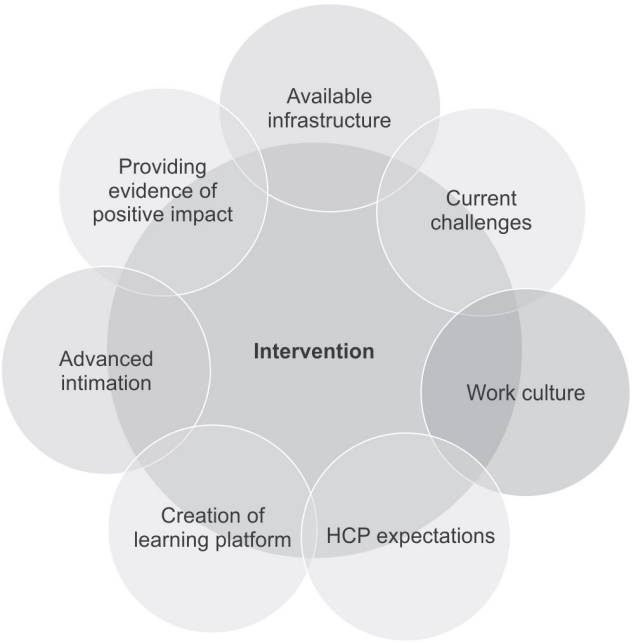


Fig. 3: Choosing the right intervention.[1] (HCP: healthcare provider)

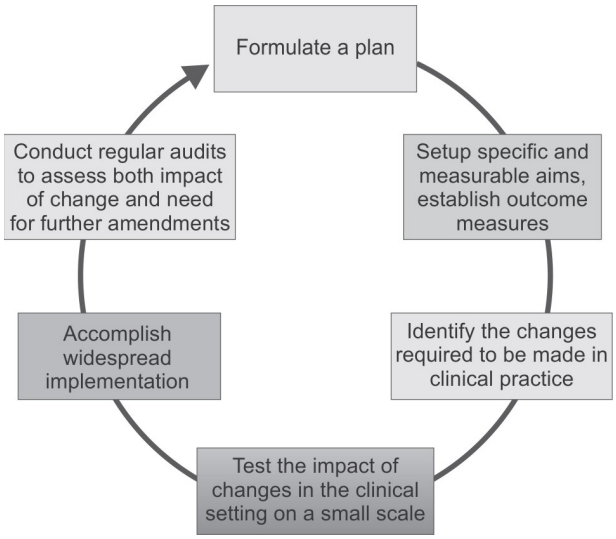


Fig. 4: Implementing effective change.

Organizational changes have been shown to be associated with psychological uncertainty since the changes affect the work, role, and overall life of the involved team members. They could also lead to work-related stress, decreased productivity, emotional exhaustion, mental health problems, and a myriad of other problems.[2]

Bureaucratized and hierarchical organizations tend to be less flexible. Therefore, they are less amenable to change and less likely to empower staff. Literature regarding acceptance of change suggests that physicians were more likely to respond with skepticism or suspicion to management-led changes.[2] Any changes initiated by healthcare providers themselves are usually the easiest to implement and resistance is rarely encountered. For management-led changes, clear advanced intimation to allow time for preparation, and providing evidence which shows identifiable value in improving patient outcomes, goes a long way in easing the acceptance **(***see* **Fig. 3)**.

Implementing effective change has been described as unfreezing old behaviors, introducing new ones, and refreezing them.[19] To ensure that changes brought on by administration or management are as physician friendly as they are patient-centric, the Swedish government has introduced the concept of "trust-based governance." "Trust-based governance" aims at integrating aspects of professional logic with managerial logic, and thus provides an effective solution to healthcare professionals using auditing, control, and performance management.[2] Though it encourages the presence of healthcare managers, the system encourages doctors to use their expertise and discretion to independently treat complex patients and make decisions based on their knowledge and skills rather than limit them in a rigid hierarchy.

CONCLUSION

To summarize, each ICU represents a microcosm of the healthcare sector with multidisciplinary teams, distinct work cultures, and varied infrastructural and socioeconomic limitations. Thus, while implementing any new strategy, it must be borne in mind that bringing about any such alteration would require a change in the ICU work culture and impact the daily behavior of all the team members. Furthermore, implementing effective and sustainable long-term solutions for change consists of evaluating each setup for its requirements and identifying challenges that would be encountered during implementation. The ideal solution is one, which while holding patient interests at heart, represents an amalgamation between technological, protocolized, evidence-based or people-oriented interventions.

REFERENCES

1. Bloom G, Wilkinson A, Bhuiya A. Health system innovations: adapting to rapid change. Global Health. 2018;14(1):29.
2. Nilsen P, Seing I, Ericsson C, Birken SA, Schildmeijer K. Characteristics of successful changes in health care organizations: an interview study with physicians, registered nurses and assistant nurses. BMC Health Serv Res. 2020;20(1):147.
3. Azoulay E, Timsit JF, Sprung CL, Soares M, Rusinová K, Lafabrie A, et al. Prevalence and factors of intensive care unit conflicts: The Conflicus study. Am J Respir Crit Care Med. 2009;180(9):853-60.
4. Rycroft-Malone J, Fontenla M, Bick D, Seers K. Protocol-based care: impact on roles and service delivery. J Eval Clin Pract. 2008;14(5):867-73.
5. Michailidou E. Change management in ICU. Am J Biomed Sci Res. 2020;8:524-9.
6. George EL, Tuite P. A process for instituting best practice in the intensive care unit. Indian J Crit Care Med. 2008;12:82-7.
7. Jordan PJ, Bowers C, Morton D. Barriers to implementing evidence-based practice in a private intensive care unit in the Eastern Cape. South Afr J Crit Care. 2016;32(2):50-4.
8. Pronovost PJ, Rinke ML, Emery K, Dennison C, Blackledge C, Berenholtz SM. Interventions to reduce mortality among patients treated in intensive care units. J Crit Care. 2004;19:158-64.
9. Ebell M, Shaughnessy A, Slawson D. Why are we so slow to adopt some evidence-based practices? Am Fam Physician. 2018;98:709-10.
10. Zarychanski R, Abou-Setta AM, Turgeon AF, Houston BL, McIntyre L, Marshall JC, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. JAMA. 2013;309(7):678-88.
11. Matlakala MC, Bezuidenhout MC, Botha AD. Challenges encountered by critical care unit managers in the large intensive care units. Curationis. 2014;37(1):1146.
12. Drews F, Wallace J, Benuzillo J, Markewitz B, Samore M. Protocol adherence in the intensive care unit. Hum Factors Ergon Manuf. 2012;22(1):21-31.
13. Chang SY, Sevransky J, Martin GS. Protocols in the management of critical illness. Crit Care. 2012;16(2):306.
14. Blackwood B, Alderdice F, Burns K, Cardwell C, Lavery G, O'Halloran P. Use of weaning protocols for reducing duration of mechanical ventilation in critically ill adult patients: Cochrane systematic review and meta-analysis. BMJ. 2011;342:c7237.
15. de Moraes AG, Holets SR, Tescher AN, Elmer J, Arteaga GM, Schears G, et al. The clinical effect of an early, protocolized approach to mechanical ventilation for severe and refractory hypoxemia. Respir Care. 2020;65(4):413-9.
16. Girbes ARJ, Marik PE. Protocols for the obvious: Where does it start, and stop? Ann Intensive Care. 2017;7:42.
17. Kavanagh BP, Nurok M. Standardized intensive care. Protocol misalignment and impact misattribution. Am J Respir Crit Care Med. 2016;193(1):17-22.
18. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, et al. Mortality after fluid bolus in African children with severe infection. N Engl J Med. 2011;364(26):2483-95.
19. Al-Abri R. Managing change in healthcare. Oman Med J. 2007;22(3):9-10.
20. Kim MO, Coiera E, Magrabi F. Problems with health information technology and their effects on care delivery and patient outcomes: a systematic review. J Am Med Inform Assoc. 2017;24:246-50.

21. Langhan ML, Riera A, Kurtz JC, Schaeffer P, Asnes AG. Implementation of newly adopted technology in acute care settings: a qualitative analysis of clinical staff. J Med Eng Technol. 2015;39:44-53.
22. Gabriel MH, Jones EB, Samy L, King J. Progress and challenges: implementation and use of health information technology among critical-access hospitals. Health Aff (Millwood). 2014;33(7):1262-70.
23. Guenter H, van Emmerik H, Schreurs B, Kuypers T, van Iterson A, Notelaers G. When task conflict becomes personal: The impact of perceived team performance. Small Group Res. 2016;47:569-604.
24. Cullati S, Bochatay N, Maître F, Laroche T, Muller-Juge V, Blondon KS, et al. When team conflicts threaten quality of care: A study of health care professionals' experiences and perceptions. Mayo Clin Proc Innov Qual Outcomes. 2019;3(1):43-51.
25. Kleinpell R, Zimmerman JJ. Implementing clinical practice changes in critical care: lessons learned in a national collaborative of over 60 ICU teams. Anaesthesiol Intensive Ther. 2017;49(5):437-40.
26. Institute for Healthcare Improvement. (2005). Science of improvement: how to improve. [online] Available from: http://www.ihi.org/resources/Pages/HowtoImprove/ScienceofImprovementHowtoImprove.aspx [Last accessed March, 2022].

CHAPTER 109

The Current State of Clinical Information Systems in Critical Care in India

Anuj Clerk, Biren Chauhan, Krunalkumar Patel

INTRODUCTION

Medical field is advancing rapidly and so it is obvious that the quantum of information is rising at a galloping rate. Ever-growing volumes of information, not only about patients' clinical data sets but also about administrative areas (quality, safety, codes, equipment, maintenance, etc.), is increasing fast. Keeping track of the dynamics of change in all these data sets is beyond the capacity of a human being, unless one takes resort to computerized information systems. Computer-based clinical information system (CIS) helps not only to acquire and manage data but also facilitate assimilation into actionable intervention regimes, which are then made available to the bedside team for timely actions for better patient care.

Recognizing the importance of CIS, the American Board of Medical Specialties has added Certificate in Clinical Informatics in their list and all modern hospitals have the post of Chief, Clinical Information Services. In India, due to heterogeneity in resource allocation for CIS in various critical care units, we have all states of CIS in our intensive care units (ICUs), right from fully automatized paperless ICUs to all paper without any computer systems. Recently, there has been massive upsurge in the use of computer technology in the healthcare sector. Changes happening at the national government-sponsored healthcare sector have given a new boost to the use of already progressive computer-based health information in the private sector. This chapter will give information on the currently available CIS in India with a mix of clinicians as well as administrators' viewpoints.

CIS AT A LARGE-SCALE NATIONAL LEVEL AND ITS PROJECTED IMPACT AT HOSPITAL LEVEL

Taking cues from the National Health Policy, 2017 (NHP 2017), the government of India launched a health scheme called "Ayushman Bharat Pradhan Mantri Jan Arogya Yojana (PM-JAY)" which is a classic example of large-scale use of health information technology (IT).[1] This scheme is technology driven, digitally equipped, completely paperless, and seamlessly integrated with its empanelled healthcare providers. This giant health information system not only made possible collection of such a large metadata but also information so collected and collated are of great value to public health researchers for better planning of future healthcare needs of the country. In September, 2021, the government announced Ayushman Bharat Digital Mission (ABDM) to bridge gaps among various stakeholders of the healthcare ecosystem. Building blocks of ABDM will be Unique Health ID for every citizen, robust Health Facility Registry (HFR) and Healthcare Professionals Registry (HPR) and digitally stored Patient Health Records (PHR).

The changes in health care at the top (national level) are expected to percolate as mandatory digitalization of many aspects of health care. Many hospital information systems (HISs), also called CIS, which are already in use, will get a boost. This is a much-needed thrust to resolve intersystem software mismatch, which prevents assimilation of healthcare data not only between hospitals but also country at large. In the current scenario, no hospital, clinic or nursing home, or ICU can afford to lag behind in adopting and upskilling themselves in use of CIS.

CLINICAL INFORMATION SYSTEM: WHY IN MODERN ICU?

As time is muscle in acute coronary syndrome, brain in stroke, time is life in ICUs. To deliver optimal care, any intensive care professional has to collect data from various screens [monitors, intra-aortic balloon pump (IABP), injection pumps, air mattress pump, warmer, ventilator, extracorporeal membrane oxygenation (ECMO) console, etc.], various sources [bedside charts, past records, films, X-ray, computed tomography (CT) scan, magnetic resonance imaging (MRI), etc.], and various reports (pathology, radiology, operating room notes, emergency room notes, catheterization laboratory notes). Then he/she needs to analyze these collected data to reach a conclusion and make and document a treatment plan. Optimal

implementation of treatment plans and regimes is the final step. The effect of patient management needs to be analyzed using the same information from CIS. To do this in a timely manner with a cacophony of alarms in intensive care has become challenging or at times impossible for an average human being. Automatization of these tasks requires compilation of information in CIS at the onset but software incompatibilities between data sources are prohibitive. Many inputs are subjective with marked interobserver variability, which makes datasets inaccurate at best and makes a standard (computerized) algorithmic approach misleading. Dynamic dataset in intensive care setting (ICS) needs integration of timed physiologic inputs in many linear as well as nonlinear analytical tools, which is impossible for routine software, designed mainly for commercial and stock-keeping purposes.[2,3] Thus, one needs a CIS designed to serve clinicians' need in ICU. Many of large corporates or medical colleges have purchased commercially available ones or got their software designed indigenously. These software not only facilitate day-to-day functioning but also pave the way for generation of a large database (BIGDATA) which can be used for machine learning and application of artificial intelligence to create better and cost-effective services. Integration of biomedical and healthcare data has potential to revolutionize the medical therapies and personalized medicine, but it requires a cautious approach to prevent derailment of the established healthcare system.[4]

At inception, such CIS was limited to clinical tasks like ordering, display of laboratory results or radiology images, and at times printing discharge summaries from the system. Now modern CIS has evolved to semiautomatic (requires manual data entry by ground team) or fully integrated and automatic systems. India being the providers of IT professional to the world, it is obvious that we have a large number of agencies making software solutions today. As the number of CIS available in the market increases, one needs guidance of selecting which one suits best for their unit or institute at large.

CURRENT CIS (HIS) SOFTWARE'S BASIC FEATURES AND COST CONUNDRUM

Every IT solution has broadly two major aspects—software and hardware. CIS is software aspect and hardware is there to support and extract maximum benefits of CIS software. Every software solution has again two major areas to look into. Back end is like the brain of the system and front end is the body of the system. Every software is run on fundamental blocks of logic and rule. So, any CIS software one is looking at has to be validated from logic and rule that has gone into developing CIS software. This helps one to critically evaluate and choose from the currently available CIS solutions **(Fig. 1)**.

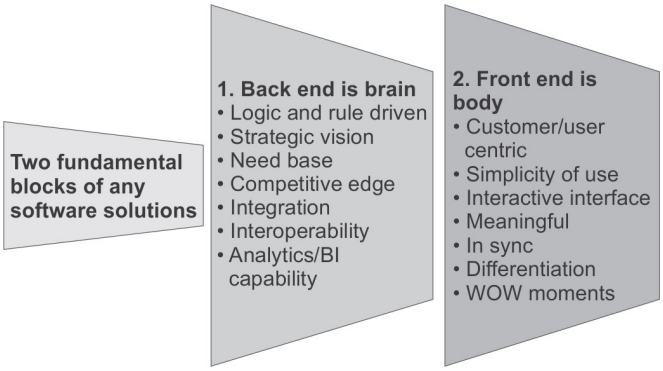


Fig. 1: Fundamental blocks of a clinical information systems. (BI: business intelligence)

TABLE 1: Few of the currently available clinical information system (CIS) providers globally and locally.

Multinational global companies	*India-specific companies and their HIS software*
• Cerner Corporation • Allscripts • Athenhealth • Epic Systems • Microsoft • Salesforce • SAP • IBM	• TCS Medmantra • Wipro HIS • Attune • Akhil • Suvarna HIS • eClinicalworks • Manorama Infosolutions • Palash Healthcare • Birlamedisoft • Gemini • Medstar HIS • eHospital

(HIS: hospital information system)

CIS SOFTWARE SOLUTION PROVIDERS AND COST COMPARATIVES

Global companies offering CIS software solutions are much more costly (anywhere around 75 lakhs or more) when compared to Indian companies. Indian providers are cost-effective in short as well as long run. Few large hospital provider chains also have an in-house team of software developers and use their homegrown CIS as it is highly customized to their requirements **(Table 1)**.

On an average, global CIS providers are—five to six times more costly as compared to their Indian counterparts. Recently, subscription-based models have come up where companies do charge on use basis or per bed per day basis which apportions cost for the buyer over a period of time. However, one has to compare features offerings versus initial cost, plus yearly maintenance cost, and cost of initial capital that goes behind implementing CIS software in a hospital. From an administrator's eyes, one needs to evaluate the cost of CIS in terms of man-hours saved, value addition to customers, system efficiency and tangible and intangible savings, quality care outcomes, etc., for better decision-making while purchasing suitable HIS.

HOW TO EVALUATE A GIVEN CIS? A MATRIX SYSTEM

Before making purchase of CIS software, one has to enlist their own requirements and expectations from CIS software. Requirements must be well elaborated and documented keeping not only past experiences or present needs but future needs as well. Growth plans of the hospital or ICU must take precedent while listing down the requirements. Major thrust has to be on both clinical and nonclinical workflows where HIS software can come in to simplify, streamline, and act as an enabler rather than hindrance. The requirement matrix has to be contextual, realistic, and simplified. The matrix has to be from the perspective of patient and end user and not only from the clinician or management perspective. This is the common error one should get rid of while enlisting requirements for HIS software. One can group the requirements under patient management system, clinical management system, patient support system, and administrative system.

Once the requirement list is ready, multiple HIS software solution providers can be requested for the demonstration where critical features can be evaluated. Evaluation should be done jointly by Chief Operative Officer, Medical Director, and multidisciplinary team comprising mid-level managers, end users, diverse team of clinicians, and top management.

HIS SOFTWARE SOLUTION—ADOPTION CYCLE

To reach to the desired end result of any HIS (CIS), one is expected to pass through the adoption cycle shown in **Figure 2**.

CIS SOFTWARE SOLUTION—360° EVALUATION MATRIX

Table 2 shows the matrix for analysis of evaluation of CIS software. Shortlisted CIS software can be taken up for further discussions and negotiation on cost, features, migration, and implementation exercise, etc., to close the purchase. On-site visit to the places where the solution is being practiced will be more rewarding and revealing.

Challenges during Adoption of a New CIS Software

No adoption process of new CIS software is free from challenges and hurdles. Time and cost overrun are the end result of poor planning and preparedness. CIS purchase is only one part of CIS adoption. The real challenge lies during the migration and implementation phase. Few common challenges faced by any healthcare institution and possible solutions are given in **Table 3**.

Multidisciplinary team approach form beginning, involving larger team and empowering them, creating change managers within system and nurturing vendor association as key stakeholder will ease out these challenges along with sound planning and leading the change from the front.

Limitations of Using CIS in Modern ICUs

Morrison et al., studied effect on interpersonal communication and hurdles in ICU round in their 25 bedded ICU in before and after introduction of fully integrated electronic patient record. They did it by recording ICU

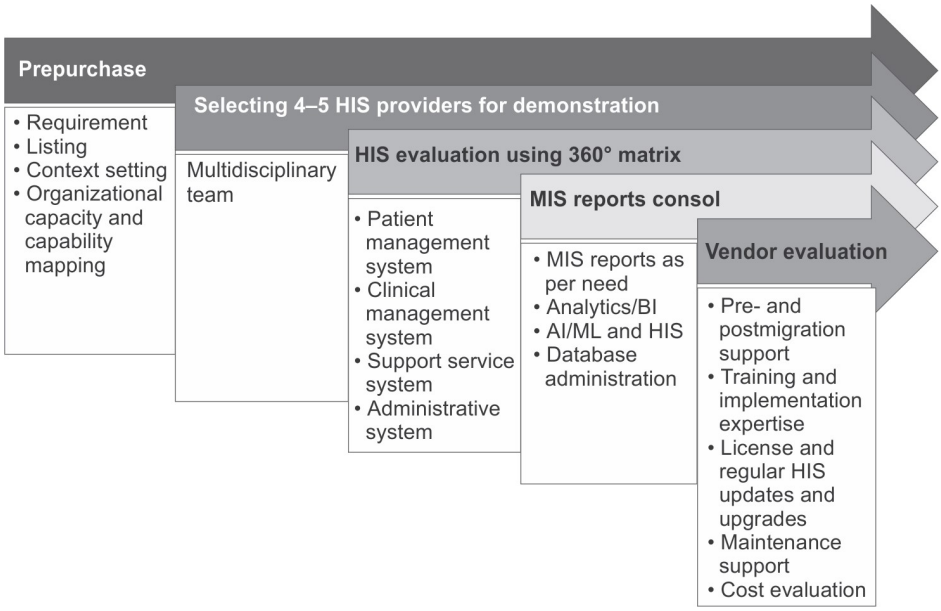


Fig. 2: Process of selection and implementation cycle for clinical information system (CIS). (AI: artificial intelligence; BI: business intelligence; HIS: hospital information system; MIS: management information system; ML: machine learning)

TABLE 2: Clinical information system software solution—360° evaluation matrix.

360° HIS software evaluation matrix					
		Performance scoring (Likert scale)			
Group and subgroups	***Key aspects***	***Demo HIS 1***	***Demo HIS 2***	***Demo HIS 3***	***Demo HIS 4***
Patient management system	• Emergency department workflow • OPD workflow • IPD workflow				
Clinical management system	• ICU workflow • Ward workflow • OT workflow • Laboratory sciences workflow				
Support services management	• Radiology workflow • Pharmacy workflow • Allied clinical and nonclinical services workflow				
Inventory management	Supply chain module				
Revenue cycle management	• Registration and admission • Billing • Claims management • Finance and accounts				
MIS reports console	Daily/weekly/monthly reports and data for decision-making				
Analytics/BI	Analytics and performance management				
Modules	Patient/user/department/administration				
Database administration	Data capturing, data processing, storage, privacy, security, retrieval, analytics				
Vendor support	Requirement understanding, HIS configuration, workflow validation, training, hardware compatibility, integration, interoperability, scalability				
Migration support	360° migration, pre- and postmigration support				
Implementation support	Pre- and postimplementation support				
Licenses and upgradation support	• Compliance and updates as and when arrives to optimize • HIS performance				

(BI: business intelligence; HIS: hospital information system; IPD: inpatient department; ICU: intensive care unit; MIS: management information system; OPD: outpatient department; OT: operation theater)

rounds on video and interpreted for study parameters.[5] After implementation, the doctor who stood in front of the computer (rather than large ICU charts and files) had data visible to him only and rest could see hardly anything. Due to this, others could no longer focus on the patient data. It was noted that team members had difficulty in entering the conversation and impairing communication. It took almost 1 year for the team to readjust themselves by juniors taking print from the system, physician standing back a little, and larger fonts and enlarged images being used on the screen so that everyone can see. Questions were invited at the end of each patient in order to facilitate discussion. Thus, one would expect new problems generated due to implementation of new CIS in a system.[6] However, one must be ready to modify or adapt oneself and CIS with everchanging information load from various courses in ICU.

LEGAL REQUIREMENTS FOR DATA STORAGE AND RETRIEVAL

Various central and state laws make it imperative for hospital to maintain electronic health records (EHRs) of their patients and must produce to competent authority as and when required by law. Patients must get their health records on demand. Protecting personal health data of every patient is very essential and legally binding. The IT Act, 2000[7] largely governs the data security and exchange in all sectors including health care. In addition, the Ministry

TABLE 3: Hurdles and proposed solutions while adopting clinical information system in intensive care unit.

Problems faced by ICU team while switching over to new CIS	
System-related	***Possible solutions***
Hardware shortage, wear and tear	Optimal planning, timely upgrade
Network issues (not able to retrieve stored data on time)	Better planning hardware at inception
Data migration from old to new CIS	Anticipate and make action plan before implementation
Not able to fix software glitches on time especially after hours	Optimal IT team backup (24 × 7)
End-user access and allowance by system	Optimize access privileges from outset
Limitation in privileges to access core system by ground team. Wait for next working day	Telecomputing even after hour support
Teething trouble during introduction	Anticipate and make provisions for added support
Not storing data	Technical support, options of backing up on local system
Data protection	Password protection
Initially heavy dependence on CIS support team of vendor and time delays in getting solutions to problems	Have local IT team trained so system get independent from vendor support after a deadline
Not in system so cannot do	Availability of alternative path to perform and timely integration in the system
End user-related	
Typing speed and errors	Time and proactive attitude to adopt CIS
Cannot make drawing in notes, software, and hardware limits	Draw on paper, scan, and attach
Lack of end-user training and its effectiveness	Optimal and repetitive training of ground team Have adequately trained trainers first
Only one member can use a system at a time	Optimal planning and redesign the way ground team functions
Too slow or resistant in adopting new technology	Repeated training and support by IT team
Not willing to adopt and gets irritated	Adopt or perish pressure from the authorities
Password sharing	Team morale and discipline building with new CIS
Makes system limitation or failure scapegoat for all shortfalls	On-site IT support and alternative pathway for execution of essential tasks
Misuse of internet access	Optimal credentialing and firewalls
Blames system but never helps in optimizing CIS	Team ownership of CIS (software adapted to your needs)

(CIS: clinical information system; ICU: intensive care unit; IT: information technology)

of Health and Family Welfare (MoHFW) has drafted and proposed DISHA Act (Digital Information Security in Healthcare Act) to govern data security in the healthcare sector. Through the DISHA Act,[8] the government intends to setup the National Digital Health Authority to promote and adopt eHealth Standards, enforcing data privacy and security for EHRs and storage and exchange of EHRs. Recent development around data security, safety, and usage of data on various social media platforms posed major challenge and threat to national security and paved way for The Personal Data Protection Bill, 2019,[9] which after enacting into an act will have impact on digital health records too. Globally and nationally, data security and privacy is a major concern and evolving very rapidly and in the Indian context, a regulatory framework at multiple levels is a near-future possibility. This is going to impact the way health care is practiced and delivered by hospitals. This emphasizes the need for formal training of medical students on EHRs, data privacy, security, and usage and exchange of health data of patients.

CONCLUSION

Clinical information system in critical care is need of the hour and must be adopted carefully. Utmost care needs to be exercised while selecting and adopting a CIS. Storage and retrieval of data from the database to facilitate its use for research, machine learning, or application of artificial intelligence is often a neglected aspect. With introduction of ABDM, we anticipate uniform integration of healthcare data across systems (private and government) and across the nation that can pave way for new era in healthcare management.

REFERENCES

1. Ministry of Health and Family Welfare, Government of India. (2017). National Health Policy, 2017. [online] Available from: https://www.nhp.gov.in/nhpfiles/national_health_policy_2017.pdf [Last accessed March, 2022].
2. Buchman TG. Novel representation of physiologic states during critical illness and recovery. Crit Care. 2010;14(2):127.
3. De Georgia MA, Kaffashi F, Jacono FJ, Loparo KA. Information technology in critical care: Review of monitoring and data acquisition systems for patient care and research. Scientific World J. 2015;2015:727694.
4. Dash S, Shakyawar S, Sharma M, Kaushik S. Big data in healthcare: management, analysis and future prospects. J Big Data. 2019;6(1):54.
5. Morrison C, Jones M, Blackwell A, Vuylsteke A. Electronic patient record use during ward rounds: a qualitative study of interaction between medical staff. Crit Care. 2008;12(6):R148.
6. Lapinsky SE. Clinical information systems in the intensive care unit: primum non nocere. Crit Care. 2009; 13(1):107.
7. Ministry of Electronics & Information Technology, Government of India. (2000). Information Technology Act 2000. [online] Available from: https://www.meity.gov.in/content/information-technology-act-2000 [Last accessed March, 2022].
8. Ministry of Health and Family Welfare, Government of India. (2017). Digital Information Security in Healthcare, Act [Draft for Public Consultation], 2017. [online] Available from: https://www.nhp.gov.in/NHPfiles/R_4179_1521627488625_0.pdf [Last accessed March, 2022].
9. PRS Legislative Research. (2019). The Personal Data Protection Bill, 2019. [online] Available from: https://prsindia.org/billtrack/the-personal-data-protection-bill-2019 [Last accessed March, 2022].

CHAPTER 110

Challenges and Issues in Intensive Care Nursing in India: How to Overcome Them?

Susruta Bandyopadhyay, Manoj Kumar Rai, Manish Bharti

WHAT IS CRITICAL CARE NURSING?

Critical care nursing has been identified as a specialized job for >50 years. It was not difficult to understand that the intensive care units with their load of sick patients and their array of gadgets would require a special group of nurses. Presently the training standards for such nurses and their pattern of employment varies from country to country. Indian Society of Critical Care Medicine (ISCCM) in its Experts Committee Statement on intensive care unit (ICU) planning and designing states that the ICUs need one is to one nursing for the very critical patients (like those who are on mechanical ventilation) and at least two nurses for three patients for the less critical ones.[1] However, it does not state the training standards for these nurses. The Society on its part runs a training and diploma course for the critical care nurses.

MANNING IN CRITICAL CARE NURSING

Even across the first world countries, there are wide variabilities in the patient-to-nurse ratio, training standards, and training methods for the critical care nurses. For example, in the USA, 37% of the nurses are attached to the ICUs which would mean a total number of around 200,000, however when one looks into the number of nurses who are members of the American Association of Critical Care Nursing (AACCN), the actual number may be around 2% of the total nursing strength. In Canada, the number of critical care nurses is 18,000, in UK, it is about 3,000, in Europe around 20,000, and in Australia around 10,000. The patient–nurse ratio also varies. Although the standard recommendation is, one to one nursing for very critical patients, often the ratio slips to one registered nurse (RN) for two such patients, in USA, UK, and other countries. Sometimes the number of nurses are made up with enrolled nurses (ENs) who work under the supervision of the RNs, the latter being trained to a level of university graduation.[2]

Training of the Critical Care Nurses

The training standards of such nurses also vary from country to country. While in USA, the nurses need to have a 2 years training before appearing for the exit examination, in Canada, they need just an orientation session lasting a few days. The Australian College of Critical Care Nursing issued a position statement in 2006, which have been subsequently updated several times. This statement discusses the commitments of a critical care nurse, it also emphasizes the need for a clinical learning environment. It divides the level of training in the entry level, the postgraduate level, and the specialist level. This model has been later adapted by a few other countries.[3]

Attrition of the Nursing Force

A major ailment of nursing and more so of critical care nursing is high rates of attrition. It has been seen the turnover is the highest among critical care nurses, in an average around 26%. The "Intention to Leave" (ITL) is seen as a spectrum, from the ITL the department/unit to ITL the hospital to ITL the nursing career. This phenomenon is particularly harmful for the critical care units as it takes time and effort to train critical care nurses. The major issues influencing the ITL are job satisfaction, workplace comfort and safety, remuneration, career opportunities, family workplace balance, etc. The job satisfaction is not well-defined and include many aspects such as work environment, power to take decisions, and learning opportunities.[4]

Nursing in India

The British realized the importance of building a nursing workforce in India. However, there was initially many reservations against taking up nursing as a career among the Indians. The social stigma, religion, and caste issues delayed the progress of this effort. After independence, the Indian Nursing Council was founded in 1950. Initially, they proposed a three and a half-year long General Nursing and Midwifery (GNM) diploma and a 2-year long Auxiliary

Nursing and Midwifery (ANM) diploma. Later a BSc, an MSc degree, an MPhil, and a PhD were added to the list of Nursing Qualifications. Recently, the Government of India has also initiated a course for nurse practitioners. However, even today the nurse-to-population ratio remains inadequate, 1.7 per 1,000 people instead of the stipulated 2.5. There are major differences between the urban and rural nurse population ratios. India is also losing a major number of nurses to more affluent countries as there is a general shortage of nurses across the globe. Although the condition in India is nowhere near the Philippines where 84% of the nursing force have migrated to other countries. (This has prompted persons from other professions including doctors in Philippines to retrain themselves as nurses and then migrate.) Still India needs another 2.4 million nurses to set its nurse:patient ratio right.[5]

The various nursing courses in India are given in **Table 1**.

Critical Care Nursing in India

The Indian Nursing Council gives a 1-year diploma course in critical care nursing. The Indian Society of Critical Care also has a diploma course (Indian Diploma in Critical Care Nursing). The Nurse Practitioner in Critical Care Nursing course has been introduced by the Government of India since 2017, 24 nursing colleges are offering this course and the first batch has passed out in 2020. Critical Care Nursing Society in India is vital to nurses. It was registered on 21 November 2011. It publishes the bimonthly Journal of Critical Care Nursing. It offers the Certificate Program in Critical Care Nursing (3 years), Fellowship in Critical Care Nursing (1 year), and Diploma in Critical Care Nursing (6 months). Both the Critical Care Nursing Society and ISCCM publish their own journals and the ISCCM's journal is indexed.

Although there has been all these progress in the educational aspects of the critical care nursing, the induction of such trained nurses into the system has not been done systematically. There are still no standards of critical care nursing nor are the domains of a nurse holding a degree of critical care nursing well demarcated.[6]

The national accreditations board for the hospitals (NABH) has stipulated the nurse–patient ratios in different areas of critical care **(Table 2)**.

Problems Ailing the Nursing Sector and Critical Care Nursing

Although there are some 300,000 seats for nursing in various institutes, the gap between the demand and supply of the nursing personnel remains high. The majority of the institutes provide the GNM, ANM, and the BSc courses. There is less demand for the higher courses and specializations as the career opening for these qualified nurses is still inadequate. There is also some general loss of interest in nursing as a career. This can be attributed to several factors, long and arduous working hours, relatively less remuneration, short and straight career path (the more ambitious often have a singular goal of getting a foreign placement), workplace violence, and insecurity.

Those who do take up critical care nursing as a career face some other problems too. As already mentioned the domain of a critical nurse and a critical care nurse practitioner still remains ill demarcated. Ongoing training facilities such as CME (continuing medical education) are lacking. There are very few research opportunities for the nurses. Last but not the least, the attrition rate is the highest among the nurses working in the critical care area.[7]

The Way Forward

There has been an increasing stress on the development of the nursing sector in the recent years. Particularly, the stipulation of the National Accreditation Board for Hospitals (NABH) on nursing numbers and standards have made it mandatory for the hospitals to have adequate trained nurses. The recent reforms by the government like introduction of the courses like nurse practitioners may further open up career opportunities for the interested students. The organizations like the NABH may bring in stipulations which will demarcate the areas and responsibilities for the critical care nurses. Many of the teaching institutions for the nurses are using highly qualified nurses for dual purpose of nursing and teaching. This increases their utilization, responsibility, and remuneration. It also creates excellent learning environments for the students. The standards of education and training for the aspirants for critical care nursing should be more regularized and structured. Perhaps the different organizations who are training critical care nurses should

TABLE 1: The various nursing courses in India.

S. No.	Course	Number of institutions	Number of seats
1	ANM	1,927	55,254
2	GNM	3,040	122,017
3	BSc	1,752	88,211
4	MSc	611	11,853

(ANM: Auxiliary Nursing and Midwifery; BSc: Bachelor of Science; GNM: General Nursing and Midwifery; MSc: Master of Science)

TABLE 2: The nurse–patient ratios in different areas of critical care.

S. No.	Department, area	Nurse:patient ratio per shift
1	ICU:Ventilated beds	1:1
2	ICU:Other beds	1:2
3	High dependency units	1:3
4	Emergency room: Ventilated	1:1
5	Emergency room: Others	1:4

join hands in this effort. More efforts should be given in regular training, skill learning programs for the nurses. More researches in nursing issues should be encouraged.[7] We are hoping for brighter days.

REFERENCES

1. Rungta N, Zirpe KG, Dixit SB, Mehta Y, Chaudhry D, Govil D, et al. Indian Society of Critical Care Medicine Experts Committee consensus statement on ICU planning and designing, 2020. Indian J Crit Care Med. 2020;24(Suppl 1):43-60.
2. Gill FJ, Leslie GD, Grech C, Latour JM. A review of critical care nursing staffing, education and practice standards. Aust Crit Care. 2012;25(4):224-37.
3. Rn JG, Rn FL, Rn DM, Wilson L, Mned RN, Blakeman R. Position Statement ACCCN Position Statement on Critical Care On behalf of the Australian College of Critical Care Nurses. 2017.
4. Cortese CG. Predictors of critical care nurses' intention to leave the unit, the hospital, and the nursing profession. Open J Nurs. 2012;2(3):311-26.
5. Gill R. Nursing Shortage in India with special reference to International Migration of Nurses. Soc Med. 2011;6(1): 52-9.
6. Gnanadurai A. Critical care nursing in India. Crit Care Nurs Clin North Am. 2021;33(1):61-73.
7. Verma A, Gomez TFH. Nursing reforms Paradigm shift for a bright future. 2016;(August):1-50.

CHAPTER 111

Gut Dysfunction in Intensive Care Unit: Recent and Future Advances in Diagnosis and Management

Avinash Tank, Kalpesh Shah, Rajeev Kumar Bansal

INTRODUCTION

Gut dysfunction is common in ICU patients[1] and it is estimated that around 62% of patients develop at least one GIT symptom for at least 1 day.[2] This is partly linked to the belief that chronic kidney disease in critically ill patients leads to increased permeability in the intestines[3] as well as due to compromised immunity in these patients. These factors lead to high rates of GIT infections, and along with morphological changes in the intestinal mucosa, significantly contribute to gut dysfunction,[4] leading to microbial alterations and deterioration of the patient's health.[3] The prognosis in such patients is generally poor[1] and a common endpoint is multiorgan failure.[4] Broadly, gut dysfunction can be defined as an impairment of GIT function and digestion. In certain critically ill patients, this may also be a sign of end-organ failure or a sign of a chronic underlying disease.

Gut dysfunction includes problems with gut motility, impairment in gut absorption capability, fistulae in the gut lining,[1] compromise in mucosal barrier integrity,[5] changes in the microbiota, and raised intra-abdominal pressure. These impairments can quickly turn into life-threatening situations.[1] Currently, there are no standardized scales to quantify the level of gut dysfunction severity.[6]

ELEMENTS OF THE GUT

Epithelium

The GIT is lined by a single-cell layer of epithelium with a surface area about of 30 m^2 which is equivalent to the area of half a badminton court. The gut epithelium is known to produce cytokines and peptides and acts as the first line of defense from invading pathogens. The epithelium is covered by a layer of mucus which prevents any contact of epithelium with the GI acidic components. The renewing capacity of the gut epithelium is remarkable and most cells take around a weeks' time to renew completely.

Microbiota

Approximately 40 trillion microbes inhabit the human gut.[3] This microbiota is essential for human existence and contributes to the proper GIT function.[1]

Immunity

One prominent fact about the gut is that it has the highest number of lymphocytes compared to all other organs in the human body. These lymphocytes are known to produce antimicrobial peptides which help fight against any invading pathogenic attack.

GUT DYSFUNCTION

Gut dysfunction is a chronic condition and can often be an early manifestation of a deteriorating critically ill patient or may present as a sole condition itself **(Fig. 1)**. Gut dysfunction may manifest as gut bleeding, breach in the intestinal tract, gut dysmotility, diarrhea, vomiting, increased intraluminal gut pressure, infection, and feeding intolerance. The main etiology for this is increased permeability of the GIT epithelium in critically ill patients which in turn gives way to the easy modification of gut

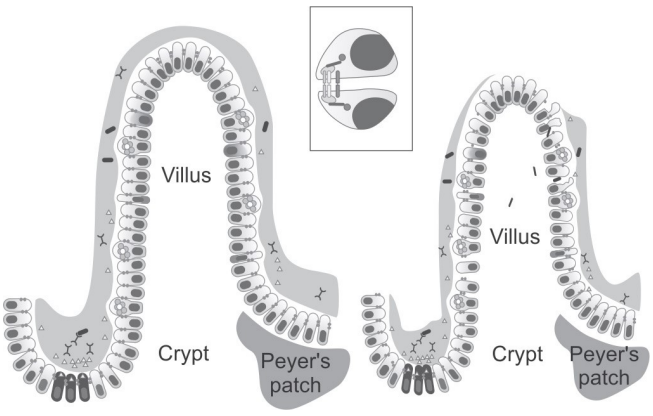


Fig. 1: Normal gut epithelium versus gut epithelium in critical illness.[3]

microbiota. Reduced immunity in critically ill patients is another major contributing factor for gut infections. In fact, the causes of changes of the gut microbial ecosystem are quite complicated. This is especially true for ICU patients who are usually subjected to lots of factors that may predispose the gut environment to changes. These factors involve medications such as antibiotics, proton-pump inhibitors and opioids, and enteral/parenteral routes of feeding.[3] Additionally, gut dysfunction is often occult and difficult to estimate in severity.[5] Gut dysfunction often leads to numerous additional illnesses in the patient,[3] first by compromising the nutrition of the patient[5] and second intestinal toxins formed due to dysbiosis spread easily to the rest of the body through various portals such as the blood and lymphatic supply.[7]

- In good health (left), intestinal stem cells divide and to the top of the villus. A continuous mucus layer surrounds the epithelium as a barrier against luminal microbes which are even recognized by secretory immunoglobulin A (IgA). Permeability is mediated via the tight junction (inset) that selectively allows solutes and water through but blocks larger molecules.
- In critical illness (right), proliferation lessens and apoptosis occurs resulting in a shorter villus length. A damaged, nonuniform mucus layer is seen. The damaged tight junction allows for hyperpermeability and reduced gut barrier function allowing bacteria to translocate into the lamina propria.

The main issue with gut dysfunction is slow gastric emptying. Conditions such as high glucose levels, opioid drugs, raised intracranial pressure, abnormal electrolyte levels, ischemia, burns, etc., contribute to this. In certain cases, gut dysfunction might even be related to aspiration pneumonia.[8] The exact mechanism of the disease is not yet clear,[5] but the biggest challenge is to prevent GIT dysmotility.

Gastrointestinal Tract Dysmotility

Gastrointestinal tract dysmotility is a common condition seen in critically ill patients.[8] The current estimates suggest that about 60% of ICU patients end up with GIT dysmotility.[9] GIT dysmotility can further be divided into upper GIT dysmotility and lower GIT dysmotility.[8] One of the most common reasons for upper GIT dysmotility is the use of opioid in ICU patients[5] and its most common manifestation is vomiting; however, other manifestations may also include nausea and intolerance to feeding.[8]

Gut Barrier Dysfunction

Gut barrier dysfunction is a common problem faced in the ICU, and in fact most patients already suffer from it at the time of admission to ICU.[7] The most common reasons for gut barrier dysfunction are: Enterocyte malfunction, hyperpermeability, mucosal changes, and low immunity. Barrier dysfunction can be detected with electron microscopy, but the drawback is that this procedure needs a biopsy.[1]

Diarrhea

Recent studies suggest using diarrhea as an indicator of malabsorption. Diarrhea may also suggest feeding intolerance, but the data in this regard are very limited. Diarrhea may also be a symptom of nonocclusive mesenteric ischemia.[1]

Gut-lymph Hypothesis

The gut-lymph hypothesis suggests that the mesenteric lymphatics cause spread of toxins from the GI tract to the lungs. Several studies have supported this theory and one countermeasure to prevent this situation is ligation of mesenteric lymphatic vessels which may otherwise commonly lead to sepsis.[3] As a matter of fact, sepsis happens to be the major cause of mortality for acute intestinal failure patients.[7]

MANAGEMENT

Investigations

Gastric Residual Volume

Gastric residual volume (GRV) is a common measure of gastric emptying. Increased GRV is an indication of feeding intolerance. However, this technique has several limitations as it cannot be used due to aspiration risk, and the measurements are still unclear.[10] The scoring system on GI failure grades gut injury based on the severity of symptoms **(Table 1)**.[10]

Ultrasound

According to latest research, an abdominal ultrasound can show significant findings of gastric emptying, gut movement alterations, and changes in intestinal dimensions and may also help detect any perforations with an ultrasound Doppler. Ultrasound may also be used in the placement of the feeding tubes.

TABLE 1: Gastrointestinal tract failure score.[10]

Criteria	*Score*
Normal	0
Enteral feed (missed) <50% of calculated requirements or no feeding for 3 days postabdominal surgery	1
Feeding intolerance or intra-abdominal hypertension	2
Feeding intolerance and intra-abdominal hypertension	3
Abdominal compartment syndrome	4

Other Tests

Raised intra-abdominal pressure is another marker of gut malfunction.[1] Increased gut permeability can be assessed by biopsy, electron microscopy, and double or triple sugar absorption test. However, these techniques have their share of limitations. Biopsies are invasive and not always recommended, whereas the sugar absorption test results might be influenced by antibiotic use and liver disorders.[7] Intestinal fatty acid, protein, and citrulline have been advocated to be used as biomarkers for gut dysfunction.[10] The gold standard for determining intestinal absorption capacity is bomb calorimetry. However, the availability of this technique is scarce.[7]

Diagnosis for dysmotility is usually difficult as the tests available are difficult to perform in an ICU setup.[9]

Treatment

The management of GIT dysfunction has always been multimodal. The main approach involves maintenance of the electrolyte balance.[1] According to latest guidelines, in a critically ill patient, enteral nutrition must be commenced within 24–48 hours. However, this approach is contraindicated in cases of acute GI injury.[11] A postpyloric route is recommended for enteral nutrition in patients who have a high risk of aspiration. Enteral supplementation with arginine and glutamine may also help to improve the gut function and integrity.[1] Certain studies also claim that enteral feeding, started within 24–48 hours, shows a better outcome in ICU patients when compared to parenteral feeding.[12] However, physicians should ensure not to overfeed the patient since the gut requires rest, and overfeeding can put undue strain on the GIT.[13]

For management of delayed gastric emptying, prokinetics such as metoclopramide, erythromycin, and domperidone are generally given. However, since domperidone cannot be given intravenously, its use in an ICU setup becomes a challenge.[1] Some studies have claimed superiority of erythromycin over metoclopramide. However, the best results have been shown with the combination of both erythromycin and metoclopramide.[7] The only limitation to this is that this combination poses a threat of tachyphylaxis and arrhythmias. Another study showed a decrease of intolerance to feeding with prokinetic medications such as erythromycin.[1] In fact, this is the major approach for managing gut dysmotility.[9] For colonic paralysis, neostigmine is a good drug of choice. It is also used for Ogilvie's syndrome. Some studies advocate the use of laxatives for gut dysfunction.[1]

Newer approaches have been used these days for managing gut dysfunction in critically ill. These mostly involve targeting gut microbes. These approaches include the use of probiotics, selectively targeting the bad gut bacteria, and fecal transplantation of microbiota from a healthy donor. These have been discussed in detail in the following section.[3] In case of sepsis, an urgent surgical intervention may be required for removal of the source of sepsis[7] since sepsis caused by gut dysfunction has a higher death rate.[13]

CURRENT RESEARCH AND FUTURE ADVANCES

The current advances in the area of gut dysfunction in ICU patients are not satisfactory.[1] Even the therapeutic approaches available for gut dysfunction do not fall under the accepted current ICU standards and protocols.[3] GRV is often used as a criterion for diagnosis; however, the results are not precise.[1] Another problem we face is the lack of clear definitions for gut dysfunction parameters for ICU patients.[5] In current times, there is no method of repairing GIT epithelium permeability in an ICU patient.[3]

Microbiota management is emerging as a new area of research for gut dysfunction management.[8] Many studies have targeted developing techniques for the growth of good health-promoting bacteria or reducing the growth of bad-disease-causing bacteria. Probiotics have been a big focus of such attempts. The results, however, are limited and not very satisfactory.

One interesting strategy that has been gaining prominence recently is fecal microbial transplantation (FMT). This technique has shown significant success in certain cases. It involves transfer of the entire microbiota from a normal donor fecal matter to an unhealthy recipient gut. This transfer in turn helps to reestablish the normal microbial ecosystem in the recipient gut. FMT has shown a good success rate of 92% in *Clostridium difficile* infections.[14]

Another approach, known as selective decontamination, involves attacking the bad intestinal bacteria selectively. This technique has shown positive results in reducing the death rates in ICU patients.[3]

The focus of the research has also been better maintenance of the mesenteric blood supply with the help of gastric tonometry for oxygenation assessment, avoidance of inflammatory mediators, and application of growth factors.[4]

Much more extensive research is still required in the management of gut dysfunction in ICU patients.[3]

CORONAVIRUS DISEASE 2019 AND GUT DYSFUNCTION

Coronavirus disease 2019 (COVID-19) was originally thought to be a respiratory disorder; however, its effects on other systems of the human body were quickly observed. In many cases, digestive symptoms were commonly seen and these include vomiting, diarrhea, nausea, and loss of appetite, and in many times, these being the presenting symptoms of the disease. According to some observations, in severe cases of COVID-19 infections, a higher number of digestive symptoms are known to occur. The gut involvement by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has

been proven by biopsy as well as at autopsy. The studies have also shown the virus to cause liver injury and damage in a few cases. In fact, the gut may serve as a route of spread of infection for SARS-CoV-2 virus.[15]

CONCLUSION

In critically ill ICU patients, gut dysfunction is prevalent and the most common cause of debilitation. All elements of the gut such as the epithelium, mucus, bacteria, and immunity can be compromised in severely unwell patients. The technology for evaluating gut function in a critically ill patient is not particularly developed at the moment. The gut is a powerful predictor of a patient's outcome in the ICU. End-organ failure or a chronic underlying disease is frequently present. Even though we now have improved means to dealing with GI dysfunction, applying these strategies in an ICU setting becomes challenging or impossible. As a result, this topic has gotten a lot of attention recently and has become a major research topic.[3]

KEY POINTS

- Gut dysfunction is a significant factor affecting the prognosis of the patient in ICU. In many cases, it is the reason for prolonging the ICU stay of the patient and may be even fatal in some.
- It not only compromises the nutritional support of the patient but it is also hypothesized that the toxins of the gut spread fast to other parts of the body. This in turn leads to multiple organ damage or injuries.
- Some of the diagnostic strategies that are used include GRV, ultrasound, biomarkers, etc. The diagnostic techniques that are currently in practice are sometimes not feasible in ICU patients.
- Similarly, the treatment strategies also become limited for an ICU setup. The treatment mostly comprises prokinetics such as erythromycin, metoclopramide, and domperidone. Patients are also put on enteral feed.
- A lot of newly developed techniques have shown better results. Some of these newer strategies are fecal transplantation, use of probiotics, and selective decontamination of GIT.
- Currently we do not have clear definitions, understanding for dealing with gut dysfunction in ICU and the technology is limited in this regard. Thus, there is a huge window open for future advances and research in the area of understanding and management of gastric dysfunction in critically ill patients.

REFERENCES

1. Blaser AR, Preiser JC, Fruhwald S, Wilmer A, Wernerman J, Benstoem C, et al. Gastrointestinal dysfunction in the critically ill: a systematic scoping review and research agenda proposed by the Section of Metabolism, Endocrinology and Nutrition of the European Society of Intensive Care Medicine. Crit Care. 2020;24(1):224.
2. Blaser AR, Malbrain MLNG, Starkopf J, Fruhwald S, Jakob SM, De Waele J, et al. Gastrointestinal function in intensive care patients: terminology, definitions and management. Recommendations of the ESICM Working Group on Abdominal Problems. Intensive Care Med. 2012;38(3): 384-94.
3. Otani S, Coopersmith CM. Gut integrity in critical illness. J Intensive Care. 2019;7:17.
4. Stechmiller JK, Treloar D, Allen N. Gut dysfunction in critically ill patients: a review of the literature. Am J Crit Care. 1997;6(3):204-9.
5. Hill LT. Gut dysfunction in the critically ill – mechanisms and clinical implications. S Afr J Crit Care. 2013;29(1):11-5.
6. Asrani VM, Brown A, Huang W, Bissett I, Windsor JA. Gastrointestinal dysfunction in critical illness: A review of scoring tools. JPEN J Parenter Enteral Nutr. 2020;44(2): 182-96.
7. Chandankhede SR, Kulkarni AP. Acute intestinal failure. Indian J Crit Care Med. 2020;24(Suppl 4):S168-S174.
8. Vazquez-Sandoval A, Ghamande S, Surani S. Critically ill patients and gut motility: Are we addressing it? World J Gastrointest Pharmacol Ther. 2017;8(3):174-9.
9. Jain D, Mahmood E, V-Bandres M, Feyssa E. Preoperative elective transjugular intrahepatic portosystemic shunt for cirrhotic patients undergoing abdominal surgery. Ann Gastroenterol. 2018;31(3):330-7.
10. Chapple LAS, Plummer MP, Chapman MJ. Gut dysfunction in the ICU: diagnosis and management. Curr Opin Crit Care. 2021;27(2):141-6.
11. Zhang D, Li H, Li Y, Qu L. Gut rest strategy and trophic feeding in the acute phase of critical illness with acute gastrointestinal injury. Nutr Res Rev. 2019;32(2):176-82.
12. Scarpellini E, Scarcella L, Romanelli G, Basilico M, Lattanzi E, Rasetti C, et al. Nutritional Status and the Critically Ill Patient: Gut Microbiota and Immuno-Nutrition in I.C.U. at the Time of SARS-COV 2 Pandemic. Gastroenterol Insights. 2021;12(2):259-69.
13. Eaton P, Faulds M. Gastrointestinal dysfunction in the intensive care unit. Surgery (Oxford). 2021;39(10).
14. Fischer M, Sipe B, Cheng YW, Phelps E, Rogers N, Sagi S, et al. Fecal microbiota transplant in severe and severe-complicated Clostridium difficile: A promising treatment approach. Gut Microbes. 2017;8(3):289-302.
15. Ma C, Cong Y, Zhang H. COVID-19 and the digestive system. Am J Gastroenterol. 2020;115(7):1003-6.

CHAPTER 112

Intensive Care Management of Acute Liver Failure: What is New?

Lalita Gouri Mitra, Juhi Chandwani, Amit Singhal

INTRODUCTION

Acute liver failure (ALF) is a rare entity, seen in previously healthy adults in their thirties.[1] It is defined as the presence of coagulopathy [international normalized ratio (INR) >1.5] and hepatic encephalopathy (HE) in a patient with an otherwise healthy liver and with illness of <26 weeks. Coagulopathy alone, in the absence of HE, is termed acute liver injury (ALI), which carries a much better prognosis. Reported incidence is one to six cases per million per year in the developed countries. Hepatotropic viruses such as hepatitis A and E are the predominant causes of ALF in the developing world, whereas-drug induced (paracetamol overdose) is the main cause of ALF in developed countries. There is overall female preponderance, especially in regions where viral causes predominate, with pregnant females accounting for 30% of such cases. In 14–20% of patients, no etiology can be determined, despite systematic investigation.[2]

ETIOLOGY

This syndrome is a manifestation of sudden and severe hepatic injury, due to multiple causes **(Box 1)**. The interval between symptom (most commonly jaundice) and HE which is the jaundice-encephalopathy (J-E) interval also indicates the likely causes, complications, and prognosis of the disease as given in **Table 1**.[3]

BOX 1: Etiology of acute liver failure.

- Viral:
  - Hepatitis A, B, D, and E
  - Cytomegalovirus
  - Epstein–Barr
  - Herpes simplex
  - Parvovirus
  - Varicella zoster
- Drugs:
  - Acetaminophen (paracetamol)
  - Nonacetaminophen (e.g., isoniazid, phenytoin, valproate, propylthiouracil, nitrofurantoin, carbamazepine, statins, flucloxacillin, and tetracyclines)
  - Recreational drugs (e.g., cocaine and amphetamine group)
- Vascular:
  - Ischemic hepatitis
  - Budd–Chiari
  - Pregnancy [preeclampsia, HELLP (hemolysis, elevated liver enzymes and low platelet count)] syndrome, fatty liver of pregnancy
- Others:
  - Wilson disease
  - Mushroom poisoning (*Amanita phalloides*)
  - Heat stroke
  - Malignant infiltration
  - Indeterminate-Cryptogenic
  - Autoimmune
  - Hemophagocytic lymphohistiocytosis (HLH)

PATHOPHYSIOLOGY

Acute liver failure is an innate immune-driven disorder.[4]

In the initiation phase, following an injurious event in the liver, macrophages originate from the Kupffer cells or bone marrow-derived monocytes. Within 12 hours of injury, there is a massive expansion of hepatic macrophages, followed by a biphasic macrophage response.

This initial tissue destructive "M1" response is followed by resolution "M2" response.

In the propagation phase, hepatocyte death results in production of large quantities of inflammatory mediators which "spill over" from the injured liver to the systemic circulation leading to systemic inflammatory response syndrome (SIRS) manifested by fever, raised leukocyte count, tachycardia, and tachypnea. Inflammatory mediators cross the blood–brain barrier and act synergistically with the elevated ammonia levels leading to HE, a hallmark of ALF. This may progress to astrocyte swelling, ICH (intracranial hypertension), and death due to complex interplay between systemic inflammation, circulating neurotoxins (ammonia in particular), and osmolar derangements such as hyponatremia.

In the resolution phase, the M2 response mediated by anti-inflammatory mediators such as interleukin 10 (IL-10) and transforming growth factor β (TGF β), from the inflamed

TABLE 1: Depending on the jaundice-encephalopathy (J-E) interval, O'Grady et al.[3] have classified fulminant hepatic failure in three groups.

Hyperacute liver failure (HALF)	*Acute liver failure (ALF)*	*Subacute liver failure (SALF)*
• Drugs/toxins • Viral • Pregnancy related • Vascular • Other	• Drugs/toxins • Viral • Pregnancy related • Vascular • Other	• Drugs/toxins • Seronegative hepatitis • Vascular • Other
Timeframe from onset of jaundice to development of encephalopathy (J-E interval)		
<7 days	7–28 days	29 days–12 weeks

liver, opposes the proinflammatory response to limit tissue injury. However, spillover of the M2 response to the systemic circulation may predispose the patient to infection and poor outcomes.[5] Therefore, ALF represents an injurious event followed by either deterioration or recovery due to regeneration.

PROGNOSIS

Outcome from ALF has improved recently especially in developed countries, with better understanding of the pathophysiology, early referrals to transplant centers, and improved critical care management.[6] Identifying etiology helps to determine prognosis and initiate etiology-specific therapies wherever possible.

Sepsis and multiple organ failure have taken over ICH as the leading cause of death.[7]

Gauging prognosis of patients is of vital importance and most institutions use laboratory parameters on admission to quantify and plan further management. Coagulopathy, advanced age, and development of encephalopathy are hallmarks of poor outcome. Prognostic tool which has stood the test of time, which has high specificity and low sensitivity, is the King's College Criteria (KCC).[6] The MELD (Model for End-stage Liver Disease) score (>30), which is commonly used for decision-making regarding liver transplantation (LT) in chronic liver disease, can be applied in ALF and has been found to be as good as KCC.[8] Clichy–Villejuif (CV) criteria (presence of HE Grade 3 and above, factor V level <20% in <30 years of age and <30% of normal in >30 years of age) is another prognostic indicator used to list ALF patients for super urgent LT.[9]

Currently, ALF prognostication is based on dynamic assessment of individual rather than static parameters at presentation. Biomarkers are being used to predict outcome with ALF. Caspase-cleaved and uncleaved cytokeratin K18 (referred to as CK18), an apoptosis cell death marker levels in blood has been found to have good prognostic value. Higher levels of caspase activation have been found in patients who had spontaneous recovery from ALF compared to those who required transplant or died. Combined with INR and creatinine levels, sensitivity and specificity were found to be higher than KCC in predicting ALF outcome; however further studies are needed.[6] Another potential biomarker which has shown promise in assessing severity and outcome in paracetamol-related ALF is human leukocyte antigen-DR (HLA-DR) monocyte expression.[8]

DIAGNOSTIC APPROACH

History and Physical Findings

Jaundice, coagulopathy, and encephalopathy in patients with no prior liver disease are the *sine qua non* for diagnosis. Patients may present with general feeling of being unwell along with nonspecific symptoms such as nausea, vomiting, lethargy, and abdominal pain.

Risk Factors

Age >40 years, chronic alcohol use, female sex, poor nutritional status, pregnancy, chronic hepatitis B, use of paracetamol for chronic pain are risk factors to be considered.[2]

Laboratory Findings

Deranged liver function tests with elevated bilirubin, aminotransferases, and INR are present in all cases. High ammonia levels of >200 μmol/L may predict an increased risk of developing ICH and needs to be monitored along with serum lactate. Complete blood count (to look for anemia and thrombocytopenia), urea, creatinine, and electrolytes are important baseline investigations. Important radiological investigations include: Ultrasound and triple phase computed tomography (CT) of the liver. This may be normal initially and hence serial studies may be needed. They help in detecting underlying chronic disease, if present and give valuable information in terms of liver morphology and surface nodularity if any, splenic enlargement, ascites, portal flow, vascular anomaly, patency, and collateral vessel formation.[10,11]

Specific patterns of derangement may help in etiological diagnosis as follows[12]:

- *Viral hepatitis*: Aminotransferases in the range of 1,000–2,000 IU/L with alanine aminotransferase (ALT) >aspartate aminotransferase (AST). Hepatitis A virus (HAV) immunoglobulin M (IgM), hepatitis B surface antigen (HBsAg), hepatitis B core antigen (HBc) IgM, anti-hepatitis C virus (HCV), anti-hepatitis E virus (HEV), cytomegalovirus (CMV) IgM, Epstein–Barr virus (EBV) IgM, herpes simplex virus (HSV) IgM, varicella-zoster virus (VZV) IgM, anti-HIV (human immunodeficiency

virus) may be positive. A low level of Factor 5 with HE may be predictive of mortality, in viral hepatitis.

- *Acetaminophen:* Low bilirubin, very high AST >3,500 IU/L and high INR. Check for elevated serum and urine paracetamol levels, acidosis on arterial blood gas measurement is an important prognostic indicator.
  - *Acute fatty liver of pregnancy/HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome*: Aminotransferases <1,000 IU/L, high bilirubin, and low platelet count
- *Ischemic hepatic injury*: Very high aminotransferases, 25–250 times of upper limit of normal, increased lactate dehydrogenase (LDH).
- *Herpes simplex*: Low bilirubin, increased amino-transferases, and leukopenia.
- *Valproate/tetracycline toxicity*: Minor-to-moderate elevation of aminotransferases and bilirubin levels.

MANAGEMENT OF ACUTE LIVER FAILURE IN INTENSIVE CARE UNIT

All patients with ALF should be managed in the intensive care unit (ICU) with input from multidisciplinary team once encephalopathy develops.[13]

Role of N-acetylcysteine

N acetylcysteine (NAC) is a precursor of glutathione and is the antidote to paracetamol toxicity. The hepatotoxic metabolite of paracetamol, N-acetyl-*p*-benzoquinone-imine (NAPQI) is inactivated by conjugation with glutathione. NAC is 100% hepatoprotective when given within 8 hours of paracetamol ingestion.

A late presentation should not preclude NAC administration.

Dose

140 mg/kg orally as a loading dose, followed by 70 mg/kg every 4 hours: or 150 mg/kg intravenously over 60 minutes as a loading dose, followed by 12.5 mg/kg/hour over 4 hours, then 6.25 mg/kg/hour.

N acetylcysteine has other benefits such as improved liver oxygenation and has antioxidant, anti-inflammatory, and immunologic effects. It has beneficial hemodynamic effects and may improve cerebral perfusion pressure (CPP).

In liver failure related to non-paracetamol etiologies, it has been found to be beneficial in patients with HE I and II. It is ineffective in advanced grades of HE. However, NAC may still have a role in mushroom poisoning and drug-induced ALF.[2]

Management of Cerebral Edema

Management of cerebral edema includes all measures for raised intracranial pressure (ICP) which include the following:[14]

- Head elevation at 30–45° with avoidance of head turning
- Maintenance of low normal partial pressure of carbon dioxide (PCO_2)
- Short-term hyperventilation during raised ICP and hyperemia (seen by elevated jugular bulb oxygen concentration)
- Maintain a mean arterial blood pressure (MAP) of at least 75 mm Hg, to target a CPP of at least 60 mm Hg
- Osmotic therapy with 20% mannitol or hypertonic saline. Target serum sodium levels of 145–155 mmol/L
- Intravenous indomethacin can be tried where hyperemia is the main contributor.
- Avoid fever. So far hypothermia has not proven to be beneficial in these patients.
- Renal replacement therapy (RRT) can be considered for ammonia clearance even in presence of normal renal functions.[15]

In the setting of grade III/IV encephalopathy, patients should be sedated and ventilated. Sedative agents such as propofol which reduces cerebral blood flow is preferred over other agents. Patient requires frequent neurological evaluation for signs of raised ICP. Factors such as pain and frequent endotracheal suctioning which may lead to ICH should be controlled and reduced.[16]

Acute Kidney Injury

Incidence of acute kidney injury (AKI) is around 70% in patients with ALF and it is associated with a poor prognosis without liver transplant. It is more common with drug-induced ALF. The need for RRT for AKI is dictated by classical indications such as acidosis, fluid overload, and hyperkalemia. The continuous modes are preferred over intermittent modes of RRT.[16] Exercise caution in using IV contrast agents and avoid nephrotoxic agents.

Pulmonary Complications

Incidence of pulmonary complications is 30%. Mild acute respiratory distress syndrome (ARDS) is usually a late presentation in the course of the disease coinciding with liver regeneration or development of sepsis.[1] Management of mild ARDS is similar to conventional management of ARDS with the caveat of careful PEEP (positive end expiratory pressure) application in presence of raised ICP. However, presence of lung injury is not considered poor prognostic marker and the outcomes are similar to those patients without ARDS.[14]

Coagulopathy

Routine correction of INR is not recommended as it obscures an important prognostic marker of liver function and the incidence of acute bleeding is low. Coagulopathy correction is advised only in patients who have active bleeding or before invasive procedures.[13]

Hemodynamics

Fluid and cardiovascular management must address the relationship between MAP and ICP. Hypotonic intravascular fluids should be avoided due to high risk of cerebral edema. Resuscitation should be with normal saline or volume expanders. Dextrose-containing fluids may be used in presence of hypoglycemia. If hypotension persists after volume resuscitation, patient should be investigated for sepsis and vasopressor agents (norepinephrine +/– vasopressin) to maintain a MAP of at least 75 mm Hg or a CPP of 55–60 mm Hg should be considered.

Most ALF patients in shock probably have relative adrenal insufficiency in spite of vascular resistance and hence hydrocortisone may be considered to improve hemodynamics to reduce systemic vasopressor requirement.[6]

Enteral Nutrition

Enteral nutrition should be initiated early. Severe protein restrictions should be avoided to prevent catabolism. At least 60 g of protein per day is advisable. Placement of nasogastric tube should be preferably done in intubated and sedated patients to avoid increases in ICP due to gagging. Oral and rectal lactulose may be considered in patients with high ammonia. Studies have shown survival benefit with lactulose, but there was no difference in the severity of encephalopathy or outcome.[6]

Control of Sepsis

High standards of infection control should be maintained to minimize nosocomial sepsis.[1] Impaired hepatic regeneration may lead to a functional immunosuppression with secondary nosocomial sepsis. Therefore, pre-emptive antibiotics have to be administered according to local culture and sensitivity patterns. Prophylactic antimicrobial therapy does not influence survival in this group of patients.[17]

The following therapies are to be initiated simultaneously depending on the etiology of ALF **(Table 2)**.[6]

Monitoring in Intensive Care Unit

Monitoring in ICU is of key importance to achieve specific targets.

Invasive arterial blood pressure:

- MAP and hence CPP
- *Blood gas analysis*: Lactate
- *Blood sugar*: Every second hourly for prevention and treatment hypoglycemia.[14]
- *Temperature monitoring:* Avoiding fever is important for controlling ICP.
- Central nervous system monitoring
- Pupillary size and reaction
- Optic nerve sheath diameter

TABLE 2: Specific management of other etiologies of acute liver failure (ALF).

Etiology	*Management*
Herpes simplex	Acyclovir
Acute fatty liver of pregnancy/HELLP syndrome	Delivery of fetus
Amanita phalloides poisoning	Benzylpenicillin, acetylcysteine, activated charcoal, and gastric lavage
Autoimmune hepatitis	Methylprednisolone
Acute hepatitis B	Tenofovir and entecavir Interferon (no evidence)
Acute Budd–Chiari syndrome	Anticoagulation, TIPSS (transjugular intrahepatic portosystemic shunt)
Acute Wilson disease	Measures to reduce serum copper such as plasmapheresis, continuous venovenous hemofiltration (CVVH), albumin dialysis, or plasma exchange

(HELLP: hemolysis, elevated liver enzymes and low platelet count)

- Transcranial Doppler
- *ICP monitoring*: Controversial and not regarded as standard of care.[18]

Emerging Therapies

Acute liver failure results in the accumulation of ammonia and inflammatory cytokines, which results in the development of cerebral edema, circulatory dysfunction, and renal failure. Extracorporeal liver support (ECLS) devices aim to remove these toxins, improve the pathophysiological features of liver failure, and thus provide a window till native liver recovers or transplant opportunity presents.[19]

An ideal ECLS should perform the functions of detoxification, biosynthesis, and regulation. None of the currently available devices **(Table 3)** satisfy all the criteria.

Plasma Exchange

High Volume Plasma (HVP) exchange defined as exchange of 15% of ideal body weight, has been shown to increase overall survival in ALF, specifically in patients who do not undergo emergency transplantation because of contraindications, and those patients who have deteriorated while waiting for a graft.[20]

LIVER TRANSPLANT

All patients presenting with ALF should be assessed for LT as this may be the only definitive option available for recovery. Early transplant referral is advised based on several prognostic evaluation systems. Aim of prognostication is to identify those patients who won't survive with medical

TABLE 3: Extracorporeal liver support devices in acute liver failure.[19]

Extracorporeal liver support devices				
Name/systems	***CVS***	***CNS***	***Biochemical***	***Survival impact***
MARS (molecular adsorbent recirculating system)	Yes	Not assessed	Yes	No
SPAD (single pass albumin dialysis)	No	No	No	No
HVP (high-volume plasmapheresis)	Yes	Yes	Yes	Yes
Biological/Bioartificial				
Human hepatocytes	Yes	Yes	Yes	No
Porcine hepatocytes	No change	No change	Yes	No

(Biochemical: statistically significant reduction in bilirubin, bile acids, creatinine, and ammonia levels; CNS: statistically significant improvement in grade of encephalopathy; CVS: statistically significant improvement in cardiovascular parameters)

BOX 2: King's College Criteria for selection of recipients for emergency liver transplants.

- Paracetamol poisoning-induced ALF
- Arterial pH <7.3 following adequate volume resuscitation
- *OR a combination of*
  - HE ≥ grade 3
  - Creatinine ≥300 µmol/L (3.4 mg/dL)
  - International normalized ratio (INR) ≥6.5
  - Non-paracetamol poisoning etiology of ALF:
    - Any grade encephalopathy and INR ≥6.5
- *OR any three of the following*:
  - INR ≥3.5
  - Age <10 years or >40 years
  - Jaundice-encephalopathy interval >7 days
  - Bilirubin ≥300 µmol/L (17 mg/dL)
  - Unfavorable cause (drug-induced, liver injury, seronegative disease)

(ALF: acute liver failure; HE: hepatic encephalopathy)

therapy alone. Higher 3-month mortality has been observed in this group, even after a liver transplant.[13] Presence of ICH and emergency nature of the disease makes the procedure challenging in this group of patients.[1] Most widely used is the KCC **(Box 2)**.

Liver transplant surgery is not universally available and <10% of liver transplants are performed in ALF.[1] Data from the US Organ Procurement and Transplantation Network (OPTN) indicate that patients with ALF who undergo LT have survival rates of 87% at 1 year and 78% at 3 years.[13] Post-LT factors such as age >60 years, cardiac issues, high-dose vasopressor, and FiO_2 >0.8 preoperatively is associated with worse outcomes. Auxiliary LT can be considered in some patients and main advantage remains not requiring lifelong immunosuppressants.[21]

CONCLUSION

Acute liver failure is a potentially reversible severe life-threatening condition from various etiologies. Timely intensive care support is essential as it rapidly progresses to multiorgan failure and brain stem herniation due to severe encephalopathy. In recent times with better understanding of the pathophysiology, improvements in intensive care management, and increased availability of transplants, outcomes have improved significantly. No single prognostic model discriminates those who will spontaneously recover and those who will require transplant. Biomarkers such as caspase-cleaved and uncleaved cytokeratin K18 (referred to as CK18) and HLA-DR monocyte expression have shown promising results in detecting spontaneous recovery from ALF but need further studies. LT remains the key and intensive critical care is needed to bridge ALF patients to transplant; however, potential candidates must be evaluated rapidly and serial assessment for surgical fitness is required to ensure good outcomes postsurgery.

REFERENCES

1. Bernal W, Wendon J. Acute liver failure. N Engl J Med. 2013;369(26):2525-34.
2. Donnelly MC, Hayes PC, Simpson KJ. The changing face of liver transplantation for acute liver failure: Assessment of current status and implications for future practice. Liver Transpl. 2016;22(4):527-35.
3. O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. Lancet. 1993;342(8866):273-5.
4. Davies LC, Jenkins SJ, Allen JE, Taylor PR. Tissue-resident macrophages. Nat Immunol. 2013;14:986-95.
5. Antoniades CG, Quaglia A, Taams LS, Mitry RR, Hussain M, Abeles R, et al. Source and characterization of hepatic macrophages in acetaminophen induced acute liver failure in humans. Hepatology. 2012;56(2):735-46.
6. Seetharam A. Intensive care management of acute liver failure: Considerations while awaiting liver transplantation. J Clin Transl Hepatol. 2019;7(4):384-91.
7. Aziz R, Price J, Agarwal B. Management of acute liver failure in intensive care. BJA Education. 2021;21(3):110-6.
8. McPhail MJ, Farne H, Senvar N, Wendon JA, Bernal W. Ability of King's college criteria and model for end-stage liver disease scores to predict mortality of patients with acute liver failure: A meta-analysis. Clin Gastroenterol Hepatol. 2016;14(4):516-25.e5.

9. Ichai P, Legeai C, Francoz C, Boudjema K, Boillot O, Ducerf C, et al. Patients with acute liver failure listed for superurgent liver transplantation in France: Reevaluation of the clichy-villejuif criteria. Liver Transpl. 2015;21(4):512-23.
10. Price J, Hogan BJ, Agarwal B. Acute liver failure: prognosis and management. In: Feagan BG, Kahrilas PJ, Jalan R, McDonald JWD, (Eds). Evidence-based gastroenterol hepatology, 4th edition. John Wiley &Sons; 2019. pp. 374-83.
11. Romero M, Palmer SL, Kahn JA, Ihde L, Lin LM, Kosco A, et al. Imaging appearance in acute liver failure: correlation with clinical and pathology findings. Dig Dis Sci. 2014;59(8):1987-95.
12. American Association for the Study of Liver Diseases. Acute liver failure update 2011. [online] Available from: http://www.aasld.org/practiceguidelines/Documents/AcuteLiverFailureUpdate2011.pdf. [Last accessed March 2022].
13. Gonzalez SA. (2017). Acute liver failure. BMJ Best Practice. [online] Available from: https://bestpractice.bmj.com/topics/en-us/1010. [Last accessed March 2022].
14. Cardoso FS, Marcelino P, Bagulho L, Karvellas CJ. Acute liver failure: An up-to- date approach. J Crit Care. 2017;39:25-30.
15. Slack AJ, AuzingerG, Willars C, Dew T, Musto R, Corsilli D, et al. Ammonia clearance with haemofiltration in adults with liver disease. Liver Int. 2014;34(1):42-8.
16. Lele AV, Wilson D, Chalise P, Nazzaro J, Krishnamoorthy V, Vavilala MS. Differences in blood pressure by measurement technique in neurocritically ill patients: A technological assessment. J Clin Neurosci. 2018;47:97-102.
17. Karvellas CJ, Cavazos J, Battenhouse H, Durkalski V, Balko J, Sanders C, et al. Effects of antimicrobial prophylaxis and blood stream infections in patients with acute liver failure: a retrospective cohort study. Clin Gastroenterol Hepatol. 2014;12(11):1942-9.
18. Butterworth RF. The concept of "the inflamed brain" in acute liver failure: mechanisms and new therapeutic opportunities. Metab Brain Dis. 2016;31(6):1283-7.
19. Karvellas CJ, Subramanian RM. Current evidence for extracorporeal liver support systems in acute liver failure and acute-on-chronic liver failure. Crit Care Clin. 2016;32(3):439-51.
20. Larsen FS, Schmidt LE, Bernsmeier C, Rasmussen A, Isoniemi H, Patel VC, et al. High-volume plasma exchange in patients with acute liver failure: An open randomised controlled trial. J Hepatol. 2016;64(1):69-78.
21. Rela M, Kaliamoorthy I, Reddy MS. Current status of auxiliary partial orthotopic liver transplantation for acute liver failure. Liver Transplant. 2017;22:1265-74.

CHAPTER 113

Caring for the Dying Patient in Indian Intensive Care Unit: Quality of Care, Ethical, and Legal Challenges

Abhishek Prajapati, Rachit Patel, Bhalendu Vaishnav

INTRODUCTION

End-of-life care (EOLC) in an intensive care unit (ICU) poses a daily challenge for clinicians across the world. A clear understanding of global and local ethical, legal, sociocultural, and spiritual considerations is required for improving standard of care. Medical interventions at the time of death can prolong the lives of people, often without assurance of meaningful existence of quality of life. It is an important obligation of a critical care expert to guide the relatives to take appropriate decision within permissible legal and ethical provisions so as to facilitate comfortable dying process and death. The legal issues relevant at EOLC are advance directives, euthanasia, withholding and withdrawing life-sustaining treatment from adults, and substitute decision-making for adults. The ethical issues include compromised autonomy, loss of personal identity, poor symptom management, and shared decision-making. This chapter discusses the current scenario about major legal and ethical challenges in Indian ICUs and shares authors' experiences about incorporation of several EOLC practices which stem from integrating the wisdom of Indian traditions with mainstream EOLC for enhancing quality of care.

LEGAL CHALLENGES

Euthanasia

Euthanasia, defined as the administration of a lethal drug by a physician as an act of mercy at the patient's request (to cause latter's death), has no legal acceptance in India. The Law Commission of India in their 196th report clearly separated euthanasia from end-of-life decisions (EOLD).[1] Withdrawal or withholding of life-support measures/treatment in a compos mentis patient is fundamentally different from euthanasia, which indicates assisted dying or an act of assistance by a healthcare worker for bringing about death.[2] However, in situations when the patient is unable to express his own right, the Law Commission (2006) did not allow the family members any access to the right of withdrawal or withholding of life-support measures. In end-of-life situations, the patient is hardly capable to decide about EOLD, which makes EOLD nearly impractical in ICU.[3]

A report of the Law Commission (2012), after the Aruna Shanbaug judgment, endorsed "passive euthanasia" on humanitarian grounds and for protecting doctors who honestly act in the best interests of patients.[4] Passive euthanasia, also known as "negative euthanasia," involves withholding of medical treatment or withholding life-support system for continuance of life rather than active intervention to enhance the dying process. This report endorsed safeguards advocated in the Aruna Shanbaug case, but for proceeding it concurred with the previous report. This landmark ruling has provided some light on issue of lawfulness of "involuntary passive euthanasia."[5] In her case, the Court ruled that withholding or withdrawal of life support was not illegal and should be allowed in certain circumstances. It further recommended a court procedure for all EOLD on incapacitated patients. The protocol to be followed in case of obtaining a legal sanction for passive euthanasia was quite practically impossible to implement in emergency and critical situations.

Errors in diagnosis/treatment or prognostication may lead to premature decisions about end of life. Personal–emotional and socioeconomic reasons may drive the family to choose discontinuation of treatment even when it is objectively premature.

Advance Medical Directives or the Living Will[6]

In Common Cause vs. The Union of India, a landmark judgment declared advance medical directives (AMD) and foregoing of life support (FLS) to be constitutionally valid when applied to incompetent patients.[6] It is a landmark judgment in response to a petition to declare right to die with dignity as a fundamental right within the fold of right to live with dignity. In Clause 177, the Supreme Court of India mentioned that there is an obligation on the part of the caregivers (both family and physician) and the State to safeguard the right to die with dignity and to receive palliative care. It accepts that a competent person can reveal

his choice to refuse treatment when the decision is required to be made. Not following the same would constitute denial of the fundamental right to Autonomy and Privacy. The Court mentioned the following procedure for making AMD operational in India:

- It should be a written document which indicates the decision relating to the circumstances in which withdrawing or withholding of medical treatment can be resorted to.
- It should be signed by the executor in presence of two attesting witnesses and countersigned by the Judicial Magistrate First Class (JMFC).
- The JMFC shall preserve one copy (hardcopy and digital format), hand over one copy to the registry of the jurisdictional District Court, and apprise immediate family members about the existence of this document.
- One copy shall also be handed over to the designated officer of the local authority (local Government/ Municipality/Municipal Corporation/Panchayat) and one to the family physician if available.
- In the event of a terminal illness of the executor, the treating physician will ascertain the authenticity thereof from the JMFC before acting upon it.
- Once the option of refusal or withdrawal of medical treatment is finalized by the treating physician, a Medical Board constituted by hospital visits the patient in the presence of relative and forms an opinion on refusal/ withdrawal of further treatment.
- After approval from the Hospital Medical Board, the physician/hospital will inform the Jurisdictional Collector about the decision.
- The Collector shall then constitute a Regional Medical Board which shall visit the hospital. If it agrees with the decision of the Medical Board of the hospital, the Chief District Medical Officer (CDMO) shall inform the decision of the Board to the JMFC.
- The JMFC will then visit the patient and authorize the decision of the Board. The Executor can revoke the document before it is implemented at any stage.

This overall tedious procedure is practically difficult to implement. The complex pathway of going through two sets of medical boards and the legal procedures would delay the FLS procedure and the relief from avoidable suffering.

Author's comments: The Indian Society of Critical Care Medicine (ISCCM)—The Indian Association of Palliative Care (IAPC) recommend[2] that a team of doctors for such decisions include caregivers across disciplines. The process should involve seeking a second opinion or involving a medical board or ethics committee within the hospital in the decision-making only if there is a conflict between family and healthcare professionals. Involving the legal fraternity (jurisdictional collectors and judicial magistrate of first class or the High Court) should only be required in case the conflicts persist after a second opinion and the intervention of the medical board or ethics committee.

ETHICAL ISSUES AND SOCIAL CHALLENGES

The four core components of medical ethics are: (1) Autonomy—patient has the right to accept or reject the treatment; (2) Beneficence—a doctor should act in the best betterment of the patient; (3) Nonmaleficence—first, do not harm; and (4) Justice—it concerns the distribution of health resources equally. Two further components of medical ethics are: (1) Dignity—the patient and healthcare workers treating the patient have the right to dignity and (2) Truthfulness and honesty—the concept of informed consent and being honest.[7]

Studies have shown marked differences in global practices of EOLC. Phua et al. found that withdrawing and withholding ventilation are considered ethically similar in western countries but not so in Asian countries.[8] According to their study, whereas majority of clinicians would not initiate life-prolonging measures, only one fifth would be comfortable in withdrawing the same. Asian ICU physicians tended to be more aggressive in their treatment compared with their western counterparts. The reasons for the same are multifactorial: (1) Difficult/ uncomfortable conversations between the ICU physician and family members, (2) physicians' perceived legal risks, (3) distrust of families toward ICU teams, (4) lack of awareness about the patient's healthcare wishes due to lack of culture of making advanced directive wishes, and (5) familial piousness and reverence. Most physicians also are apprehensive that withdrawal of support would either lead to cancellation of their license or prosecution or the act be considered against the law. This notion is reinforced by absence of any legislation on this issue. Furthermore, in nongovernment settings the decisions regarding continuation/discontinuation of treatment are heavily influenced by financial factors. The classic example of it is the widespread use of LAMA (leaving against medical advice) for the discontinuation of therapy on the grounds that the patient requested it. LAMA is an easy way where ethical principles are distorted and on the request of the patient or his family, the physician transfers his responsibility on to patients. Facilitating LAMA is indeed based on financial realities of patients/relatives. It is necessary for the clinician to be a part of shared decision-making in this situation. It is an ethical imperative, but its legal provisions remain ambiguous. We must move to the pluralistic model, which is a shared-based decision mode.[6]

A structured outline of the 11 elements of EOLC which can address various ethical issues is provided in **Box 1**.

BOX 1: End-of-life care pathway—11 elements.[2]

1. Physician's objective and subjective assessment of the dying process/medical futility. Consensus among all caregivers
2. Honest, accurate, and early disclosure of the prognosis to the family
3. Discussion and communication of all modalities of end-of-life care (EOLC) with the family
4. Shared decision-making consensus through open and repeated discussions
5. Transparency and accountability through accurate documentation
6. Ensure consistency among caregivers
7. Implementing the process of withholding or withdrawing life support
8. Effective and compassionate palliative care of the patient and appropriate support to the family
9. After death care
10. Bereavement care support
11. Review of the care process

CARE OF A DYING PATIENT: REDEFINING NARRATIVE

In moments of grief, human beings turn to wider and deeper existential dimensions of life to seek succor. However, medical professionals are not adequately trained nor tuned to offer nonabandonment response appropriately. Nonabandonment is one of a physician's central ethical obligations; it reflects a longitudinal commitment both to care about patients and to jointly seek solutions to problems with patients throughout their illnesses.[9] In end-of-life situations, this response assumes greater significance because the focus shifts from recovery to comfort.[10] The VALUE pneumonic helps in shaping a strong and caring nonabandonment response.[11]

V: Value statements by family members
A: Acknowledge family members' emotions
L: Listen to family members
U: Understand who the patient is as a person and how decisions are made in the family
E: Elicit questions from family members

A critical care specialist is placed in a unique position to fulfill this obligation for the suffering humanity, which no one else can.

End-of-life care decisions are heavily influenced by the context, culture, and spiritual beliefs of people and clinicians. An Indian sick person is surrounded by a large family at his home till the point when he is ultimately hospitalized. "Union with the divine," "being at peace," and "preserving dignity" are the three core principles of spirituality that an Indian looks for at the end of life, no matter the process of death.[12] Indian spiritual perspective has always held a view that man is not a mere biophysical entity; he is a soul—a spark of the Divine immanent in every human being—who is sheathed by body, mind, and emotions and his care and well-being extends beyond physical frame. As clinicians, we are trained with an emphasis on the biophysical model of health and avoid any exploration of death as a process of Life. Almost all religions describe it to be a process and a journey of the soul to the world's beyond and emphasize creation of a respectful and peaceful environment at the time of death. Incorporation of practices, such as customized prayer session, expanded visitation by family members, offering music, and soft and empathetic communication, can lead to improved achievement of quality parameters. They can help in "redefining" the "death narrative." These measures provide an inner strength to maintain a sense of control, comfort, connectivity (to the Divine), and identity during this time of crisis.

Our firsthand experiences in EOLC based on cognizance of this core conviction are shared here. They are a "person-centric" approach founded on recognizing spiritual needs and in connecting with the bereaved family in sharing grief as any human being should do.

- *Dialogue beyond illness as a part of quality care*: Adaptation of the "ABCDs" of dignity-conserving care (attitudes, behaviors, compassion, and dialogue) founded on principles of Indian philosophy offers a promise to improve quality of death.[13] We conducted detailed interviews of 15 preterminal patients focusing on their life experiences, wishes for future and family, and expression of gratitude. The very discussion brought about a glow on their face and strength in their voice and their suffering seemed to have lessened. The memoirs of the discussion were a great contentment to their family after death. In end-of-life moments, to look beyond disease and its cure is more than ever necessary; by connecting one to a larger reality of life, it helps psychological adaptation to factuality of death.
- *Spiritual assessment*: Spiritual assessment as part of a medical encounter is a practical first step in incorporating consideration of a patient's spirituality into medical practice at all stages of care, particularly in EOLC. We carried out assessment of spirituality in 30 ICU patients using HOPE questionnaire. The HOPE questions provide a formal tool that may be used in this process. "HOPE" denotes a questionnaire for spiritual assessment as part of a medical encounter. H—sources of hope, strength, comfort, meaning, peace, love, and connection; O—the role of organized religion for the patient; P—personal spirituality and practices; E—effects on medical care and EOLD.[14] Our study revealed that critically ill patients have huge dependence on Higher powers along with longing for support from family and healthcare team. The patients value very much the act of praying and reported that they would find better fulfillment in the journey through illness if the treating team shared such acts.

Fig. 1: Code Krishna veneration tray.

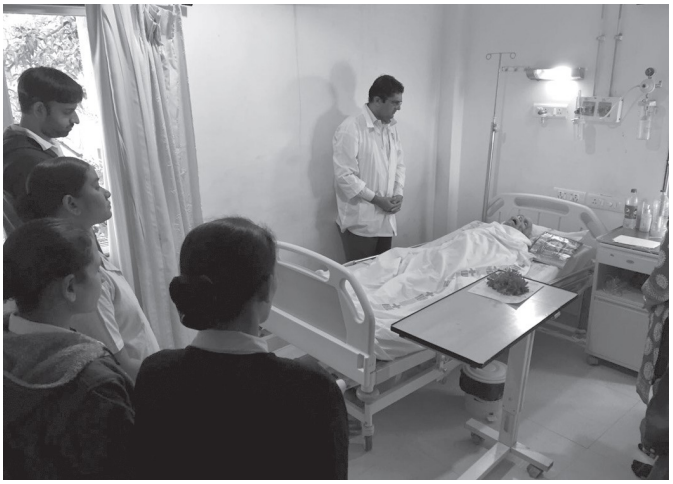


Fig. 2: Code Krishna in non-COVID ward.

Code Krishna: Blending Spiritual Wisdom with Modern Care[15]

We have institutionalized a practice named "Code Krishna" as an attempt to solemnize the event of death and respect cultural convictions of community at the Shree Krishna Hospital, Karamsad, for every death taking place in the hospital since 2016.

Process: It comprises of the treating team paying its respects and homage to the departed soul and empathizing with the bereaved family. The visible component of the practice includes members of the treating team assembling at the bedside of the deceased; team and bereaved relatives offering floral tributes to the deceased, and reciting a prayer according to the family's religious faith followed by a few minutes of meditative silence **(Figs. 1 to 3)**. The invisible component of the practice includes respectful body language for the deceased, sharing bereaved family's grief, and creating a solemn environment and a silent space amidst the action-packed environment even in a critical care unit. This forms the core of Code Krishna.

Uniqueness: By relying on the medical team exclusively (and not on any pastoral services) in this process, we ensured that the first commiserations for a bereaved family are those who have fought as competent professionals to save a patient's life, and at core being simply human, join head and heart together with the family when the destiny pronounces death. Apart from solace to the family, it also helped the treating team to overcome its own suppressed grief, reflect on meaning of life, and prevent desensitization to death events.

Evidence of success: We gathered responses of 57 stakeholders through a semistructured questionnaire. More than 90% healthcare professionals concurred with its relevance and its positive impact. Responses from the bereaved family were: "*It was beyond my wildest imagination that the treating team will pray for my mother at the time of death, care of the dying has to be like this alone*" was the comment expressed by one patient's relative. "The peace experienced during Code Krishna was so unique!"—reported one nurse. "It took away all my stress and frustration and made me feel like a simple human being!"—noted one critical care expert. The ward boy too would spontaneously join the veneration as an act of sanctifying death. Alumni of our institution reported that they have continued this practice in their work fields—carrying the flame forward. Considering that the prime purpose of hospital is to offer healing comfort, practice such as Code Krishna can go a long way in improving the quality of death through a simple yet profound act of sharing feelings surrounding a painful event of death. We believe and have experienced too that soliciting and fulfilling culture-specific wishes help to create healing moments in the story of each dying person, besides easing emotional trauma and achieving closure.

Fig. 3: Code Krishna in COVID intensive care unit.

CONCLUSION

Although peaceful and dignified death is a patient's right and an intensivist's obligation, legal, ethical, administrative, educational, and attitudinal impediments hamper its fulfillment. Recognition and respect of Indian cultural

ethos and standard operating guidelines can offer several initiatives for betterment of EOLC. The practice of human-centric communication, with respect to spiritual needs, and care of death, dying, and beyond through a protocol-based approach ("Code Krishna") have the ability to redefine the death narratives and impart a stamp of quality care.

Healing comes not from the head but from the heart.[16]

REFERENCES

1. 196th Report on Medical Treatment of Terminally Ill Patients (Protection of Patients and Medical Practitioners). (2006). Available from: https://lawcommissionofindia.nic.in/reports/rep196.pdf [Last accessed March, 2022].
2. Myatra SN, Salins N, Iyer S, Macaden SC, Divatia JV, Muckaden M, et al. End-of-life care policy: An integrated care plan for the dying: A Joint Position Statement of the Indian Society of Critical Care Medicine (ISCCM) and the Indian Association of Palliative Care (IAPC). Indian J Crit Care Med. 2014;18(9):615-35.
3. Carlet J, Thijs LG, Antonelli M, Cassell J, Cox P, Hill N, et al. Challenges in end-of-life care in the ICU. Statement of the 5th International Consensus Conference in Critical Care: Brussels, Belgium, April 2003. Intensive Care Med. 2004;30:770-8.
4. Passive Euthanasia-A Relook. 241st Report of Law Commission of India. (2012). [online] Available from: http://www.lawcommissionofindia.nic.in/reports/ rep241.pdf [Last accessed March, 2022].
5. Aruna Ramakrishna Shanbaugh vs. The Union Of India and Ors. 2011 4 SCC 454 & 524. Also:AIR 2011 SC 1290.
6. Reportable in the Supreme Court of India Civil Original Jurisdiction. Common Cause s Versus The Union of India and Another. Writ Petition (Civil) No. 215 of 2005. [online] Available from: https://main.sci.gov.in/supremecourt/2005/9123/9123_2005_Judgement_09-Mar-2018.pdf [Last accessed March, 2022].
7. Sharma H, Jagdish V, Anusha P, Bharti S. End-of-life care: Indian perspective. Indian J Psychiatry. 2013;55(Suppl 2):S293-8.
8. Phua J, Joynt GM, Nishimura M, Deng Y, Myatra SN, Chan YH, et al.; ACME Study Investigators and the Asian Critical Care Clinical Trials Group. Withholding and withdrawal of life-sustaining treatments in intensive care units in Asia. JAMA Intern Med. 2015;175(3):363-71.
9. Quill TE, Cassel CK. Nonabandonment: a central obligation for physicians. Ann Intern Med. 1995;122(5):368-74.
10. Macaden SC, Salins N, Muckaden M, Kulkarni P, Joad A, Nirabhawane V, et al. End of life care policy for the dying: consensus position statement of Indian association of palliative care. Indian J Palliat Care. 2014;20(3):171-81.
11. Cook D, Rocker G. Dying with dignity in the intensive care unit. N Engl J Med. 2014;370(26):2506-14.
12. Inbadas H, Seymour J, Narayanasamy A. Principles of spiritual care in end-of-life care in India: A historical-cultural investigation. BMJ Support Palliat Care. 2014;4 (Suppl 1):A18.
13. Chochinov HM. Dignity and the essence of medicine: the A, B, C, and D of dignity conserving care. BMJ. 2007;335(7612):184-7.
14. Anandarajah G, Hight E. Spirituality and medical practice: using the HOPE questions as a practical tool for spiritual assessment. Am Fam Physician. 2001;63(1):81-9.
15. Vaishnav B, Nimbalkar S, Desai S, Vaishnav S. Code Krishna: an innovative practice respecting death, dying and beyond. Indian J Med Ethics. 2017;2(4):289-92.
16. Sri Aurobindo Ashram. (2004). The Mother, Collected Works of The Mother, 16, 19. Pondicherry: Sri Aurobindo Ashram Publication Department. [online] Available from: https://www.sabda.in/catalog/show.php?id=cwm [Last accessed March, 2022].

CHAPTER

114

Pregnancy-associated Severe Sepsis: Present State and Challenges

Anjan Trikha, Prachee Makashir, Sunil T Pandya

INTRODUCTION

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) Committee defines sepsis as "a life-threatening organ dysfunction caused by a dysregulated host response to infection".[1] Maternal sepsis can occur during pregnancy, childbirth, postabortion, or postpartum period. Maternal physiological changes result in masking of usual signs and symptoms of sepsis. This makes the management of obstetric patients with sepsis and septic shock is very challenging. Failure to recognize maternal sepsis leads to delay in treatment and therefore high maternal, fetal morbidity and mortality.

The majority of parturients are young and healthy, however, the maternal mortality rates continue to be high and sepsis is one of the most important preventable causes for this. Incidence of sepsis in pregnancy varies between the developed and the developing world. In two recent studies from India (both North and South India) this incidence varied between 94/1000 and 165/1000[2] live births. Both the studies are from tertiary care centers implying that the incidence may be much more in rural areas. Complications caused by sepsis in pregnancy are—premature birth, fetal infections, increased fetal mortality, and maternal mortality.

RISK FACTORS AND CAUSES FOR SEPSIS

The pathogenesis due to infection includes *pneumonia* and *genital tract infections*.[3] Group A *Streptococci* and *Escherichia coli* are the predominant pathogens.[4] *E. coli* (37% of maternal sepsis cases) can lead to *chorioamnionitis* following prelabor, preterm rupture of membranes, and fetal death.[4]

Viral infections are becoming increasingly prevalent, especially with the newer strains (H1N1, SARS-Co-V-2, etc., with *influenza* being common in the later trimesters of pregnancy which causes more severe illness and fetal growth restriction, and preterm birth).[5,6]

The risk factors for maternal sepsis may be broadly categorized as obstetric-related and patient-related **(Box 1)**.

BOX 1: Obstetric risk factors for sepsis.

- Operative interventions
- Cervical cerclage
- Prolonged rupture of the membranes
- Pelvic infection
- *Group A* or *B streptococcal* infection in close contacts or family members
- Vaginal discharge
- Multiple pregnancies
- Retained products of conception
- Preterm prelabor rupture of membranes (PPROM)
- Amniocentesis or other invasive procedures

Patient-related Risk Factors for Sepsis

Patient-related risk factors for sepsis are as follows:

- Primiparity
- Congestive cardiac failure
- Chronic renal or liver failure
- Infection by the human immunodeficiency virus
- Systemic lupus erythematosus
- Diabetes mellitus
- Obesity
- Poor nutrition
- Febrile illness or antibiotic use in the 2 weeks prior to presentation.

CURRENT STATUS

Maternal sepsis is an important direct and indirect cause of maternal mortality that accounted for 10.7% (uncertainty interval 5.9–18.6) of global maternal deaths.[7] The magnitude is highest in Southern Asia where sepsis is responsible for 13.7% of all maternal deaths.[7] Sepsis is attributed as a cause for 9.7%, 11.6%, and 7.7% of maternal deaths in Africa, Asia, and Latin America/Caribbean respectively and is increasing steadily in more developed countries.[8-11] The US reported an annual increase of 10% in maternal mortality between 1998 and 2008 and the UK Obstetric Surveillance System reported an incidence of severe sepsis of 4.7 out of 10,000 maternities in 2014.[8-11]

The risk of infectious morbidity is 5–20% higher in a cesarean section (CS) compared to a vaginal delivery with the highest risk for a CS after the onset of labor, lower for an elective CS, and least for an operative or instrumental vaginal delivery.[11]

CHALLENGES

The management strategies of sepsis in nonpregnant patients are standardized. However, managing sepsis in pregnancy is very challenging as mostly all studies in sepsis exclude pregnant women resulting in a lack of a standardized management approach.

Challenges faced by clinicians are as follows:

- The hemodynamic and biochemical changes in pregnancy, increased physiological reserve, immune adaptive state, and late presentation during the course of disease. Importantly, it affects two or multiple lives.
- The clinical signs and symptoms of several pregnancy-associated conditions mimics sepsis and septic shock, e.g., hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, acute fatty liver of pregnancy (AFLP), eclampsia, cardiomyopathy, embolic disorders, etc. Further, these disorders can be complicated by *concomitant sepsis* during the course of the disease.
- Only a few sepsis scoring systems are available for these patients, as Surviving Sepsis Campaign (SSC) guidelines and protocolized sepsis bundles for management of sepsis are there for the general population.
- The blood gases and many laboratory values are altered in pregnancy.
- The *gravid uterus* may impede ultrasound-guided fluid status assessment and response.

DIAGNOSIS OF MATERNAL SEPSIS

The diagnosis of maternal sepsis is not straightforward. Hyperdynamic circulatory state in pregnancy and vasodilatation due to progesterone can lead to a fall in blood pressure and consequent compensatory *sinus tachycardia* that can mask the cardiovascular symptoms associated with sepsis and are detectable only when shock becomes severe or uncompensated.[12] Maternal quick SOFA (qSOFA) is suggested for assessment of early signs of organ dysfunction as depicted in **Table 1**.[13]

TABLE 1: Obstetrically modified qSOFA score.

	Score	
Parameter	***0***	***1***
Systolic blood pressure (mm Hg)	≥90	<90
Respiratory rate	<25 breaths/minute	≥25 breaths/minute
Altered mentation	Alert	No alert

THE MODIFIED EARLY OBSTETRIC WARNING SYSTEM

The modified early obstetric warning system (MEOWS) is used for early recognition of signs of sepsis and to intervene early as it has 89% sensitivity and 79% specificity to identify maternal morbidity. The MEOWS uses a color code system to warn of the need for further consultation with the trigger initiated if there is one red or two yellow triggers. The MEOWS considers heart rate per minute, temperature, blood pressure, respiratory rate, oxygen saturation, pain score, and neurological responses. The Maternal Early Warning Score and Maternal Early Warning Trigger Tool are other scoring systems used to identify maternal sepsis. The use of these tools reduced mortality by 18% but are limited by a very low positive predictive value.[14]

MANAGEMENT OF SEPSIS IN PREGNANCY

Most of the management of sepsis in pregnancy is extrapolated from the SSC guidelines for nonobstetric patients.[15] After the initial respiratory stabilization, the first hour bundle is followed-blood drawn for cultures and investigations (including lactate), administration of 30 mL/kg of crystalloids as bolus if there is hypotension, broad-spectrum antibiotics, and vasopressor agents to maintain a mean arterial blood pressure of at least 65 mm of mercury. Subsequent intravenous fluids are administered depending on the hemodynamic parameters. It is essential to avoid supine hypotensive syndrome, and the medications used must be safe for the fetus. Different monitoring modalities used for assessing the fluid responsiveness are urine output, central venous pressure monitoring, bedside transthoracic cardiac echocardiogram; the best is to use one with which the clinical team is comfortable. Reliability of the passive leg raising test is not clearly proven in different trimesters of pregnancy and merits further study.[16] Studies have suggested targeted and restrictive fluid strategies to minimise the risk of pulmonary edema, by maintaining a negative fluid balance in obstetric patients and thereby curtailing high morbidity and mortality.[17]

Ventilation Strategies for Pregnant Women

The ventilation strategies for pregnant women are adapted from those for the general, nonpregnant population as well. The maternal arterial ($PaO_{2)}$ must be maintained at more than 70 mm Hg and partial pressure of carbon dioxide ($PaCO_2$) at less than 60–70 mm Hg to ensure fetal oxygenation and placental perfusion. Prone ventilation in pregnancy can significantly improve oxygenation of pregnant women with severe acute respiratory distress syndrome (ARDS)[18] but may be difficult in patients with *gravid uterus*. Extracorporeal membrane oxygenation (ECMO) is increasingly used in pregnancy, and the rates of maternal and fetal survival were 80% and 70% respectively without a significant increase in

hemorrhage.[19] Other modalities that have been sporadically used in such parturients when conventional methods of ventilation fail are—airway pressure release ventilation, high-frequency oscillatory ventilation, and extracorporeal membrane oxygenation.[20]

Hemodynamic Monitoring

This involves fetal and maternal monitoring. Fetal well-being has to be monitored regularly with fetal heart monitors if available. The markers for global perfusion are serial measurements of lactate and the mixed venous oxygen saturation (SvO_2) even in pregnant patients. As the normal SvO_2 in the 3rd trimester is around 80% and this value being significantly higher than the normal population, even near normal values for SvO_2 may actually be inadequate for obstetric septic patients. The value of 65% as directed by SSC guidelines is followed due to the paucity of any data for acceptable target values. *Vasoactive drugs* such as *noradrenaline* and *vasopressin* are the agents of choice in septic shock.[21] Use of dopamine, dobutamine, and milrinone is suggested in low cardiac output states. Epinephrine, however due to its β2 agonistic activity, causes uterine relaxation that can delay the progress of labor. Levosimendan by virtue of its capability of improving systolic function has been successfully used in peripartum cardiomyopathy.[22] Vasodilators such as *hydralazine* and *nitroglycerin*, and diuretics like frusemide are fairly safe in pregnancy. *Milrinone* increases the cardiac output without tachycardia and dilates the pulmonary vessels. Hence, it is used in pregnant patients with low cardiac output states such as mitral stenosis and pulmonary hypertension.[23] For recommending these medications for regular usage in obstetric critical care, more reports are awaited **(Box 2)**.

BOX 2: Sepsis management in pregnant and postpartum women.[24]

- Have a low threshold of diagnosing sepsis in pregnant women and those who have recently delivered
- Both the unborn child and the mother are important but maternal stabilization should be the priority
- Standard guidelines regarding fluid resuscitation as per Surviving Sepsis Campaign should be followed
- Early use of vasopressors is suggested for managing hypotension as there is a high risk of developing pulmonary edema
- Early sampling for cultures, investigations, and administration of antibiotics that are safe for the fetus are mandatory
- Regular and intense monitoring of the mothers hemodynamic parameters and the fetal heart is required
- Possibility of surgical intervention to treat source control should always be considered
- Shifting septic parturients to higher centers or intensive care units for advanced management including ventilatory support should always be considered before the patient deteriorates

For low resource settings, a simple yet clinically relevant scoring system should be in place. A maternal sepsis bundle (FAST-M) has been recently developed by international consensus and includes fluids, antibiotics, source identification, and control, transfer (to appropriate higher-level care), and monitoring (of both mother and neonate as appropriate).[24,25]

CONCLUSION

Maternal sepsis continues to be challenging for obstetricians, physicians, and intensivists. Early detection and prompt management are key factors for better maternal and fetal outcomes. Monitoring parameters and drug treatment may vary from nonobstetric patients. Current therapies are based on SSC guidelines. Specific and evidence-based protocols are required in the optimum management of maternal sepsis.

SUGGESTIONS AND FURTHER STUDIES

There is a need for standardization of screening criteria, identifying early warning signs of sepsis in pregnancy, and structuring of a pregnancy sepsis bundle with clear criteria for shifting such mothers to higher centers keeping into consideration both rural and urban areas. Separate guidelines would be required for low-resource areas.

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-10.
2. Kumari A, Suri J, Mittal P. Descriptive audit of maternal sepsis in a tertiary care centre of North India. Int J Reprod Contracept Obstet Gynecol. 2018;7(1):124-7.
3. Acosta CD, Harrison DA, Rowan K, Lucas DN, Kurinczuk JJ, Knight M. Maternal morbidity and mortality from severe sepsis: a national cohort study. BMJ Open. 2016;6(8):e012323.
4. Surgers L, Bleibtreu A, Burdet C, Clermont O, Laouénan C, Lefort A, et al. Escherichia coli bacteraemia in pregnant women is life-threatening for foetuses. Clin Microbiol Infect. 2014;20(12):O1035-41.
5. Naresh A, Fisher BM, Hoppe KK, Catov J, Xu J, Hart J, et al. A multicenter cohort study of pregnancy outcomes among women with laboratory-confirmed H1N1 influenza. J Perinatol. 2013;33(12):939-43.
6. Mak TK, Mangtani P, Leese J, Watson JM, Pfeifer D. Influenza vaccination in pregnancy: current evidence and selected national policies. Lancet Infect Dis. 2008;8(1):44-52.
7. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A-B, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323-33.
8. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006;367(9516):1066-74.
9. Waterstone M, Bewley S, Wolfe C. Incidence and predictors of severe obstetric morbidity: case-control study. BMJ. 2001;322(7294):1089-93; discussion 1093-4.

10. Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife D, Garrod D, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG. 2011;118 Suppl 1:1-203.
11. Acosta CD, Knight M, Lee HC, Kurinczuk JJ, Gould JB, Lyndon A. The continuum of maternal sepsis severity: incidence and risk factors in a population-based cohort study. PLoS One. 2013;8(7):e67175.
12. Guinn DA, Abel DE, Tomlinson MW. Early goal directed therapy for sepsis during pregnancy. Obstet Gynecol Clin North Am. 2007;34(3):459-79.
13. Greer O, Shah NM, Sriskandan S, Shiranee, Johnson MR. Sepsis: Precision-based Medicine for Pregnancy and the Puerperium. Int J Mol Sci. 2019;20(21):5388.
14. Singh S, McGlennan A, England A, Simons R. A validation study of the CEMACH recommended modified early obstetric warning system (MEOWS). Anaesthesia. 2012;67(1):12-8.
15. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Crit Care Med. 2021;49(11):e1063-143.
16. Vårtun Å, Flo K, Wilsgaard T, Acharya G. Maternal functional hemodynamics in the second half of pregnancy: a longitudinal study. PLoS ONE. 2015;10(8): e0135300.
17. Afessa B, Green B, Delke I, Koch K. Systemic inflammatory response syndrome, organ failure, and outcome in critically ill obstetric patients treated in an ICU. Chest. 2001;120(4): 1271–7.
18. Samanta S, Samanta S, Wig J, Baronia AK. How safe is the prone position in acute respiratory distress syndrome at late pregnancy? Am J Emerg Med. 2014;32(6):687.e1–3.
19. Sharma NS, Wille KM, Bellot SC, Diaz-Guzman E. Modern use of extracorporeal life support in pregnancy and postpartum. ASAIO J. 2015;61(1):110-4.
20. Trikha A, Singh P. The critically ill obstetric patient—recent concepts. Indian J Anaesth. 2010;54(5):421-7.
21. Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. Lancet. 2018;392(10141):75-87.
22. Benlolo S, Lefoll C, Katchatouryan V, Payen D, Mebazaa A. Successful use of levosimendan in a patient with peripartum cardiomyopathy. Anesth Analg. 2004;98(3):822-4.
23. Bassily-Marcus AM, Yuan C, Oropello J, Manasia A, Kohli-Seth R, Benjamin E. Pulmonary hypertension in pregnancy: critical care management. Pulm Med. 2012;2012:709407.
24. Lissauer D, Cheshire J, Dunlop C, Taki F, Wilson A, Smith JM, et al. Development of the FAST-M maternal sepsis bundle for use in low-resource settings: a modified Delphi process. BJOG. 2020;127(3):416-23.
25. Albright C, McCartney S, Hitti J. (2018). Identification and Management of Sepsis in Pregnancy: Obstetric Consensus Statement. [online] Available from https://providerresource.uwmedicine.org/women-s-health) [Last accessed March, 2022].

SECTION

20

Extracorporeal Membrane Oxygenation and Extracorporeal Cardiopulmonary Support

CHAPTER 115

Multimodality Extracorporeal Life Support

Poonam Malhotra Kapoor

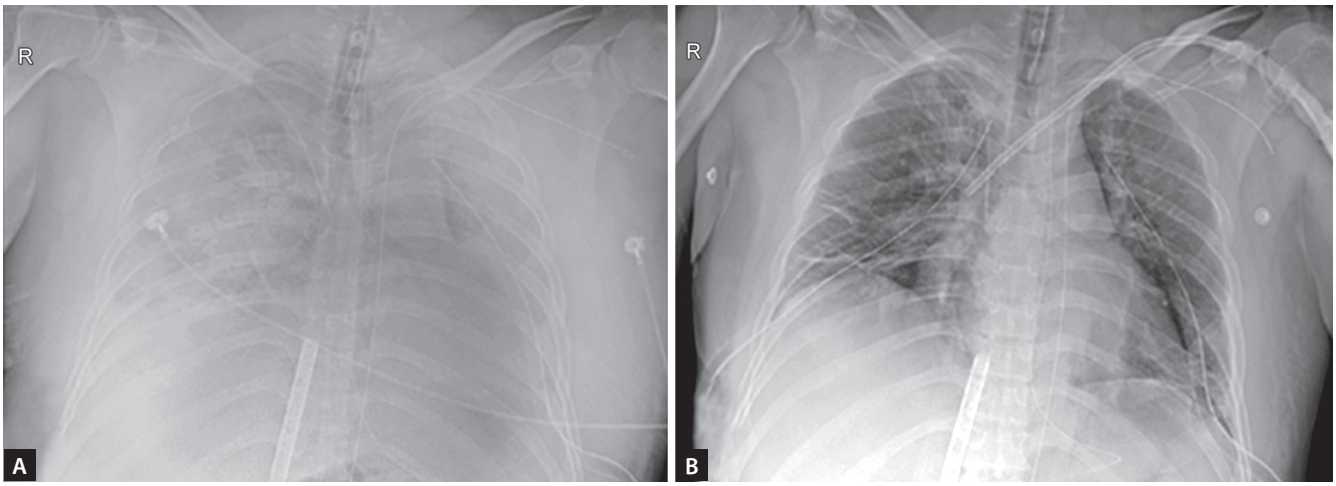
DEFINITION

"It is broadly utilization of extracorporeal life support (ECLS) judiciously through selection and configuration of its different modes, under different life medical conditions, to have more positive patient outcomes."

INTRODUCTION

Extracorporeal membrane oxygenation of all types, whether venovenous ECMO (VV-ECMO) and venoarterial ECMO (VA-ECMO) or ECMO for cardiopulmonary resuscitation (ECPR) or extracorporeal life support (ECLS), intends to support life in severe cardiorespiratory failure. When ECLS is used as multimodality, it is the combination of two or more modes in various combinations. Use of two or more of these modes of ECLS by modifying the circuit or separately during the same run needs a better understanding of the physiology as they are meant to be complementary to each other.[1] The term multimodal ECLS also implies using ECLS judiciously in two or more situations, e.g., ECLS for COVID-19 in a diabetic patient who goes into acute kidney injury and shock in the intensive care unit (ICU) **(Figs. 1A and B)**, or as described by Rybalko et al., who used extracorporeal therapies successfully after ECMO resuscitation in a pediatrics kidney transplant recipient.[2] In the latter patient who was 30 months of age a large number of extracorporeal blood purification methods (plasma exchange by a *CytoSorb* and *lipopolysaccharide adsorption*) were used when ECMO was already on for the management of cardiac arrest following a *renal transplant*. The patient outcomes were good. So multimodality extracorporeal therapy helped as a positive outcome. In recent times multimodal therapies are being increasingly used with variable success. This chapter briefly outlines the same.

We do know that ECMO aided resuscitation, improves survival after a refractory cardiac arrest, secondary to arrhythmias, in children and adults, then does a conventional cardiopulmonary resuscitation (CPR) alone.[3] However, multiorgan failure due to ischemia-reperfusion injury or electrolyte disturbance or due to multiple transfusions is inevitable during ECMO runs. These complications of ECMO with multiorgan failure can be obtunded by the



Figs. 1A and B: (A) Severe pulmonary edema and bilateral pleural effusions are observed on the chest radiograph; (B) Pulmonary edema was improved after venoarterial venous extracorporeal membrane oxygenation.

BOX 1: Multimodal extracorporeal therapies.

- ECMO and IABP
- ECMO
- ECMO and percutaneous VAD
- ECMO with CytoSorb
- ECMO with CRRT
- ECMO with plasmaphereses

(CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; VAD: ventricular assist device)

BOX 2: VA-ECMO scenarios needing multimodal support.

- ECMO in acute heart failure
- ECMO for cardio diabetes
- ECMO for CAD in low cardiac output
- ECMO for cardiogenic shock
- ECMO for myocarditis
- ECMO for cardiac critical care

(CAD: coronary artery disease; ECMO: extracorporeal membrane oxygenation; VA-ECMO: venoarterial extracorporeal membrane oxygenation)

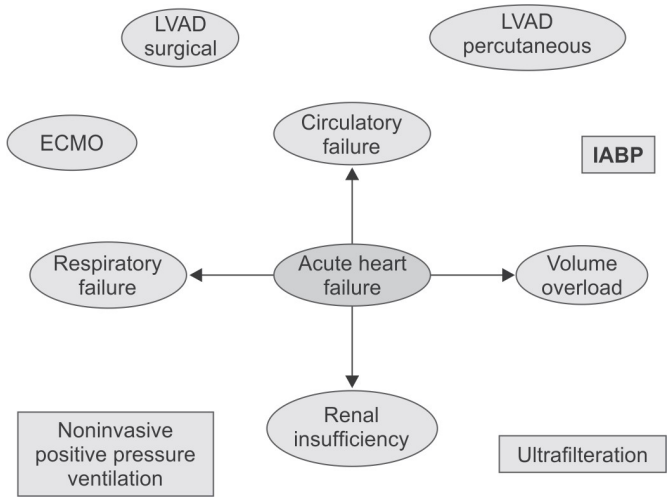


Fig. 2: Multimodality ECLS (VA-ECMO) in many different cardiac critical conditions.
Source: Adapted with permission from Kapoor PM. Resistant Hypertension with Heart Failure and ECMO. In: Chopra HK, Nanda NC, Narula J, Wander GS, Manjunath CN, Chandra PN (Eds). Hypertension New Frontiers: A Textbook of Cardiology, 1st edition. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2021. pp. 913-28.

use of extracorporeal modalities such as plasma exchange, continuous renal replacement therapy (CRRT) to overcome thrombocytopenia associated multiorgan failure and decrease the rising alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and creatinine kinase (CK) levels. Adsorption with lipopolysaccharides or CytoSorb to remove the inflammatory cytokines or a CRRT to improve the renal function is all multimodal extracorporeal therapies in clinical practice today **(Box 1)**.[4-7]

HEART FAILURE AND MULTIMODAL EXTRACORPOREAL MEMBRANE OXYGENATION

Whether it is for heart failure, or for cardiodiabetes or for a coronary artery disease (CAD) patient in low cardiac output in the ICU or for cardiogenic shock in **Box 2** or myocarditis, the VA-ECMO use in the cardiac critical care patient is on the rise. The difference between peripheral and central VA-ECMO and adding an alternative cannula for enhancing cardiac output remains a multimodal challenge to the intensivist **(Fig. 2)**.[8,9]

EXTRACORPOREAL MEMBRANE OXYGENATION AND INTRA-AORTIC BALLOON PUMP

Extracorporeal membrane oxygenation and intra-aortic balloon pump (IABP) was the first mechanical step to be considered in earlier times. The IABP counterpulsation unloads the left ventricle (LV) by afterload reduction.[10]

BOX 3: Percutaneous approaches to left ventricle venting locations.

- Left atrium
- Aorta/IABP
- Transaortic
- Transeptal

The IABP alone may not be sufficient to completely unload the LV—this has paved the way, for use of left atrium (LA) venting surgically or adopting the use of percutaneous short-term mechanical devices.

EXTRACORPOREAL MEMBRANE OXYGENATION AND PERCUTANEOUS VENTRICULAR ASSIST DEVICE

Percutaneous ventricular assist devices (VADs) are on the rise, due to their noninvasive approach to implantation.[11] Percutaneous approaches of LV venting include, as enlisted in **Box 3**, placing a venting cannula in the pulmonary artery or into the LA through a transseptal or transaortic approach. The Impella and TandemHeart devices are devices used today, to unload the LV.[11]

TANDEMHEART PERCUTANEOUS VENTRICULAR ASSIST DEVICE

Use for LV support: This is not appropriate in RV failure. The ECMO cannulas are inserted percutaneously through the femoral vein and advanced across the intra-arterial septum into the LA. The pump withdraws oxygenated blood from the LA and returns it to the femoral arteries via arterial cannulas. Provides up to 5 L/min of flow can be used for up to 14 days **(Fig. 3)**.

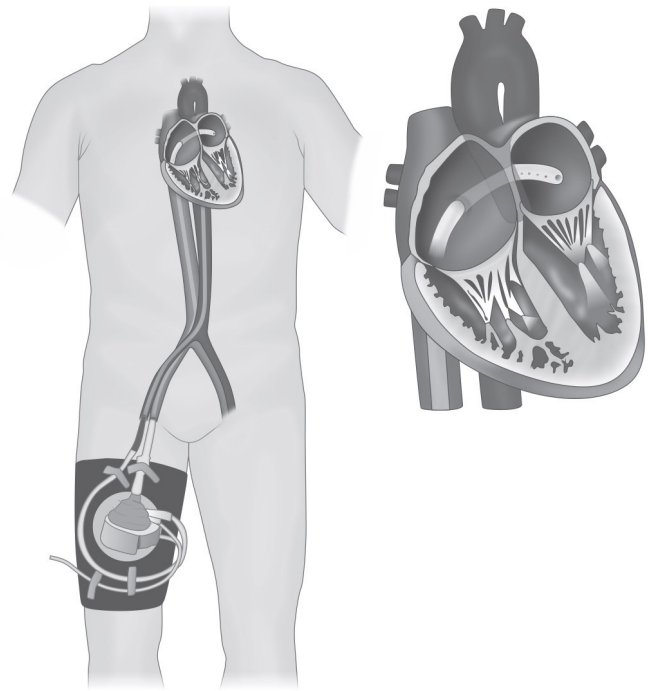


Fig. 3: TandemHeart.

TABLE 1: Different configurations of Impella percutaneous ventricular assist device.

Configuration	*Maximum flow rate*
• Impella 2.5	• 2.5 L/min
• Impella CP	• 3.0–4.0 L/min
• Impella 5.0	• 5.0 L/min
• Impella 5.5	• 6.0 L/min

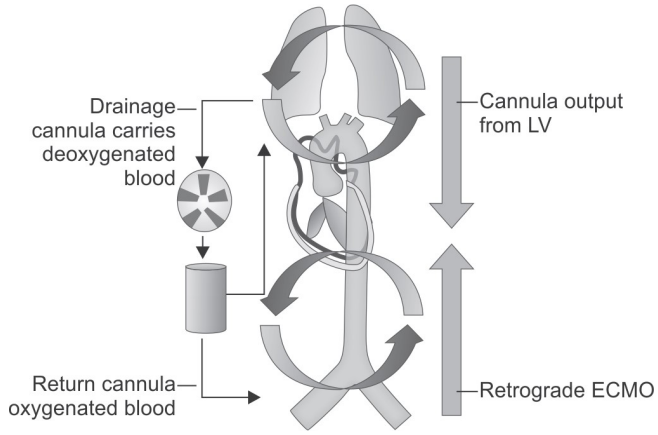


Fig. 4: The diagram indicates circulation in the case of venoarterial venous extracorporeal membrane oxygenation.

EXTRACORPOREAL MEMBRANE OXYGENATION AND IMPELLA

In a condition of increased afterload and high end-diastolic volume, the role of a percutaneous device such as Impella (Abiomed, Danvers, MA) plays a physiological role of increasing cardiac output, increasing oxygen supply, and decreasing oxygen demand and Impella's/outflow is placed in the aortic root and it provides an active flow, depending on its setting and the aorta-LV pressure gradient. Impella, increases the forward flow, in the wake of an increased LV afterload, its pump support setting (the P level), and the aorta-LV pressure gradient. Not, just the flow, Impella, also increases the oxygen supply as the flow is dependent on the microvascular resistance and the aortic pressure. As it unloads the LV and decreases the end-diastolic pressure by *Laplace's law*, it also reduces the microvascular resistance and wall tension, thus making oxygen supply and demand optimally.[12]

ECPELLA

The Impella (Abiomed, Denvers, MA) is the most favored percutaneous device today. The Impella is catheter mounted, micro axial flow pump, capable of drawing 2.5–6.0 L/min of blood from the LV into the aorta, across the aorta valve. Current use of combined VA-ECMO and Impella, is called *ECPELLA* and as discussed above is the best measured to unload the LV.

As shown by Pappalardo et al.,[13] the ECPELLA mode of ECMO in surgery with the percutaneous Impella, shows improved outcomes, but following weaning from ECMO, the patients had higher ejection fractions as well, on their 34 ECPELLA patients.[13]

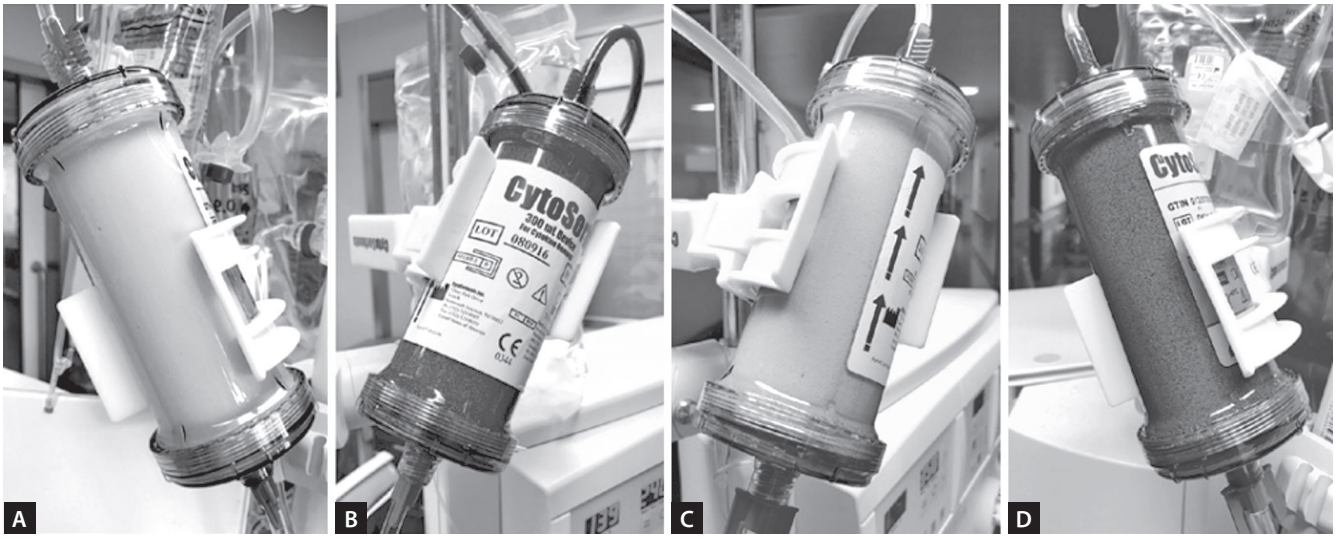
ECPELLA showed a decrease in mortality and no difference in hemolysis, bleeding, renal failure, or stroke from VA-ECMO alone patients.[14] Truby et al., prompted that LV venting is done early that led to higher myocardial recovery[15] Impella and ECPELLA are contraindications in LV thrombus mechanical aortic valve and, severe aortic regurgitation patients. ECPELLA may be replaced here with an IABP with VA-ECMO peripheral and systemic arterial disease in all these patients should be ruled out first, before starting an ECPELLA. ECPELLA allows early weaning and this is reassuring in VA-ECMO patients. More scientific evidence will make its use easier.

Different configurations of Impella are known as outlines in **Table 1**.

The Impella 2.5/CP is FDA approved to provide support up to five days and Impella 5 is approved for up to 10 days.[10]

EXTRACORPOREAL MEMBRANE OXYGENATION AND CentriMag

Ventricular assist device can be used for LV and/or RAV support wherein the cannula is typically inserted via a midline sternotomy. It is capable of delivering flows up to 9.9 mL/min can be used for up to 30 days **(Fig. 4)**.



Figs. 5A to D: CytoSorb® before, during, and after use. (A) After priming with saline before connecting to the patient; (B) During adsorption; (C) After use in a patient with hyperinflammation; (D) After use in a patient with hyperinflammation, rhabdomyolysis, and hemolysis.

EXTRACORPOREAL MEMBRANE OXYGENATION IN DIFFERENT CLINICAL CONDITIONS: MULTIMODAL EXTRACORPOREAL LIFE SUPPORT, ECMO, AND CYTOKINE ADSORPTION THERAPY

Cytokine adsorption therapy in combination with ECMO is now, being used with a good success rate in patients with acute respiratory distress syndrome (ARDS) and in sepsis. CytoSorb with ECMO is a promising treatment today in ICUs to prevent complications of sepsis with a fast reduction in biomarkers such as procalcitonin (PCT) and C-reactive protein (CRP) levels. The VV-ECMO remains high flow mode only, with effective mortality outcomes **(Figs. 5A to D)**.[16]

Inside the CytoSorb, adsorber the blood volume is around 150 mL. The manufacturer approves a blood flow through the CytoSorb of 150 mL/min,[17] whereas the approval by the manufacturer is of blood flow ranging from 100 to 700 mL/min.

The adsorption range of CytoSorb includes pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), inflammatory mediators, myoglobin, and bilirubin—thus making ECMO with cytokine adsorption therapies a very efficient therapy to combat inflammatory markers in ECMO sepsis. The use of the two together is on the rise. This and the ease of use in ECMO circuits, has already resulted in high-frequency use in many centers **(Fig. 6)**.

EARLY AND TIMELY ECMO ALONE IS BENEFICIAL

Extracorporeal membrane oxygenation should only be inserted in a patient with a reversible pathology. 30 days outcomes with early ECMO-assisted PCI were positive in ST-elevation myocardial infarction (STEMI) patients in most studies.[18]

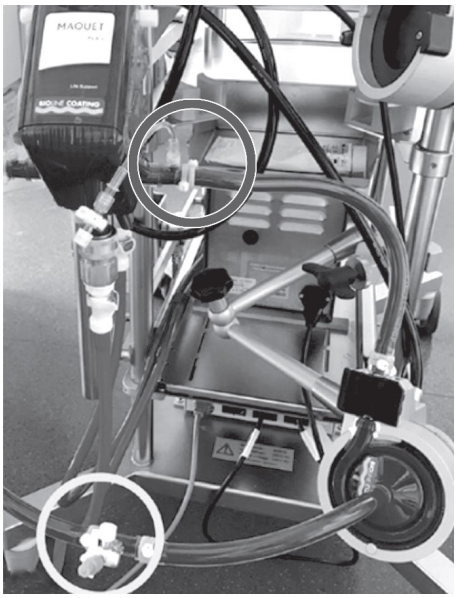


Fig. 6: Connection of cytokine adsorption therapy into standard ECMO circuits. A Rotaflow® ECMO circuit with 3-way stopcocks for connection of additional devices before (white circle) and after (gray circle) the rotor flow pump.
(ECMO: extracorporeal membrane oxygenation)

EXTRACORPOREAL CARDIOPULMONARY RESUSCITATION

Extracorporeal membrane oxygenation can also be initiated percutaneously with ongoing CPR, i.e., extracorporeal CPR (E-CPR). It aims to restore circulation during cardiac arrest in conjunction with ongoing advanced life support strategies. E-CPR has resulted in improved in-hospital survival free from major neurologic impairment.[19,20] Surgical assistance is not always necessary. Financial implications are difficult to determine due to the complexity of the intervention.

PUMPLESS ECMO: EXTRACORPOREAL CARBON DIOXIDE REMOVAL WITH DIALYSIS

In a pumpless ECMO circuit, the entire process is dependent on the patient's cardiac output. In arteriovenous extracorporeal membrane oxygenation (AV-ECMO), the blood flows from the femoral artery through the semipermeable membrane and gets passively returned to the femoral vein. Thus, the cardiac output of the patient drives the pumpless ECMO circuit **(Figs. 7A and B)**.

$ECCO_2R$ GAS EXCHANGE PHYSIOLOGY CO_2 REMOVAL IS EXTRACORPOREAL THERAPY IMPROVE CO_2 REMOVAL

The body produces about 25 mol/min of carbon dioxide. It is well known that 1 L of blood with a partial pressure of carbon dioxide ($PaCO_2$) of 5 kPa contains around 500 mL of carbon dioxide in some newer machines such as the PrismaLung and the Hemolung, the $ECCO_2R$ mode is combined with dialysis, to combat renal failure. This multimodal ECLS will soon be marketed globally

Why do we need to use $ECCO_2R$?

As the $PaCO_2$ rises in ECMO, the work of breathing increases and minute ventilation begins to fail. So, we need extracorporeal carbon dioxide removal ($ECCO_2R$) devices that are specialized ECMO devices that predominantly focus on CO_2 removal. The *primary advantage* of an $ECCO_2R$ device is the reduced blood flow through the circuit. The *primary use* of $ECCO_2R$ device is to use it as a bridge to recovery in cases of severe acidosis when mechanical ventilation fails and an acute need for an intervention, like protective lung ventilation is needed. This latter is especially useful in ARDS patients **(Box 4)**.[21]

MULTIMODAL USE OF ECMO WITH CONTINUOUS RENAL REPLACEMENT THERAPY

Continuous Renal Replacement Therapy Combined with ECMO for Acute Kidney Injury in ICU Patients

Catheter-related complications can easily be overcome by incorporating the ECMO and CRRT circuits together. There are significant complications seen at the time of catheter insertion reasons. Catheter maintains and due to infection and mechanical placing the drainage or return access CRRT cannulas before the blood pump, will deliver a low-pressure alarm, and placing after the blood pump, will give a high-pressure alarm.[22,23] So adjustment of cannulas positions to prevent the alarms is needed from the time to time.

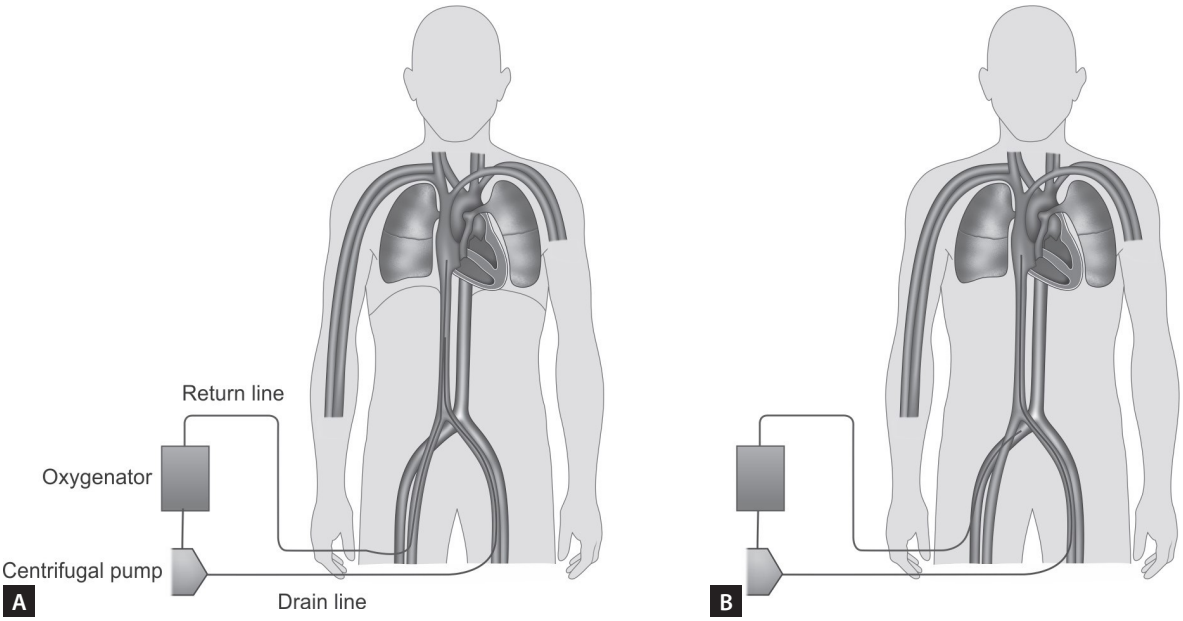
Extracorporeal Membrane Oxygenation and Continuous Renal Replacement Therapy for COVID-19 Pneumonia

During the COVID-19 pandemic, a propitious treatment mode for the development of COVID-19 pneumonia was the use of blended ECMO and CRRT therapy. The important

BOX 4: Indications of $ECCO_2R$ in ARDS.

- ARDS with lung-protective ventilation (LPV)
  - Tidal volume ~ 6 mL/kg
  - Evidence ~ <4 mL/kg (ultra-protective ventilator) even better than 6 mL/kg
- COPD exacerbation or status asthmaticus
- Bridge to lung transplant

(ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease)



Figs. 7A and B: (A) Venoarterial (VA); (B) Venovenous modes of extracorporeal membrane oxygenation .

parameters are shown in **Table 2** comparing CRRT with conventional therapy and hemofiltration.

Continuous renal replacement therapy to be conventional hemofiltration, is well laid out in **Table 2**. Where in, there are CRRT rules over conventional hemofiltration in terms of regulating electrolyte disturbances and clearance of inflammatory mediators. CRRT adjusts the body's immunity by improving the microcirculation, eliminating the interstitial edema, and enhancing the cells cellular oxygen uptake capacity. CRRT also helps remove the inflammatory mediators related to secondary sepsis such as TNFX, IL-6, and IL-8 and this boosts the chances of patients' survival.[24,25] CRRT thus has greater clinical advantages. It obtunds the severe acute respiratory syndrome (SARS) COVID-19 viral effectively, especially when combined with ECMO and immunotherapy. It is easy to integrate a CRRT circuit into the existing ECMO circuit.

The way to do it is as follows: The inlet or access port of the hemofilter is connected to the ECMO circuit after the ECMO blood pump connection.

TABLE 2: Parameters comparing CRRT with conventional therapy and hemofiltration.

Parameters	*Conventional*	*Hemofiltration*	*CRRT*
CVS tolerance	√	+	+++
Metabolic regulation	√	+	++
Constant plasma oncotic pressure	√	+	++
Correction of acid-based and electrolyte disorder	√	+	++
Clearance of inflammation mediators related to sepsis (TNFX, IL-6, IL-8)	√	+	+++

(CRRT: continuous renal replacement therapy; CVS: cardiovascular)

There are many advantages of using ECMO with CRRT as enumerated in **Boxes 5 and 6**. Longer filter life was achieved with this method than when CRRT was performed through independent venous access.

ADDITION OF AN INLINE HEMOFILTER INTO THE ECMO CIRCUIT

An in-line hemofilter or CRRT circuit may be integrated into the ECMO circuit. The inlet limb (access port) of a hemofilter can be connected after the blood pump, and the outlet limb (return port) is typically connected prior to the membrane oxygenator **(Fig. 8)**. This approach is less costly compared to CRRT, but the disadvantages include a lack

BOX 5: Indications of CRRT-AKI while on ECMO.

- Refractory hypoxemia
- Refractory metabolic acidosis
- Refractory pulmonary edema due to fluid overload, not responding to diuretics
- Symptomatic uremia
- Hemodynamic instability
- Advanced multiorgan dysfunction besides kidney
- Massive fluid transfusion
- Severe AKI

(AKI: acute kidney injury; CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation)

BOX 6: Advantages of CRRT with ECMO.

- Safe and effective technique[26]
- Overcomes and correct electrolyte disturbances
- CRRT and ECMO allow greater fluid management making the ECMO duration much shorter[27]
- Platform for additional organ support therapies[28]
- Provides more accurate fluid management during ECMO[29]

(CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation)

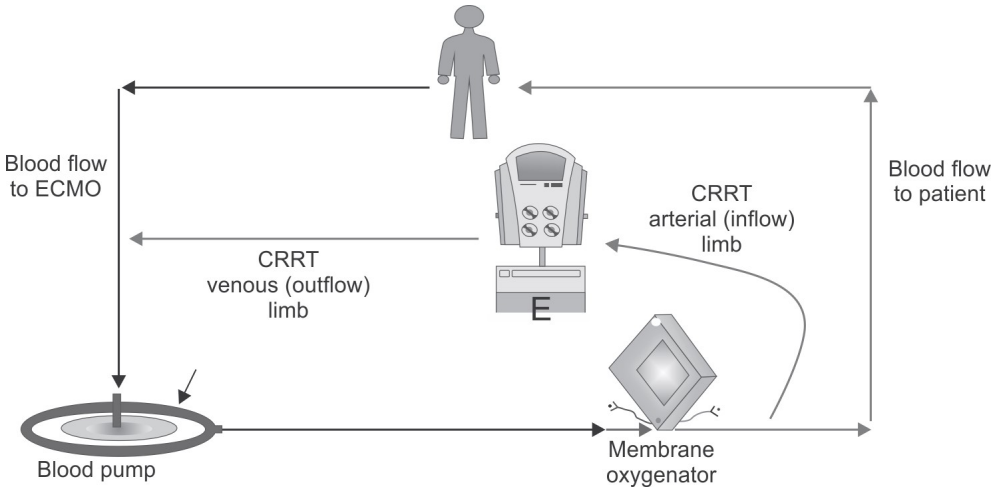


Fig. 8: CRRT combined with ECMO. In this example, the inflow to the CRRT machine is distal to the oxygenator and the outflow from the CRRT machine returns to the ECMO circuit proximal to the blood pump.
(CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation)

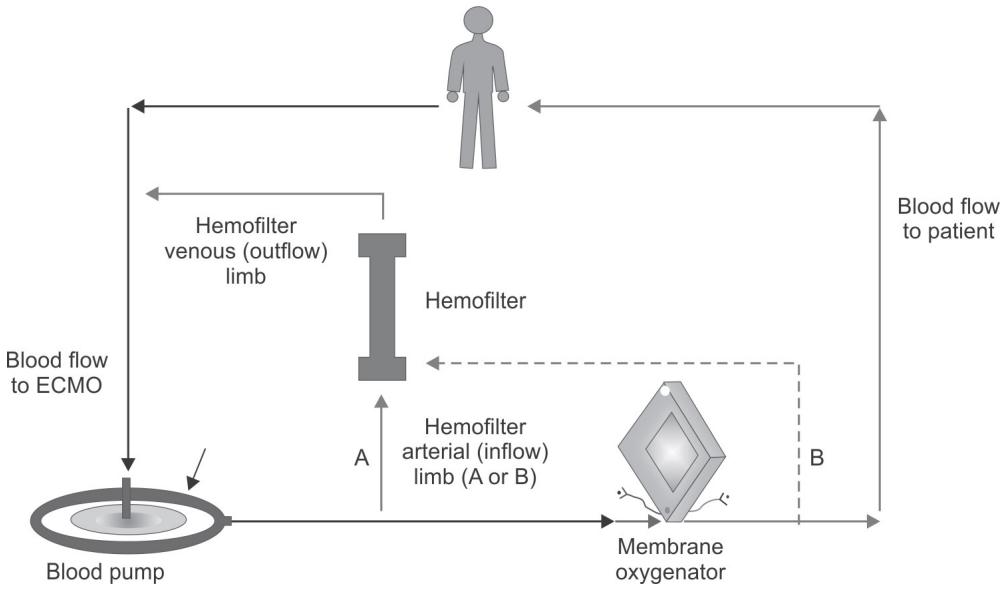


Fig. 9: Inline hemofilter combined with ECMO. The inflow to the hemofilter is typically distal to the blood pump, either between the pump and oxygenator or distal to the oxygenator. The outflow from the hemofilter typically returns prior to the blood pump, but can also return prior to the oxygenator.
(ECMO: extracorporeal membrane oxygenation)

BOX 7: CRRT and lactic acidosis.

- CRRT or IHD should only considered in treatment of patient with severe lactic acidosis of the patient has other indications for initiations of dialysis such as volume overload, metabolic disturbances.
- Filtered lactate clearance by high volume CRRT is small compared with overproduction of lactic acid in septic shock.
- Therefore, lactic acidosis alone should not be the sole indication for the initiation of CRRT.

(CRRT: continuous renal replacement therapy; IHD: ischemic heart disease)

of pressure alarms and poor control of net ultra-filtration. A stopcock or similar instrument to restrict blood flow can be added but may increase the risk of thrombosis or hemolysis. SCUF is typically the most common modality used for renal replacement therapy (RRT) with a hemofilter, the blood flow through which is driven by the ECMO pump as CRRT combined with ECMO is shown by the arrow **(Fig. 9, Box 7)**.

Successful use of extracorporeal therapies after ECMO resuscitation in a pediatric kidney transplant recipient showed that CRRT was initiated with the rationale to treat AKI and fluid overload was successful! Starting the adsorption therapy was the safest and the most beneficial approach, it allowed for—clinical stabilization, controlled multiple organ dysfunction MODS, and supported a positive clinical outcome. The technical connection of extracorporeal therapies to the ECMO circuit was feasible and did not affect the flow of the ECMO system and did not lead to increased clotting in most literature cases quoted so far.[30]

THERAPEUTIC PLASMA EXCHANGE IN SEPSIS

Fonseka et al. in 2018 reported that in countries of South East Asia, where pulmonary hemorrhage due to leptospirosis, is rampant, it may be prudent to add ECMO as an adjuvant treatment to plasmapheresis to control the pulmonary hemorrhage.[31]

Insufficient evidence exists to recommend plasma exchange as adjunctive therapy for patient with sepsis or septic shock. Rigorous randomized controlled trials evaluating clinically relevant patient-centered outcomes are required to evaluate the impact of plasma exchange in this condition. The significant debate over the risks/benefits of TPE in sepsis and MODS could be of benefit in prothrombotic forms of sepsis and MODS. In case of the risk of the increased immunosuppressive effect, plasmapheresis may be an important adjuvant to conventional treatment to reduce mortality in patients with severe sepsis or septic shock. Plasmapheresis is a safe procedure in the treatment of septic shock.

EXTRACORPOREAL MEMBRANE OXYGENATION AND PLASMAPHERESIS: IS THERE A ROLE?

The membrane separator and the centrifuge separator are two main therapeutics procedures, used to separate plasma from the blood cells. Each of the two methods has its own distinct advantages as shown in **Figures 10A and B**. Thus separators are used to remove, plasma from the blood.

Earlier, Mei Chong et al. had concluded, that cardiac congenital disease patients who are critical and require a therapeutic plasma exchange may improve tremendously

Figs. 10A and B: Plasmapheresis using the membrane and procedure separator.

BOX 8: Extracorporeal photopheresis indications.

- Cutaneous T-cell lymphoma
- Chronic GVHD
- Acute GVHD
- Lung transplantation[32]

(GVHD: graft versus host disease)

with the use of simultaneous ECMO, with improvement in both platelet count and thrombocytopenia.[32]

EXTRACORPOREAL PHOTOPHERESIS USED FOR CONTROLLING PULMONARY HEMORRHAGE

The indications of extracorporeal photopheresis are listed in **Box 8**.

CONCLUSION

The combinations of ECMO with CRRT, CytoSorb, plasmapheresis, IABP, or VAD are now seen in most modern ICUs as a part of multiple organ support therapy, MOST, termed "multimodal ECLS". Need for newer, next-generation machines for above are need of the hour to get all components of multimodal ECLS together,[33] in such a way that they can maintain patient safety looking out for organ recovery and stopping the accompany therapy at the correct time, is the need today. Optimal timing, drugs, and skilled staff and anticoagulation in the right doses is all that is required at present and learn more about multimodal ECLS therapies.

REFERENCES

1. Bezemer J, Diamantopoulou S, Jewitt C, Kress G, Mavers D. (2012). Using a Social Semiotic Approach to Multimodality: Researching Learning in Schools, Museums and Hospitals. [online] Available from https://eprints.ncrm.ac.uk/id/eprint/2258/4/NCRM_working_paper_0112.pdf. [Last accessed March, 2022].
2. Rybalko A, Pytal A, Kaabak M, Rappoport N, Bidzhiev A, Lastovka V. Case Report: Successful Use of Extracorporeal Therapies After ECMO Resuscitation in a Pediatric Kidney Transplant Recipient. Front Pediatr. 2020;8:593123.
3. Milella L, Ficarella M, Calabrese G, Sisto M, Grieco N, Moliterni P, et al. Our Four Years Experience of Hemoadsorption, Albumin and Heparin Treatment for Paediatric Sepsis: Let's Give a Chance in Multifactorial Pathological Conditions. Am J Pediatrics. 2020;6(3):207-17.
4. Extracorporeal Life Support Organization Evolving Outcomes of ECMO Support in COVID-19 Patients: Findings from the International ELSO Registry. (2020). [online] Available from: https://www.elso.org/Registry/Statistics/InternationalSummary.aspx. [Last accessed March, 2022].
5. Ikegami S, Jitsuiki K, Nagasawa H, Nishio R, Yanagawa Y. Suspected virus-inducing severe acute respiratory distress syndrome treated by multimodal therapy including extracorporeal membrane oxygenation and immune modulation therapy. Cureus. 2020;12(6):e8768.
6. Jose B, Sebastian RT, Smitha M, Augustine J. Successful right atrium-pulmonary artery ECMO in an infant with severe necrotizing pneumonia and bilateral bronchopleural fistula. Indian Pediatr. 2020;57(3):269-70.
7. Gerdung CA, Ross BC, Dicken BJ, Bjornson CL. Pneumonectomy in a child with multilobar pneumatocele secondary to necrotizing pneumonia: Case Reports in Pediatr and review of the literature. Case Rep Pediatr. 2019;2019:2464390.
8. Kapoor PM. In: Chopra HK, Nanda NC, Narula J, Wander GS, Manjunath CN, Chandra PN (Eds). Hypertension New Frontiers: A Textbook of Cardiology, 1st edition. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2021; pp. 913-28.
9. Meani P, Lorusso R, Pappalardo F. ECPella: Concept, Physiology and Clinical Applications. J Cardiothorac Vasc Anesth. 2022;36(2):557-66.
10. Petroni T, Harrois A, Amour J, Lebreton G, Brechot N, Tanaka S, et al. Intra-aortic balloon pump effects on macrocirculation and microcirculation in cardiogenic shock patients supported by venoarterial extracorporeal membrane oxygenation*. Crit Care Med. 2014;42(9):2075-82.
11. Meani P, Gelsomino S, Natour E, Johnson DM, Rocca HB, Pappalardo F, et al. Modalities and Effects of Left Ventricle Unloading on Extracorporeal Life support: a Review of the Current Literature. Eur J Heart Fail. 2017;19(Suppl 2):84-91.
12. Burkhoff D, Sayer G, Doshi D, Uriel N. Hemodynamics of Mechanical Circulatory Support. J Am Coll Cardiol. 2015;66(23):2663-74.
13. Pappalardo F, Schulte C, Pieri M, Schrage B, Contri R, Soeffker G, et al. Concomitant implantation of Impella® on top of veno-arterial extracorporeal membrane oxygenation may improve survival of patients with cardiogenic shock. Eur J Heart Fail. 2017;19(3):404-12.
14. Patel SM, Lipinski J, Al-Kindi SG, Patel T, Saric P, Li J, et al. Simultaneous Venoarterial Extracorporeal Membrane Oxygenation and Percutaneous Left Ventricular Decompression Therapy with Impella Is Associated with Improved Outcomes in Refractory Cardiogenic Shock. ASAIO J. 2019;65(1):21-8.

15. Truby LK, Takeda K, Mauro C, Yuzefpolskaya M, Garan AR, Kirtane AJ, et al. Incidence and implications of left ventricular distention during venoarterial extracorporeal membrane oxygenation support. ASAIO J. 2017;63(3):257-65.
16. Napp LC, Ziegeler S, Kindgen-Milles D. Rationale of Hemoadsorption during Extracorporeal Membrane Oxygenation Support. Blood Purif. 2019;48(3):203-14.
17. Douflé G, Roscoe A, Billia F, Fan E. Echocardiography for adult patients supported with extracorporeal membrane oxygenation. Crit Care. 2015;19:326.
18. Meersch M, Küllmar M, Wempe C, Kindgen-Milles D, Kluge S, Slowinski T, et al. Regional citrate versus systemic heparin anticoagulation for continuous renal replacement therapy in critically ill patients with acute kidney injury (RICH) trial: study protocol for a multicentre, randomised controlled trial. BMJ Open. 2019;9(1):e024411.
19. Joannidis M. Continuous renal replacement therapy in sepsis and multisystem organ failure. Semin Dial. 2009;22(2):160-4.
20. Semaan C, Charbonnier A, Pasco J, Darwiche W, Saint Etienne C, Bailleul X, et al. Risk Scores in ST-Segment Elevation Myocardial Infarction Patients with Refractory Cardiogenic Shock and Veno-Arterial Extracorporeal Membrane Oxygenation. J Clin Med. 2021;10(5):956.
21. Blijdorp K, Cransberg K, Wildschut ED, Gischler SJ, Houmes RJ, Wolff ED, et al. Haemofiltration in newborns treated with extracorporeal membrane oxygenation: a case-comparison study. Crit Care. 2009;13:R48.
22. Kapoor PM. Echocardiography in Extracorporeal Membrane Oxygenation. Ann Cardiac Anaesth. 2017;20(5):1.
23. Combes A, Brodie D, Bartlett R, Brochard L, Brower R, Conrad S, et al. Position paper for the organization of extracorporeal membrane oxygenation programs for acute respiratory failure in adult patients. Am J Respir Crit Care Med. 2014;190(5):488-96.
24. Platts DG, Sedgwick JF, Burstow DJ, Mullany DV, Fraser JF. The role of echocardiography in the management of patients supported by extracorporeal membrane oxygenation. J Am Soc Echocardiogr. 2012;25(2):131-41.
25. Dado DN, Ainsworth CR, Thomas SB, Huang B, Piper LC, Sams VG, et al. Outcomes among Patients Treated with Renal Replacement Therapy during Extracorporeal Membrane Oxygenation: a Single-Center Retrospective Study. Blood Purif. 2020;49:341-7.
26. Santiago MJ, Sánchez A, López-Herce J, Pérez R, del Castillo J, Urbano J, et al. The use of continuous renal replacement therapy in series with extracorporeal membrane oxygenation. Kidney Int. 2009;76(12):1289-92.
27. Rubin S, Poncet A, Wynckel A, Baehrel B. How to perform a haemodialysis using the arterial and venous lines of an extracorporeal life support. Eur J Cardiothorac Surg. 2010;37(4):967-8.
28. Chen H, Yu RG, Yin NN, Zhou JX. Combination of extracorporeal membrane oxygenation and continuous renal replacement therapy in critically ill patients: a systematic review. Critical Care. 2014;18(6):675.
29. Sucosky P, Dasi LP, Paden ML, Fortenberry JD, Yoganathan AP. Assessment of current continuous hemofiltration systems and development of a novel accurate fluid management system for use in extracorporeal membrane oxygenation. J Med Devices. 2008;2:035002-1.
30. Gist KM, Misfeldt A, Sahay RD, Gorga SM, Askenazi DJ, Bridges BC, et al. Acute Kidney Injury and Fluid Overload in Pediatric Extracorporeal Cardio-Pulmonary Resuscitation: A Multicenter Retrospective Cohort Study. ASAIO J. 2021.
31. Fonseka CL, Lekamwasam S. Role of Plasmapheresis and Extracorporeal Membrane Oxygenation in the Treatment of Leptospirosis Complicated with Pulmonary Hemorrhages. J Trop Med. 2018;2018:4520185.
32. Chong M, Lopez-Magallon AJ, Saenz L, Sharma MS, Althouse AD, Morell VO, et al. Use of therapeutic plasma exchange during extracorporeal life support in critically ill cardiac children with thrombocytopenia-associated multi-organ failure. Front. Pediatr. 2017;5:254.
33. Giani M, Scaravilli V, Stefanini F. Continuous renal replacement therapy in venovenous extracorporeal membrane oxygenation: A retrospective Study on regional citrate anticoagulation. ASAIO J. 2020;66(3):332-8.

CHAPTER

116

Futility in Extracorporeal Circulation with Mechanical Devices

Venkat S Goyal, Pranay Oza, Samir Gami

INTRODUCTION

The word "futility" is derived from the Latin word "futilis," literally meaning "pouring out easily" or "leaky" and hence considered of no use or worthless. In terms of critical care, futility is "interventions that prolong life without achieving an effect that the patient can appreciate as a benefit."[1] With the advancement in medical therapy, the emerging problem in critical care is the futility of treatment. Many patients in the critical care unit receive therapies that prolong their life without any hope of meaningful survival. Our measures of outcomes should not just be surviving to discharge but it should have good long-term survival with adequate neurological, psychological, and functional recovery.

Since almost a decade or more extracorporeal life support (ECLS) is also emerged as a mainstream therapy (from experimental a few decades back) with increasing indications and decreasing contraindications. As the ECLS can sustain life for days, weeks, and months together; we have to be very mindful about the *ethical utility* of it. The goal of ECLS should be to prolong the life and not to prolong death. ECLS should be used as a bridge to recovery or transplant. If either of these criteria cannot be achieved then continuing or initiating ECLS is considered to be inappropriate and futile.[2]

However, medical futility remains ethically, technically, and legally a controversial issue. There are a lot of gray areas which require clarifications. Also, it is different from country to country. Futile treatment is against the three key principles of ethics, viz., beneficence, nonmaleficence, and distributive justice, and in most of the time autonomy is no longer applicable as most of the patients are not capable of deciding.

IMPACT OF FUTILE TREATMENT

Continuing futile treatment in intensive care units (ICUs) impacts not only the patient but also to relatives of the patient, ICU staff, other patients, and society as a whole. To the patient, futile treatment prolongs his suffering and prolongs the natural dying process. It also has a heavy toll on the critical care team especially the nursing staff as they feel continuing treatment as tragic, futile, misguided, or harmful. This is compounded with a heavy ICU load.

Sometimes, in case of resource limitations, futile patient can deprive some other patient who can be benefitted with intensive care facilities. This will raise the ethical dilemma of distributive justice.

Many of critical care utilize lots of resources both financial and nonfinancial, in self-paying patients, the financial implication will make the relatives financially drained also. In case of the nation or a community-sponsored, it can increase the health budget and thereby negative effect in the society.

This impact is much more when the patient is on ECLS, as it involves lots of manpower and finances. Also, the ECLS facilities are limited so it will create resource limitations also and will deprive some patients from lifesaving treatment. Hence it is very important to have an appropriate ECLS-utilization.[3]

PROBLEMS INCURRED

It is crucial to allocate resources responsibly but how to execute is a big issue. It is difficult to make a clear decision due to a lack of clear evidences.[4,5] Secondly, in most of the time the decision regarding initiating critical care treatment especially of the ECLS are taken with a lack of time, information, and therapeutic alternatives. It is very difficult to weigh the likely survival of one individual against the less likely survival of many.

Also, with the uncertainty about the outcomes compounded with misunderstanding, emotional distortion, and patients' trust in expertise, it is practically difficult to get true informed consent and apply ethical principles.[6-8] Many of the times the discussion of futility is been discussed with family before initiating ECLS but the consent for termination of care (if required) may not be taken or valid before initiation of therapy as the consent might be given in duress.[5] The decision regarding the futility is also influenced

by religious belief, cultural background, personal values, local legalization, peer pressure, and fear of litigation.[8] What is more vital in futility care is the communication with the family member which is time-consuming. Spending sufficient time may be difficult in a busy ICU. Another problem is changing duty of house physician which can lead to a mixed message to the family and which makes them confused. Also repeated questions from the demanding family members and surrogates regarding prognosis (which is definitely unclear), creates anxiety in physician and that may lead to avoidance of family.

METHODOLOGY

Theoretically, it is easy to talk about the futility of treatment but the question comes about who will decide the futility of treatment, when the treatment is to be considered futile and how to execute it.

Who?

Futility of treatment is usually a medical decision but also it involves the moral and emotional aspects of the family or surrogate. Decisions are difficult to take and it depends on *individual* and *institutional policy*. Decision should not be made by a single person but should be taken after due consideration of all the clinical data and discussing various aspects of patient treatment with ICU colleagues, both senior and junior, and liaising with extracorporeal membrane oxygenation (ECMO) directors. Decision made after group discussion will help to avoid resentment, miscommunication, or abrupt changes in management during the subsequent ECMO run. The families should be involved in discussions and kept closely informed, the final decision should remain with physician-in-charge.[7,9,10] Physician-in-charge should act in best interest of patient and take the final decision as neither patient nor the relatives of the patient have the cognitive capacity to decide.[11]

Criteria for Futile Treatment

It is important to define criteria for labeling given treatment as futile when patient is already on life support therapy and/or on ECLS. Patient with an extensive neurological injury such as brain dead or in persistent vegetative state secondary to massive cerebral or posterior territory infarct, ischemic-hypoxic encephalopathy, or massive intracranial (IC) bleed should be considered for futility as even if their primary organ recovers, neurological recovery is unlikely.

Patient with irreversible lung or cardiac injury diagnosed while on ECMO and surgical correction or assist device or transplant is not the feasibility which can be considered for futility. However, thorough clinical documentation of irreversibility is an essential component; irreversibility should not just be defined because patient is just on ECMO for a few weeks to months. There are sufficient data supporting reasonable outcomes in severe acute lung injury with prolonged venovenous extracorporeal membrane oxygenation (VV-ECMO) (>30 days) so it is difficult to define futility on the basis of number of days on ECMO. Authors have personal experience of good functional lung recovery after 117 days on VV-ECMO with native lung recovery and almost 30% of the patient recovered and decannulated after >30 days of ECMO support. The longest ECMO run reported with good lung functional recovery is 605 days of ECLS.[12] During this pandemic, many of the national and international centers have observed prolonged VV-ECMO need and their average stay remained around 40–50 days with reasonably good lung recovery. So, the current consensus is patient should continue to be on VV-ECMO until they recover or require a lung transplant, or succumbs to some life-threatening complications.

Other cases where ECLS can be considered as futile, there are patients with severe acute respiratory distress syndrome (ARDS), severe shock, and gross multiorgan failure. However, this is controversial and should not be a lone factor to be considered for futility. This should be supported by other factors such as advanced age, statistically less-likelihood of organ recovery, or during a pandemic when there is resource limitation and we need to consider distributive justice.

For defining futile treatment, we also need to assess the likely long-term survival, function, and quality of life, and the availability and quality of rehabilitation, aftercare, and home support. These are also key factor that needs to be defined and it is difficult to make them universal as it varies enormously across different parts of the world.

How?

Once the consensus decision is made by the team of caregivers, it should be properly documented and the next plan of action about how to execute should be determined. The family should be approached regarding the decision and should be counseled about the possible outcomes and quality of life. They should be taken in confidence and make them the part of decision. They can also be counseled about the possibility of an organ donation if relevant once they start accepting futility. Counseling about the organ donation widely remains as national and institutional policy. Organ donation counseling ideally should be done by a separate team and should not be done in the same sitting.

Once the decision is made with relative's consent obtained, the goal of intensive care team is to provide them with a dignified and comfortable death. It should be remembered that the consent is given for a withdrawal or withholding the advanced treatment and not for the daily care.[13,14] One of the various forms of withholding/

TABLE 1: Do's and don'ts of futility of care.

Do's	*Don'ts*
• Establish clear channels of communication between ICU physicians and surrogates • Give realistic picture • Given enough time and address their anxiety • Strive for accuracy in prognosis • Continue excellent palliative care—aim for a dignified and comfortable death • Show firmness about the limits • Include relatives perspectives in a decision to initiate or discontinue therapy[7]	• Don't take single handed decision • Don't leave the burden of decision making entirely on surrogates • Do not avoid relatives and their questions • Do not neglect patient after DNR or DNE orders • Do not make a decision only on economic grounds

(DNE: do not escalate; DNR: do-not-resuscitate; ICU: intensive care unit)

withdrawing support should be selected. The decision can be made from the do-not-resuscitate (DNR), do-not-escalate (DNE) orders to the withdrawal of all ongoing treatment **(Table 1)**.

Do-not-resuscitate order—the treatment will continue as it is only the resuscitation efforts are withheld in the case of cardiorespiratory arrest.

Do-not-escalate order—here no new therapies are started but current interventions are maintained, this can be for any new therapies or might be specific for certain procedures such as intubation, dialysis, continuous renal replacement therapy (CRRT), etc.

Withdrawal of life supports—here the entire treatment is stopped and all life supports are stopped. Usually, sedation dose is increased for the comfort of the patient.

It is of key importance to avoid medical futility disputes and they are usually best prevented then resolved. The best way to avoid such incidence is through frequent, careful, and sensitive communications with the family members and surrogates.

The physicians and the team members should provide families accurate, current, and frequent prognostic estimates and that should remain the same for all the team members. There should not be any disparity in communications. Physicians have to understand the emotional need of the family and understand their anxiety from their perspectives. Relatives should not feel anytime during the palliative care that patient is being neglected or left out; it is the duty of the critical care team to facilitate excellent palliative care through the course of the illness. Team should encourage the nursing staff or technicians to facilitate good patient relations. The decision-making of futility should not be kept entirely on relatives as they might find it difficult to take harsh decisions and might feel it is cruelty. They should be properly counseled and in those patients where the ECLS is bridge to nowhere, one should explain to the family about the no-escalation strategy. Physician should also seek support from spiritual and palliative care providers support for difficult cases.

BRAIN DEATH AND ORGAN DONATION ON EXTRACORPOREAL MEMBRANE OXYGENATION

Organ donation is feasible; there are ethical implications of organ donation/Epidemiology and Disease Control Division (EDCD) at this point. It is important to diagnose brain dead before proceeding for organ donation. The neurological criteria for brain death include coma, absent brain stem reflexes, and apnea. For patients on ECMO, routine apnea testing is not possible as mainly the gas exchange is through the membrane oxygenator. The mainstay of performing apnea tests on ECMO patients is to decrease the sweep gas rate to a minimum of 0.5–1 L/min while maintaining the same blood flow rate.[15] The detailed test is given in **Table 2**. However, details of brain death testing are elucidated in a separate chapter.

LEGALITY

The legality of the futility care varies from country to country. In most of the country futility of treatment is considered only after declaring patient brain dead. Concept of futility is considered as flawed if the patient and/or patient's relative's wishes and expectations are not taken care of during decision making.[16]

As per the law, a "competent" patient suffering from "terminal illness" can refuse to treatment after knowing the pros and cons of the disease and treatment and the doctor is bound to obey the same and withhold or withdraw treatment.[17] However, if the patient is "incompetent" (includes minor, person of unsound mind) and is unable to make decisions for end of life, then doctor should to take a decision in the "best interests" of the patient. The law might not apply in situations where the parents/guardians insist on continuation of life support measures. In case of persistent vegetative state, as per the recent judgment by the Supreme Court of India, the withdrawal of life support measures is legalized.[18] In this condition the decision of discontinuing life supporting measures can be taken by parents, spouse or doctors attending patient in the "best interest" of the patient.

TABLE 2: Brain dead criteria for patient on ECMO.

Prerequisite	*Neurological examination*	*Apnea test*
• Irreversible cause of coma • Exclude reversible cause such as CNS depressant drugs, electrolyte, acid-base imbalance, and endocrine disorder • Normal core temperature and hemodynamics	• No response to deep painful stimuli (except spinal reflexes) • Absent of brain stem reflexes such as pupilary reactions, corneal reflex, gag reflex, cough reflexes and oculovestibular reflex	• Try to improve oxygenation and maintain normocapnia by increasing blood flow, sweep gas, and ECMO FiO_2. • Disconnect patient from ventilator and place oxygen cannula in trachea at the level of carina. Give 5–8 L of 100% oxygen. • Maintain same blood flow rate and FiO_2 on ECMO. • Gradually decrease sweep gas rate on ECMO as low as 0.5 L/min as tolerated by patient. • Watch for any signs of respiratory movements or gasping. • Repeat ABG at the interval of 5 minutes, 10 minutes and if PCO_2 still not achieved and patient is hemodynamically stable then after 15 minutes • For VV-ECMO sample collection from arterial line, for VA ECMO sample collection from right radial and post oxygenator • Apnea test is positive if no respiratory movement and PCO_2 more than 60 mm Hg or increase by 20 mm Hg over baseline.

(ABG: arterial blood gas; CNS: central nervous system; ECMO: extracorporeal membrane oxygenation; VA ECMO: venoarterial extracorporeal membrane oxygenation; VV-ECMO: venovenous extracorporeal membrane oxygenation)

However, it requires an approval from high court; the court appoints a panel of three expert doctors to seek its medical opinion, preferentially one neurologist, one psychiatrist, and physician.

CONCLUSION

Defining futility of care during ECLS is a complex process and sensitive issue and there is no easy answer to it. We still need more evidences. We need to work upon the cost-benefit analysis,[5] the cost per life-year saved[6,3] and quality adjusted life-years. These evidences might make decision making easier for both physician and family and would not consider the decision's societal impact.[11] Good communication, ethical consultation, thorough palliative care planning, and supports from spiritual and palliative care providers can make the process of futility care smoother and acceptable.[6,10,19,20] It is essential to have National Health Policy in pandemic to prioritize the resources and should be based on pre-existing rationing plans.[6,21-24]

REFERENCES

1. Schmidt M, Bréchot N, Combes A. Ten situations in which ECMO is unlikely to be successful. Intensive Care Med. 2016;42(5):750-2.
2. Mulaikal TA, Nakagawa S, Prager KM. Extracorporeal membrane oxygenation bridge to no recovery. Circulation. 2019;139(4):428-30.
3. Crow S, Fischer AC, Schears RM. Extracorporeal life support: utilization, cost, controversy, and ethics of trying to save lives. Semin Cardiothorac Vasc Anesth. 2009;13(3):183-91.
4. Jaramillo C, Braus N. How should ECMO initiation and withdrawal decisions be shared? AMA J Ethics. 2019; 21(5):E387-93.
5. Abrams D, Combes A, Brodie D. What's new in extracorporeal membrane oxygenation for cardiac failure and cardiac arrest in adults? Intensive Care Med. 2014;40(4):609-12.
6. Kirsch R, Munson D. Ethical and end of life considerations for neonates requiring ECMO support. Semin Perinatol. 2018;42(2):129-37.
7. Bein T, Brodie D. Understanding ethical decisions for patients on extracorporeal life support. Intensive Care Med. 2017;43(10):1510-1.
8. Peetz AB, Sadovnikoff N, O'Connor MF. Is informed consent for extracorporeal life support even possible? AMA J Ethics. 2015;17(3):236-42.
9. Whitman GJR. Extracorporeal membrane oxygenation for the treatment of postcardiotomy shock. J Thorac Cardiovasc Surg. 2017;153(1):95-101.
10. Abrams DC, Prager K, Blinderman CD, Burkart KM, Brodie D. Ethical dilemmas encountered with the use of extracorporeal membrane oxygenation in adults. Chest. 2014;145(4):876-82.
11. Nardo DM, Ore AD, Testa G, Annich G, Piervincenzi E, Zampini G, et al. Principlism and personalism. Comparing two ethical models applied clinically in neonates undergoing extracorporeal membrane oxygenation support. Front Pediatr. 2019;7:312.
12. MacLaren G. When to initiate ECMO with low likelihood of success. Critic Care. 2018;22(1):217.
13. Vincent JL, Schetz M, De Waele JJ. "Piece" of mind: end of life in the intensive care unit statement of the Belgian Society of Intensive Care Medicine. J Crit Care. 2014;29:174-5.
14. Rubenfeld GD. Principles and practice of withdrawing life-sustaining treatments. Crit Care Clin. 2004;20(3):433-51, ix.
15. Talahmaa M, Degeorgia M. Apnea Testing for the Determination of Brain Death in Patients Supported by Extracorporeal Membrane Oxygenation. J Neuro Res. 2016;6(1):28-34.
16. Steinhorn DM. Termination of extracorporeal membrane oxygenation for cardiac support. Artif Organs. 1999;23(11): 1026-30.

17. Rao MJ. (2006). 196th Report on Medical Treatment to Terminally Ill Patients (Protection of Patients and Medical Practioners). [online] Available from www.lawcommissionofindia.nic.in/reports/rep196. [Last accessed March, 2022].
18. Supreme Court of India. Reportable item no. 1A, Court no.6, Section X. writ petition no. 115 of 2009, Aruna Ramchandra Shanbaug Vs Union of India. [online] Available from www.supremecourtofindia.nic.in/outtoday/ wr1152009. [Last accessed March, 2022].
19. Meltzer EC, Ivascu NS, Stark M, Orfanos AV, Acres CA, Christos PJ, et al. A survey of physicians' attitudes toward decision-making authority for initiating and withdrawing VA-ECMO: results and ethical implications for shared decision making. J Clin Ethics. 2016;27(4):281-9.
20. Courtwright AM, Robinson EM, Feins K, Carr-Loveland J, Donahue V, Roy N, et al. Ethics committee consultation and extracorporeal membrane oxygenation. Ann Am Thorac Soc. 2016;13(9):1553-8.
21. Ting PS, Chen L, Yang WC, Huang TS, Wu CC, Chen YY. Gender and age disparity in the initiation of life-supporting treatments: a population-based cohort study. BMC Med Ethics. 2017;18(1):62.
22. Cronin AJ. End-of-life care in advanced kidney disease: ethical and legal issues and key challenges for black and minority ethnic groups. J Ren Care. 2014;40(Suppl 1):16-22.
23. Kissoon N, Bohn D. Use of extracorporeal technology during pandemics: ethical and staffing considerations. Pediatr Crit Care Med. 2010;11(6):757-8.
24. Truog RD, Thiagarajan RR, Harrison CH. Ethical dilemmas with the use of ECMO as a bridge to transplantation. Lancet Respir Med. 2015;3(8):597-8.

CHAPTER

117

Referral for Extracorporeal Life Support: Right Time

Riyan Sukumar Shetty, Vimal Bhardwaj, Muralidhar Kanchi

INTRODUCTION

Extracorporeal life support (ECLS) utilizes the highest sophistication in technology for the treatment of respiratory and cardiac failure. Its utility has rapidly expanded, especially post the coronavirus disease-2019 (COVID-19) pandemic. As a constantly evolving modality, it has come a long way from being just the last resort/salvage therapy to being the treatment modality of choice in a number of life-threatening scenarios requiring cardiopulmonary support. However, there is scarcity of evidence not only about the use of ECLS but also the right timing of ECLS initiation. ECLS and extracorporeal membrane oxygenation (ECMO) are terms used synonymously and mean the same.

Why is timing everything?

Metabolism is a life-sustaining process involving oxygen (O_2) consumption and carbon dioxide (CO_2) production which is approximately 3 cc/kg/min with a rate of oxygen consumption equal to CO_2 production. Metabolism increases with activity, certain drugs, fever, and hormones and decreases with hypothermia, sleep, and paralysis.

In order to suffice for metabolism at varying proportions according to bodily needs, the amount of oxygen available for delivery to the tissues in the bloodstream (oxygen delivery or DO_2) should be five times the actual consumption by tissues (VO_2).

Oxygen is transported in the blood bound to hemoglobin and also dissolved in plasma. This is called the *oxygen content* and is measured as mL/dL.

Oxygen content in blood = % saturation [Hb (g/dL) % saturation 1.34 mL O_2/g] and O_2 (pO_2 0.003 mL/mm Hg/dL)

Oxygen delivery is the oxygen content in arterial blood times the cardiac output delivered to the metabolizing tissue. DO_2 in normal adults is 600 cc/m^2/min. The normal VO_2 at rest is 120 mL/min/m^2. Normally DO^2 is 5 times the VO_2. Hence, 20% of the oxygen is consumed at the tissue level leaving 80% in venous blood. Therefore, the normal arterial oxygen of a patient breathing air is pO_2 90 mm Hg, saturation 100%, and O_2 content 20 mL/dL and the normal venous oxygen is pO_2 40 mm Hg, saturation 80%, and content 16 mL/dL[1] **(Fig. 1)**.

RELATIONSHIP OF DO_2 AND VO_2 IN VARIOUS CONDITIONS

Shock is loss of homeostasis leading to mismatch in oxygen delivery and oxygen consumption. A primary goal of managing any critically ill patient is to maintain DO_2/VO_2 close to normal (5:1). With ECMO, we have the ability to control DO_2 regardless of native lung function. As mentioned if this critical demand-supply mismatch cannot be maintained by safe conventional treatment or in other terms, if interventions themselves are damaging [high ventilator supports, high fraction of inspired oxygen (FiO_2), high dose of vasopressors] then ECMO might be an ideal alternative by its ability to meet DO_2 regardless of native lung function thereby restoring DO_2/VO_2 ratio[2] **(Fig. 2)**.

To reap the full benefit of ECMO it is very relevant to limit potentially detrimental interventions to avert irreversible organ injury and thereby enhancing overall outcomes.

CHOICE OF ECMO THERAPY

Venovenous extracorporeal membrane oxygenation (VV-ECMO) primarily supports respiratory function helping in resolving hypoxia and hypercarbia. In VA-ECMO, both respiratory and hemodynamic functions are supported and is used in circulatory failure **(Fig. 3)**.

ECMO IN SEVERE RESPIRATORY FAILURE

Initial randomized control trial (RCT) by Zapol et al., did not show a long-term survival benefit.[3] Early results of ECMO had less favorable outcomes and this was attributed to the crude technique, heterogeneity in mechanical ventilation strategies and timing of initiation of ECMO.

Interest in ECMO gained momentum during the H1N1 Pandemic which was followed by two major RCTs. In 2009, conventional ventilatory support versus extracorporeal

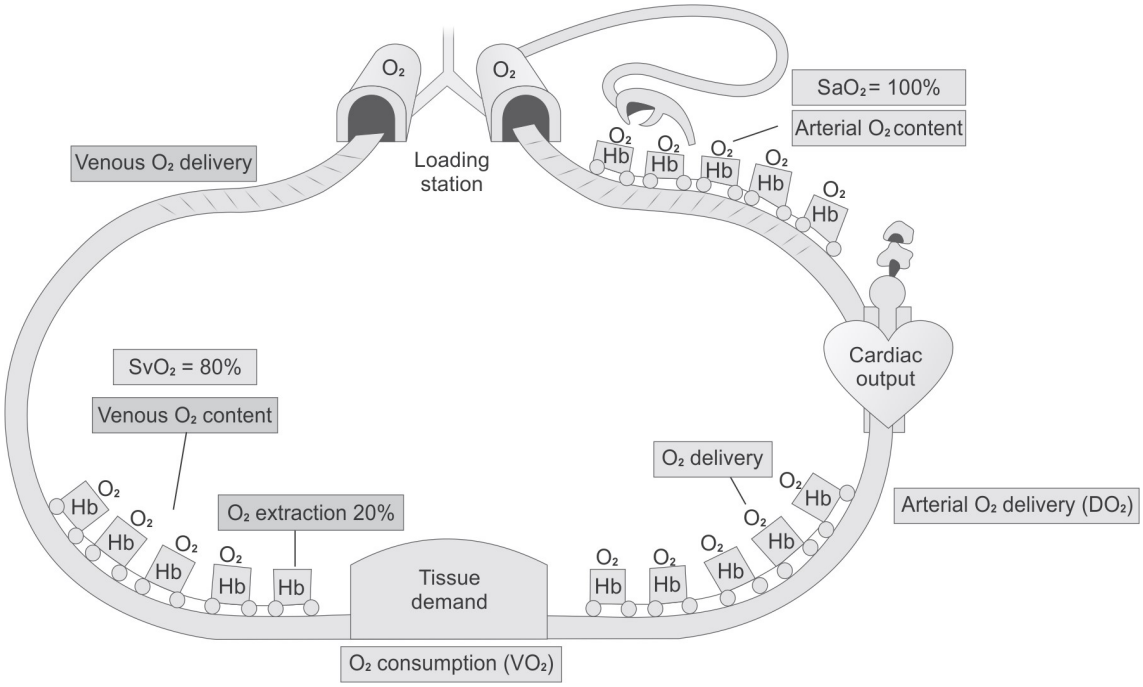


Fig. 1: Oxygen delivery.

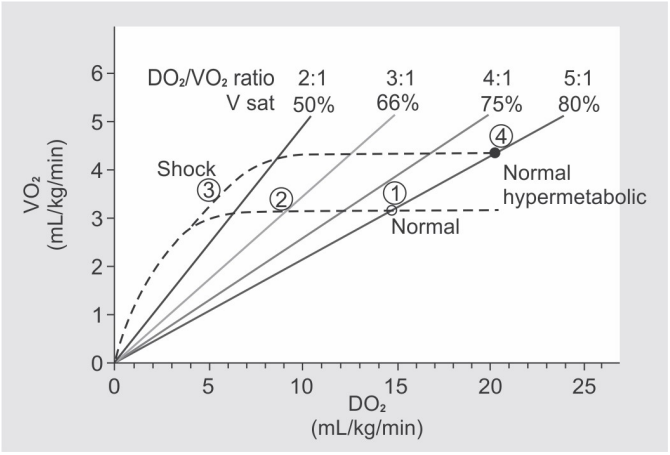


Fig. 2: In health the DO_2/VO_2 ratio is 5 (Point 1) signifying Normal aerobic metabolism, which suffices during periods of hypermetabolism like exercise (Point 2). When the DO_2 is less than twice VO_2, oxygen supply is inadequate to meet the metabolism demands and anaerobic metabolism predominates resulting in lactic acid and rather than CO_2. DO_2: VO_2 ratio less than 2:1 leads to features of metabolic acidosis, and progressive organ failure (Point 2,3).[1]

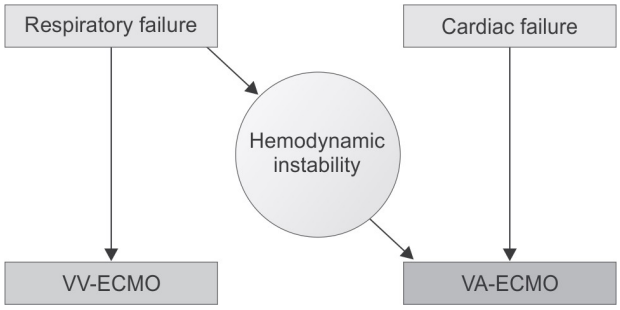


Fig. 3: Choice of ECMO therapy.

membrane oxygenation for severe adult respiratory failure (CESAR) trial randomly assigned 180 patients with severe acute respiratory failure to either be referred to a single ECMO center or undergo continued conventional management. It showed an absolute risk reduction of death by 16% in patients randomized to receiving ECMO.[4]

In 2018, ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial which randomized 249 patients with severe acute respiratory distress syndrome (ARDS) to receive early VV-ECMO or conventional low tidal volume, low-pressure ventilation showed an absolute risk reduction of 11% in patients randomized to ECMO along with improved oxygenation and decreased incidence of renal failure.[5]

Also, a recent meta-analysis in 2019 which included 25 RCTs showed significantly lower 28 days mortality supported the use of ECMO as an early strategy in severe ARDS patients.[6,7]

During the COVID-19 pandemic, NHS England ECMO services reported an overall survival rate of 74% with ECMO during the first wave which was on par with respiratory failure secondary to other causes. During the second wave, concerns about delaying initiation of lung-protective invasive ventilation compared to the first wave led to longer ECMO runs and subsequently less reversible severe lung disease.[5]

Indications

- Potentially reversible severe respiratory failure (e.g., PaO_2/FiO_2 of <50 mm Hg for ≥3 hours or PaO_2/FiO_2 of <75 mm Hg for ≥6 hours)[5]

TABLE 1: Lung injury score (Murray score)

	0	1	2	3	4
PaO_2/FiO_2 (mm Hg)	≥300	225–299	175–224	100–174	<100
PEEP (cm H_2O)	≤5	6–8	9–11	12–14	≥15
Compliance (mL/cm H_2O)	≥80	60–79	40–59	20–39	≤19
CXR quadrants infiltrated	Normal	1	2	3	4

Final Murray score: Sum of all 4 individual scores divided by 4
PEEP: Positive end-expiratory pressure
Compliance = Tidal volume (mL)/$P_{plateau}$-PEEP

- Murray Score of 3 or higher[7,8] **(Table 1)**.
- Uncompensated hypercapnia with a pH of 7.20 or higher, despite a respiratory rate of >35 breaths/min, or due to life-threatening airway disease (e.g., asthma, airway trauma, or air leak)[5]
- Severe air leak syndromes[9]
- Need for intubation in a patient on lung transplant list[9]
- Immediate cardiac or respiratory collapse (pulmonary embolism, blocked airway, unresponsive to optimal.[9]

Indications for Considering ECMO Therapy in Severe Respiratory Failure

- Unsuccessful trial of ventilation in the prone position for 6 hours or more (unless contraindicated)[7]
- Unsuccessful optimal respiratory management with lung-protective ventilation after discussion with an ECMO center[7]
- Murray score 2.5–3.0[9] **(Table1)**.

Relative Contraindications

- Indices of low potential to recover [e.g., a respiratory ECMO survival prediction (RESP) score of ≤3][7] **(Table 2)**
- Receiving invasive mechanical ventilation for 7 days or more[5,9]
- Clinical frailty scale category ≤3[10] **(Fig. 4)**.
- Refractory multiorgan failure[7]
- Severe neurological injury[7]
- Cardiac arrest for >15 minutes[7]
- Major pharmacologic immunosuppression (absolute neutrophil count <400/mm^3)[9]
- Central nervous system (CNS) hemorrhage that is recent or expanding[9]
- Nonrecoverable comorbidities such as major CNS damage or terminal malignancy[9]
- Age—an increased risk with increasing age[9]

MURRAY SCORE

It was originally developed by John Murray to assess the severity of acute lung injury in ARDS. Murray Score was later used in the conventional ventilation or ECMO for severe adult respiratory failure (CESAR) trial to help determine which patients with ARDS were appropriate for ECMO.[8] Murray score, even though not validated for referral for ECMO, has been widely used as a helpful tool for referral and initiation of ECMO. Murray score now is sometimes also referred to as lung injury score[7] **(Table 1)**.

RESPIRATORY ECMO SURVIVAL PREDICTION SCORE

The respiratory ECMO survival prediction score (RESP) has been developed by the Extracorporeal Life Support Organization (ELSO) and the Department of Intensive Care at The Alfred Hospital, Melbourne. It is designed to assist prediction of survival for adult patients undergoing ECMO for respiratory failure. It should not be considered for patients who are not on ECMO or as a substitute for clinical assessment[11] **(Table 2)**.

When calculating the RESP score, the number of days on a high-flow nasal cannula should not count towards the total number of days on ventilation. If the patient receives continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV) for >1 day before intubation, the number of days on CPAP or NIV would count towards the total number of days on mechanical ventilation if CPAP or NIV was used for >12 hours/day on average and the PaO_2/FiO_2 was <150 mm Hg (with a FiO_2 of >60%, a $PaCO_2$ of <30 mm Hg, or a respiratory rate of >25 breaths/min); the $PaCO_2$ was >50 mm Hg or the $PaCO_2$ had been increasing since CPAP or NIV use, or both; or the inspiratory tidal volume (if measured) was greater than 95 mL/kg predicted body weight.[7]

CLINICAL FRAILTY SCALE

The clinical frailty scale (CFS) is a judgment-based frailty tool that evaluates specific domains including comorbidity, function, and cognition to generate a frailty score ranging from 1 (very fit) to 9 (terminally ill). The association of CFS score with clinical outcomes highlights its utility in the care of the aging population[10] **(Fig. 4)**.

TABLE 2: "Immunocompromised" is defined as hematological malignancies, solid tumor, solid organ transplantation, human immunodeficiency virus, and cirrhosis.

Parameter	***Score***
Age (years)	
18 to 49	0
50 to 59	–2
≥60	–3
Immunocompromised status	–2
Mechanical ventilation prior to initiation of ECMO	
<48 hours	3
48 hours to 7 hours	1
>7 d	0
Acute respiratory diagnosis group (select only one)	
Viral pneumonia	3
Bacterial pneumonia	3
Asthma	11
Trauma and burn	3
Aspiration pneumonitis	5
Other acute respiratory diagnoses	1
Nonrespiratory and chronic respiratory diagnoses	0
Central nervous system dysfunction	–7
Acute associated (nonpulmonary) infection	–3
Neuromuscular blockade agents before ECMO	1
Nitric oxide uses before ECMO	–1
Bicarbonate infusion before ECMO	–2
Cardiac arrest before ECMO	–2
$PaCO_2$ mg Hg	
<75	0
≥75	–1
Peak inspiratory pressure, cm H_2O	
<42	0
≥42	–1
Total score	–22 to 15

Hospital survival by risk class		
Total RESP score	**Risk class**	*Survival*
≥6	I	92%
3 to 5	II	76%
–1 to 2	III	57%
–5 to –2	IV	33%
≤–6	V	18%

"Immunocompromised" is defined as hematological malignancies, solid tumor, solid organ transplantation, human immunodeficiency virus, and cirrhosis.
"Central nervous system dysfunction" diagnosis combined neurotrauma, stroke, encephalopathy, cerebral embolism, and seizure and epileptic syndrome.
"Acute associated (nonpulmonary) infection" is defined as another bacterial, viral, parasitic, or fungal infection that did not involve the lung.

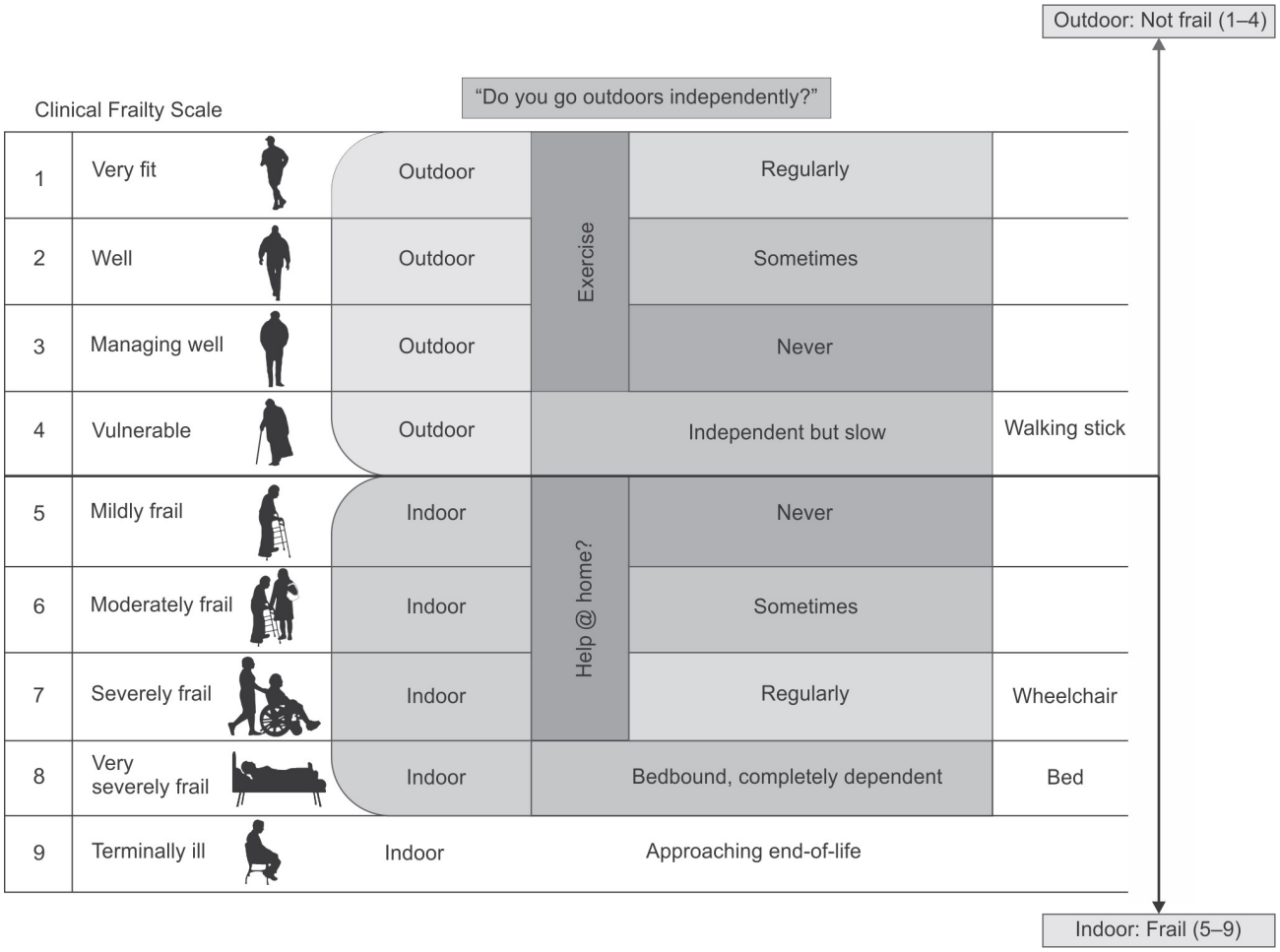


Fig. 4: Clinical Frailty score.

CAUSES FOR ECMO IN SEVERE RESPIRATORY FAILURE

- ARDS with primary lung injury from infection, aspiration, or trauma
- Primary graft dysfunction following lung transplantation (within 7 days)
- Bridge to lung transplant (BTT)
- Pulmonary vasculitis
- Postpneumonectomy
- Pulmonary embolism
- Acute airway obstruction
- Status asthmaticus and acute exacerbation of chronic obstructive pulmonary disease (COPD)

REFERRAL FOR ECMO IN SEVERE CARDIAC FAILURE

Extracorporeal membrane oxygenation (ECMO) plays a crucial role in managing refractory hemodynamic compromise and respiratory insufficiency thereby facilitating organ perfusion. The scope of usage has gone beyond the conventional indications of cardiogenic shock and cardiac arrest. ECMO is being considered in a wide array of clinical conditions as shown in **Figure 3**.

The interest in VA-ECMO has been increasing in view of the equivocal role of intra-aortic balloon pulsation (IABP).[12] VA-ECMO in cardiogenic shock is considered only after all other relatively less-invasive measures have been attempted. These include volume resuscitation, high vasopressor requirements, IABP, and mechanical ventilation.

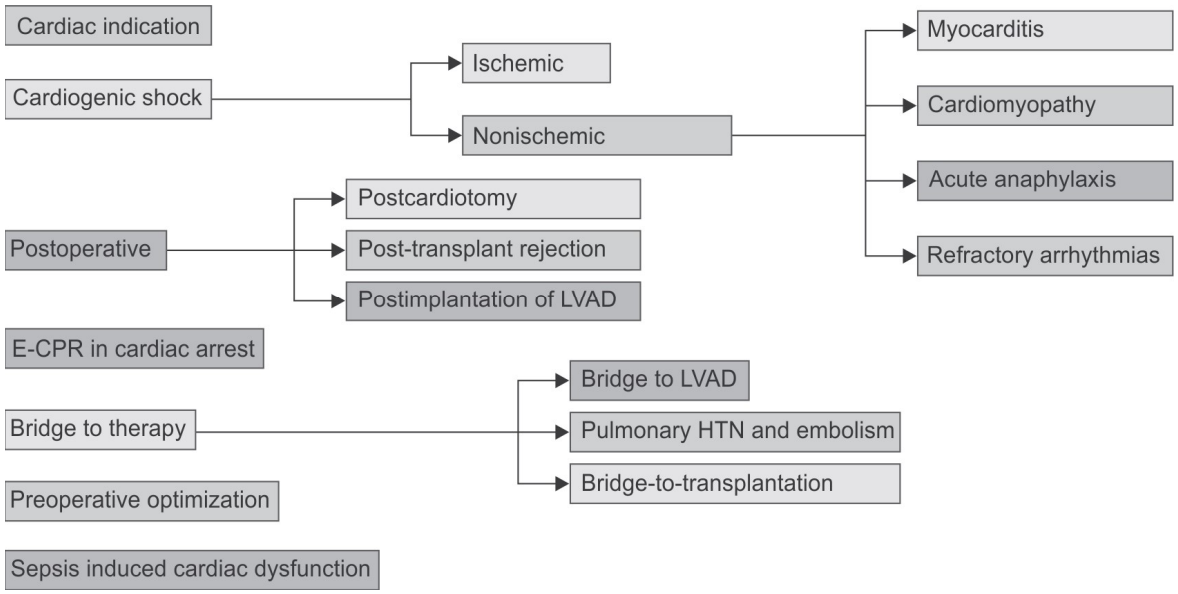
Indications for ECMO in Severe Cardiac Failure (Flowchart 1)

- Low cardiac output (cardiac index of <2 L/min/m^2)[13]
- Lactate levels of >2.8 mmol/L[13]
- Central venous O_2 saturation of <65%[13]
- Hypotension (systolic blood pressure of <90 mm Hg)[13]

Referral for Extracorporeal Cardiopulmonary Resuscitation

Extracorporeal cardiopulmonary resuscitation (ECPR) is the application of ECMO in patients where conventional cardiopulmonary resuscitation (CPR) measures are unsuccessful in achieving sustained return of spontaneous

Flowchart 1: Common indications of ECMO in cardiac failure.



circulation (ROSC). Sustained ROSC is deemed to have occurred when chest compressions are not required for 20 consecutive minutes following cardiac arrest.[14] ECPR has been employed in both in-hospital cardiac arrest and out-of-hospital cardiac arrest. A recent consensus statement from ELSO showed survival to hospital discharge after ECPR is 29% with >85% survivors falling into favorable neurological outcomes.[14]

Inclusion Criteria for Extracorporeal Cardiopulmonary Resuscitation

- Age <70 years[15]
- Witnessed arrest[16]
- Arrest to first CPR (no-flow interval) <5 minutes (i.e., bystander CPR)[16]
- Initial cardiac rhythm of ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT), pulseless electrical activity (PEA)[16]
- Arrest to ECMO Flow <60 minutes (low flow interval)[16]
- End-tidal CO_2 >10 mm Hg during conventional CPR before cannulation for ECMO[16]
- Intermittent ROSC or recurrent VF[16]
- Signs of life during conventional CPR may be a positive predictive factor for survival[16]
- The absence of previously known life-limiting comorbidities (e.g., end-stage heart failure/chronic obstructive pulmonary disease/end-stage renal failure/liver failure/terminal illness) and consistent with patient's goals of care[16]
- No known aortic valve incompetence (>mild aortic valve incompetence should be excluded)[16]

CONCLUSION

As there are limited centers delivering ECMO services, it is prudent to develop robust strategies to enable early referral and prompt management. This might potentially avoid a proportion of patients developing progressive and irreversible organ injury.

The referring hospital follows a standardized approach for referral to an ECMO team at an ECMO center. Each patient should be assessed on an individual basis, preferably by two ECMO specialists for initiation of ECMO. This referral gives an opportunity for a multispeciality, team-based approach delivering high-quality therapies coupled with the necessary logistics for streamlining care.

Patients who are eligible for ECMO but clinically unstable, precariously supported by intensive care salvage therapies are at risk for deterioration during conventional transport. The referral gives an opportunity to consider early initiation of ECMO in the referring center to ensure safer transport.

Advent of ECMO has given a ray of hope to patients not responding to conventional therapies. There is an ardent need to strengthen the referral pathways in our country to broaden our reach and maximize therapeutic benefits to our patients.

REFERENCES

1. Bartlett RH. Physiology of Gas Exchange During ECMO for Respiratory Failure. J Intensive Care Med. 2017;32(4):243-8.
2. Bartlett R, Conrad S: The Physiology of Extracorporeal Life Support. In: Brogan TV, Lequier L, Lorusso R, MacLaren G, Peek G (Eds). Extracorporeal Life Support: The ELSO Red Book, 5th edition. Ann Arbor, Michigan: Extracorporeal Life Support Organization; 2017. pp. 31-47.

3. Zapol WM, Snider MT, Hill JD, Fallat RJ, Bartlett RH, Edmunds LH, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. JAMA. 1979;242(20):2193-6.
4. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. 2009;374(9698):1351-63.
5. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med. 2018;378:1965-75.
6. Aoyama H, Uchida K, Aoyama K, Pechlivanoglou P, Englesakis M, Yamada Y, et al. Assessment of Therapeutic Interventions and Lung Protective Ventilation in Patients With Moderate to Severe Acute Respiratory Distress Syndrome: A Systematic Review and Network Meta-analysis. JAMA Netw Open. 2019;2(7):e198116.
7. Camporota L, Meadows C, Ledot S, Scott I, Harvey C, Garcia M, et al. NHS England ECMO Service. Consensus on the referral and admission of patients with severe respiratory failure to the NHS ECMO service. Lancet Respir Med. 2021;9(2):e16-7.
8. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis. 1988;138(3):720-3.
9. Extracorporeal Life Support Organization. (2017). Guidelines for Adults Respiratory Failure. [online] Available from https://www.elso.org/Portals/0/ELSO%20Guidelines%20For%20Adult%20Respiratory%20Failure%201_4.pdf. [Last accessed March, 2022].
10. Church S, Rogers E, Rockwood K, Theou O. A scoping review of the Clinical Frailty Scale. BMC Geriatr. 2020;20(1):393.
11. Schmidt M, Bailey M, Sheldrake J, Hodgson C, Aubron C, Rycus PT, et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. Am J Respir Crit Care Med. 2014;189(11):1374-82.
12. Napp LC, Kühn C, Bauersachs J. ECMO in cardiac arrest and cardiogenic shock. Herz. 2017;42(1):27-44.
13. Banga S, Challa A, Patel AR, Singh S, Emani VK. The Patient Selection Criteria for Veno-arterial Extracorporeal Mechanical Oxygenation. Cureus. 2019;11(9):e5709.
14. Richardson ASC, Tonna JE, Nanjayya V, Nixon P, Abrams DC, Raman L, et al. Extracorporeal Cardiopulmonary Resuscitation in Adults. Interim Guideline Consensus Statement From the Extracorporeal Life Support Organization. ASAIO J. 2021;67(3):221-8.
15. Goto T, Morita S, Kitamura T, Natsukawa T, Sawano H, Hayashi Y, et al. Impact of extracorporeal cardiopulmonary resuscitation on outcomes of elderly patients who had out-of-hospital cardiac arrests: a single-centre retrospective analysis. BMJ Open. 2018;8(5):e019811.
16. Lorusso R, Whitman G, Milojevic M, Raffa G, McMullan DM, Boeken U, et al. 2020 EACTS/ELSO/STS/AATS expert consensus on post-cardiotomy extracorporeal life support in adult patients. ASAIO J. 2021;67:e1-43.

CHAPTER 118

Transport with ECS

Deepak Govil, Praveen Kumar, Vivek Kakar

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) or extracorporeal life support (ECLS) is an accepted lifesaving therapy for refractory respiratory and cardiac failure. Akin to many other advanced therapies, ECMO is resource intensive and requires high level of expertise. Thus, it has been suggested to consolidate the therapy only to high-volume centers to improve outcomes and also for better utilization of resources. Many countries have dedicated and limited centers for ECMO, necessitating frequent transport of critically ill patients.

Patients with severe respiratory or cardiac failure might be too unstable to be transported without a mechanical support and placing the patient on ECLS before initiating the transfer is now deemed feasible and safer method of transport for such unstable patients. The first inter facility transport of patient on ECLS dates back to 1975 by Bartlett and his colleagues. With constant advancements in the technology, the therapy has become as compact as ventilators and thus facilitating safe transport of such patients for longest of distances.[1]

Transport of patients with ECMO has been defined into two different categories.[2] Primary transport involves assessment, cannulation and initiation of ECMO in the referring facility, followed by transport to the ECMO center. Secondary transport involves transport of patients who are already on ECMO at the referring facility. This method of secondary transport was popularized by Combes et al. where ECMO cannulation and initiation is done by a peripheral hospital (spoke) and then referred to the high volume ECMO center (hub), and this is famed as Hub and Spoke model.[3] Facilities with capabilities of primary transport are generally well equipped to do secondary transports and hence we would restrict our discussion to primary transport of patients with ECLS.

Primary ECMO transport can be divided into various parts **(Table 1)**. Time is the essence with the project of primary transport, especially for patients referred for veno-arterial ECMO for cardiogenic shock as irreversible multiorgan failure can rapidly set in and thus ECMO might become futile.

EXTRACORPOREAL MEMBRANE OXYGENATION TEAM

Hospitals providing primary transport should have dedicated teams. As time is of extreme importance, the team should be mobilized similar to code or stroke teams in the hospital. The composition of transport team for primary transport differs in various institutes. The core team should contain two physicians trained in ECMO cannulation and management, one perfusionist, critical care transport nurse, and an ambulance paramedic. Various institutes have different other team members such as separate cannulation physician or surgeon, separate ECMO physician, scrub nurse, respiratory therapist extending to 10–15 member teams, but the core team remains the same.[1,2,4] Larger the team, difficult are the logistics to assemble in quick time, transfer to the referring facility needs larger movement vehicles. Hence, the entire

TABLE 1: Primary transport of extracorporeal membrane oxygenation (EMCO) patients.

Step 1	• Activation of mobile ECMO team • Mobilization and transport of personnel and equipment to the referring facility
Step 2	• Final assessment of patient for suitability of ECMO • Decision on ECMO configuration • ECMO cannulation, initiation, and stabilization
Step 3	Safe transport of patient to the ECMO center

team should be adroit in management of patient on ECMO, in additional to ventilator, infusions, anticoagulation, and monitoring enroute.

TRANSPORT PROTOCOL AND EQUIPMENT

The transportation process should be initiated immediately after the patient has been accepted for primary transport. This includes mobilization of team, equipment, and vehicles for transport. In our center, we send a standard checklist to the referring facility to determine the medical support the patient currently is on, resources available for a complex procedure, and also request for consent and availability of two units of red blood cells available for the procedure. The contents in the checklist are enumerated in **Box 1**. All the necessary supplies lacking at the referring facility need to be added with the equipment.

Few centers have dedicated equipment for transport purposes and not used for in-hospital support of patients.[5] Economic viability of such models is feasible only in extremely high-volume centers. Constant set of equipment and medical supplies need to be arranged and carried by the ECMO team. A checklist-based verification should be done every time before transport **(Box 2)**. This is dedicated to ECMO-related equipment and should be done in addition to the standard checks for critical care transport of any patient.

It is extremely critical for the ECMO team to reach the referring facility in time to initiate ECMO cannulation, as the patient may deteriorate before the arrival of the team. After initiation of ECMO, first and foremost priority is stabilization of the patient before return transport. This might prolong the ground time at the referring facility and the team should be prepared with additional doses of medications and extra equipment, refreshments if necessitate.

BOX 1: Prototype checklist to the referring facility.

- *Current medical support*—especially vasopressors, inotropes, and sedative hypnotics
- *Nature of invasive lines*—if the patient has invasive lines in the right internal jugular vein, femoral artery, and veins, request to secure another arterial and venous access for medical infusions and monitoring. The existing lines in the right jugular and femoral vein/artery should not be removed.
- *Availability of equipment*:
  - Ultrasound machine with linear and echocardiography probe
  - Activated clotting time (ACT) machine
- Cross match and arrange two units of packed red cells
- Consent to be signed by the next of the kin
- To create extra space around the bed for cannulation (only if safely possible)
- Medical summary of the patient and all imaging reports (including the images) should be loaded in a removal disk to be handed over

Transport Vehicle

Transport of patients with ECMO can be safely accomplished by road and air. Depending on the distance and urgency, a helicopter, fixed wing aircraft, or a road ambulance can be used for the transport **(Table 2)**. Aeromedical transport of patients will also depend on the weather conditions and if or not the helicopter has the ability to fly in adverse weather conditions. Extracorporeal life support organization (ELSO) has recommended transport by ground ambulance for a distance up to 400 km (250–300 miles), use of helicopter for a distance up to 650 km (300–400 miles) and fixed wing aircrafts for distances beyond them.[2] Few reports of transport through commercial airlines exist, but it is not the routine mode of transport.

Hospitals equipped with helipads may also prefer helicopters for shorter distance, especially for urgent ECMO cannulations. Transport by fixed wing aircrafts, involves to-and-fro movement from the hospital to the airports by either ground ambulance or helicopters, and thus involving multiple points of handling of patient and equipment, and often involve multiple personnel inadequately trained in handling such critically ill patients. Thus, transport by fixed wing aircrafts is more complex and needs experienced teams and coordination. In most of the situations, the same vehicle is used to transport the team to the referring facility and back with the patient to the ECMO center. Institutions using large transport teams for primary transport might need multiple vehicles to transport the personnel, equipment, and the patient.

BOX 2: Extracorporeal membrane oxygenation (ECMO) transport: equipment checklist.

- Centrifugal pump and a console
- Emergency pump for hand cranking
- Primed ECMO circuit—connected to the machine
- Additional ECMO circuit
- *Cannulas*: Venous cannula 55 cm and 28 cm (sizes 21–29 Fr) and arterial cannulas 15 cm (sizes 15–21 Fr). Preferably two sets
- J tipped guidewires—150, 180, and 250 cm
- Percutaneous insertion kits with step vessel dilators from size 8 Fr till 26 Fr
- Sterile surgical instruments set
- Drapes, including whole body drapes
- Other instruments necessary for cannulation: Chlorhexidine, sutures, sterile dressings, ECMO fixators, and connectors
- Additional sets of clamps and scissors
- Extra oxygen cylinder (additional to the existing one on ECMO console and other ones in the transport vehicle)
- Portable USG/Echo machine, with probe covers
- Infusion pumps with all medical infusions, the patient is currently on
- Portable ventilator and monitor compatible with invasive hemodynamic monitoring

TABLE 2: Transport vehicles for extracorporeal membrane oxygenation (ECMO) transport.[2]

Properties	*Road/ground ambulance*	*Helicopter*	*Fixed wing aircraft*
Distance	400 km (250–300 miles)	650 km (300–400 miles)	Any distance
Team	4–5 members	Smaller team needed (3–4 members), including flight paramedic	Larger teams depending on the size of aircraft
Noise	Limited noise	Extremely noisy needing ear protection	Less noisy when compared to helicopter
Loading of equipment and patient	Easy	Easy, but space limitation	Relatively difficult, needs a ramp for easy loading and also the entry point into the aircraft in narrow on fixed wing air crafts
Cost	Less	Expensive	Expensive

The stretcher on the transport vehicle should be modified to accommodate all the equipment. A base platform can be created and attached over the foot end of the stretcher. The ECMO machine and ventilator both can be anchored to the stretcher based on the weight the stretcher can accommodate.

Environment Situations

Extreme rain, wind, ice, and snow can affect safe transport. Ground transport of patients is less affected by weather conditions. Air transport is frequently affected by adverse weather conditions. The assessment for the appropriateness of weather conditions for flying should exclusively be made by the pilot and the medical team should not be part of such discussions. Flights and helicopters capable of flying in instrument flight rule conditions, need to take off from the airports and hence not suitable for hospital-to-hospital transport. Transport of patients in cold environment is challenging and patients on ECMO are prone for severe hypothermia. The polyester blankets used in ambulances are less effective in maintain normothermia, especially in windy conditions and vapor barrier and insulation should be used to minimize hypothermia.[6]

Long Distance International and Intercontinental Transports

International transfer of patients has now become feasible. The team should be aware of electric socket and gas outlet configuration of the country they are set out to. It is best to ask the referring facility to send photographs of the same, so understanding prevails if or not the additional equipment is needed. Also, the team should be carrying passports, visa documents, additional refreshments, and local currencies to be prepared for unforeseen delays. If the space in the transport aircraft permits, carrying additional ECMO trained personnel should be considered.

BOX 3: Complications during extracorporeal membrane oxygenation (ECMO) transport.

Specific to EMCO:
- Bleeding from cannulation site
- Circuit dislodgment or accidental decannulation
- Circuit rupture
- Pump head thrombosis
- Oxygenator failure
- Battery loss
- Inadequate circuit flow
- Hypothermia

Other complications:
- Cardiac arrest
- Hemodynamic instability
- Loss of gas supply
- Landing in wrong airport/destination, accidents of transport vehicles

COMPLICATIONS

With high-volume centers the complications are extremely low, albeit present **(Box 3)**. Mortality has been reported during transport and one center has reported two deaths in 20-year period.[7] Close to 6.2% of transports have been reported to have been complicated by adverse events.[8] Bleeding is the most common ECMO-related complication reported.[8] Other complications such as circuit rupture, dislodgment of cannulas, pump thrombosis is infrequent, but the team should be prepared for as replacing cannulas and connecting another circuit is extremely exhausting and needs intense experience and stability. Other complications such as socket failure, oxygen supply failures, battery loss leading hand cranking for long durations can occur.[4,7]

CONCLUSION

Transport of patients on ECMO is safe and feasible. The ECMO team should be masterly competent in all aspects of transport, including ECMO physiology, cannulation and machine, should be experienced in all aspects of intensive care medicine, transport of critically ill patient, and also adroit in dynamics of air transport.

REFERENCES

1. Broman LM, Holzgraefe B, Palmér K, Frenckner B. The Stockholm experience: Interhospital transports on extracorporeal membrane oxygenation. Crit Care. 2015;19(1): 6-11.
2. Brechot N, Fan E, Pellegrino V, Brodie D. ELSO Guidelines for ECMO Transport. ELSO. 2015;(May 2015):1-6.
3. Broman LM. Inter-hospital transports on extracorporeal membrane oxygenation in different health-care systems. J Thorac Dis. 2017;9(9):3425-9.
4. Coppola CP, Tyree M, Larry K, DiGeronimo R. A 22-year experience in global transport extracorporeal membrane oxygenation. J Pediatr Surg. 2008;43(1):46-52.
5. Broman LM, Dirnberger DR, Malfertheiner MV, Aokage T, Morberg P, Næsheim T, et al. International Survey on Extracorporeal Membrane Oxygenation Transport. ASAIO J. 2020;66(2):214-25.
6. Haverkamp FJC, Giesbrecht GG, Tan ECTH. The prehospital management of hypothermia—An up-to-date overview. Injury. 2018;49(2):149-64.
7. Bryner B, Cooley E, Copenhaver W, Brierley K, Teman N, Landis D, et al. Two decades' experience with interfacility transport on extracorporeal membrane oxygenation. Ann Thorac Surg. 2014;98(4):1363-70.
8. Broman LM, Frenckner B. Transportation of critically ill patients on extracorporeal membrane oxygenation. Front Pediatr. 2016;4:4:63.

CHAPTER 119

Death Declaration in Patients on ECS

Sanjay Nihalani, Kalpana Krishnareddy, Hossam Elshekhali

INTRODUCTION

Brain death in most countries is determined using neurological criteria and apnea test. Ancillary tests are used in cases where complete neurological examination or apnea test cannot be done. However, there is significant variability in testing for brain death between different countries with some countries using only neurological criteria with apnea test to diagnose while others require ancillary test also to confirm. In addition, there is variability in testing with regards to the number of physicians required, timing between first and second tests and the type of ancillary tests used. In extracorporeal life support (ECLS/ECS), brainstem testing is further complicated by the physiology of ECLS (affecting CO_2) and pharmacokinetic changes affected by the circuit.

DIAGNOSIS OF DEATH USING NEUROLOGICAL CRITERIA

Brain death is defined as irreversible cessation of all functions of the brain including brainstem. Brain death declaration requires presence of irreversible coma of a known etiology, absence of all brainstem reflexes and presence of a positive apnea test. The prerequisites for performing apnea test include: core temperature ≥ 36°C, systolic BP > 90 mm Hg, absence of the effect of sedative or paralyzing agents, severe electrolyte, and acid-base disturbances.[1] *Normally apnea test is considered positive if there is rise in $PaCO_2$ ≥ 60 mm Hg or at least 20 mm Hg rise above baseline and absence of spontaneous breathing.* Apnea test is considered negative if there is an observed respiratory movement either seen during the test or detected by ventilator. Occasionally, *self-cycling* of the ventilator may falsely suggest presence of spontaneous respiratory efforts. In this case, increasing the flow trigger or changing it to pressure trigger removes this artifact. Apnea test is abandoned in cases where patient becomes hemodynamically unstable or hypoxic. In patients where apnea test cannot be performed, ancillary tests for confirming brain death are required. Although brain death is a clinical diagnosis, many countries use ancillary tests routinely as required by law.

CHALLENGES OF BRAINSTEM TESTING ON EXTRACORPOREAL MEMBRANE OXYGENATION

Extracorporeal membrane oxygenation (ECMO) is an ECLS system that supports heart and lungs in patients with reversible cause of refractory cardiac and respiratory failure as a bridge to destination (recovery, transplant). *ECLS and ECMO are terms that are often used synonymously* have rapidly expanded across the world since 2009 following H1N1 pandemic. Indications for its use continue to expand including use of ECLS during cardiopulmonary resuscitation. Neurological complications resulting in brain death is not uncommon in patients on ECLS. Occurrence of ischemic stroke, intracerebral hemorrhage or hypoxic brain injury has been well reported. Increasing use of extracorporeal cardiopulmonary resuscitation (ECPR), other expanding indications, and use of anticoagulation all increase the risk of neurological injury and subsequent brain death. These neurological injuries may be due to preexisting neurological disease, hypoperfusion of brain due to deranged cerebral autoregulation, reperfusion injury postresuscitation, microemboli, thrombosis, rapid changes in blood gas, and intracranial bleed due to development of coagulopathy or anticoagulant use and Harlequin syndrome (differential hypoxia-induced cerebral dysfunction) in the case of peripheral veno-arterial (VA) ECMO.

Extracorporeal membrane oxygenation can impact testing of brainstem function and apnea test in two ways. Firstly, pharmacokinetic changes can occur due to sequestration of drugs in particular sedatives and opiates; and secondly, ECMO physiology with CO_2 exchange across the membrane may affect the performance of the apnea test.[2]

PHARMACOKINETIC CHANGES ON EXTRACORPOREAL MEMBRANE OXYGENATION

Extracorporeal membrane oxygenation circuit affects serum concentration of drugs, through adsorption and absorption, leading to change in kinetics, mainly clearance. It is also been described that some drugs including sedatives and

potentially muscle relaxants is released from the membrane into the circulation of the patient even after discontinuation and therefore increasing their effective half-life. This will affect in establishing the reversible causes of coma and even apnea test. In the event, where there is a doubt that drugs may be affecting unconscious state, apnea, and absent brainstem reflexes, specific drug levels should be requested or other interventions such as administration of a reversal agent and/or train of four can be done to check for reversibility of some sedatives and for residual paralysis where appropriate.

The elimination half-lives of sedative drugs should be taken into consideration before a formal neurological examination. The commonly used agents in the intensive care unit (ICU) with their elimination half-lives are mentioned in **Table 1**.[3] *When drug effect suspected-drug level should be sent and wait for 4–5 half-lives of the offending drug to be eliminated.*

APNEA TESTING

Unlike patients on mechanical ventilation, gas exchange for patients supported on ECMO occurs mainly through the membrane oxygenator. Carbon dioxide elimination is dependent on the sweep gas flow rate in the circuit. Extracorporeal removal of CO_2 must be taken into consideration when performing apnea testing on ECMO, and sweep gas flow titrated slowly to prevent large acute changes in cerebral $PaCO_2$.

Different ECMO types [veno-venous (VV), VA, or hybrid modes] have different effects on oxygen and carbon dioxide levels to which the brainstem is exposed and this in turn affects the apnea test. In VV ECMO, ECMO blood flow is in series with the patient's circulation whereby blood is drawn from either the femoral or internal jugular vein and the fully oxygenated and decarboxylated blood is returned to the right atrium. In the right heart, the blood mixes with indigenous venous blood which then passes through the lungs where further gas exchange may occur depending on the function of diseased lung and this in turn enters into the systemic circulation. Hence, the arterial blood gas levels will be same at any of the arterial sampling sites in a patient. Therefore, the change in CO_2 partial pressure measured at any arterial site is the correct reflection of the CO_2 to which the brainstem is exposed.[2]

TABLE 1: Elimination half-lives of commonly used sedative and narcotic agents in the intensive care unit.

Drug	*Elimination half-life*
Midazolam	2–4 hours
Propofol	30–90 minutes
Fentanyl	219 minutes
Morphine	170 minutes

In VA ECMO, ECMO blood flow is in parallel with the systemic circulation whereby blood is drawn from the femoral or internal jugular vein and the highly oxygenated and decarboxylated blood is returned into the artery (usually femoral artery in case of peripheral and directly into the aorta in case of central ECMO). In patients with peripheral VA ECMO the $PaCO_2$ level in the cerebral circulation may be different from the $PaCO_2$ in some systemic arterial sampling sites due to the variable location of a mixing point of blood between indigenous pulmonary-cardiac blood flow and ECMO circuit blood flow in the aorta. Therefore, to be sure that blood gas measurements must be taken from multiple sites (including post-membrane and systemic arterial sites furthest from the ECMO return flow) and $PaCO_2$ levels taken from various sites should be checked when assessing the absence of neurological responses. In case of VA or hybrid veno-veno-arterial (VVA) ECMO both right arm and femoral blood samples need to be checked to see difference in measurement in the systemic blood gas. The site most distal to the return arterial flow should show a minimum rise in pCO_2 of at least 3.75 mm Hg (0.5 kPa) from baseline in order to confirm the diagnosis.[4]

When it comes to testing for brain death in patients on VA or VV ECMO, clinical criteria would remain the same but clinicians need to bear in mind the impact of ECMO circuit on the pharmacokinetics of certain sedatives and challenges associated with apnea testing.[4] In the event where brainstem reflexes cannot be tested or inconclusive, ancillary tests should be obtained as per local guidelines. It is important to seek guidance from a neurologist or a neurointensivist when ancillary tests are required.

Steps for Apnea Testing on Extracorporeal Membrane Oxygenation

Testing can be done with any of ECMO circuit types (VV, VA, or hybrid VVA).[4]

- Set the sweep gas FiO_2 at 1.0.
- Increase the sweep gas flow rate to maximum transiently and then decrease again to "sigh" the oxygenator membrane and remove condensation.
- The blood flow on ECMO should be adjusted to ensure PaO_2 > 75 mm Hg (10 kPa) when sampling any site.
- Airway should be suctioned to ensure patency and clear of secretions.
- A recruitment maneuver may need to be performed to improve gas exchange in lungs.
- Obtain a baseline arterial blood gas (ABG) from all sites described above and then decrease the sweep gas flow rate by 0.5 L/min every 5 minutes. Blood gases should be taken every 5 minutes until the $PaCO_2$ is ≥45 mm Hg (6.0 kPa) and initial pH < 7.4 or H^+ > 40 nmol/L. In patients where bicarbonate is increased, $PaCO_2$ may need to be adjusted further to reach the desired pH.

The sweep gas flow rate should not be decreased below 0.5 L/min (essential for avoiding hypoxia).

- Disconnect the ventilator and connect Mapleson C circuit with inline $EtCO_2$ monitoring and adjust valve to give approximately continuous positive airway pressure (CPAP) of 10 cm H_2O to the lungs.
- Decrease the sweep gas flow rate by 0.5 L/min every 5 minutes and do an ABG every 5 minutes till all measured *$PaCO_2$ values have increased by at least 3.75 mm Hg (0.5 kPa) above the initial level*. The sweep gas flow rate should not be decreased below 0.5 L/min.
- Observe for any evidence of spontaneous breathing in the form of chest rise, evidence of spontaneous breathing on $EtCO_2$ monitor and/or movement of the reservoir bag of circuit. This has to be done for a minimum of 5 minutes.
- Stop the test if there is significant hypoxia or hemodynamic instability, if respiratory effort is seen or if adequate increase in $PaCO_2$ is not there.

Strategies to Increase CO_2 for Apnea Test

In order to increase CO_2 for apnea test, sweep gas flow on ECMO is decreased to a minimum of 0.5–1 L/min. Other methods that have been used to increase CO_2 levels during apnea test include addition of gas mixture containing 3% CO_2 and 97% O_2 (carbogen) through the ventilator or CO_2 directly into the ECMO circuit.[5] Madden et al. conducted a retrospective review of apnea tests using the carbogen for brain death determination on 5 subjects on ECMO and found that in all 5 cases, the carbogen resulted in rise of CO_2 to the desired target level with 100% accuracy and apnea testing was done with no adverse effects.[6]

CHALLENGES WITH ANCILLARY TESTS

In a large meta-analysis, apnea test could confirm brain death in 78% patients on ECMO.[7] In the rest it failed due to development of hypoxia, hemodynamic instability, or absence of appropriate increase in CO_2. In the event where clinical examination or apnea test cannot be performed, ancillary tests are required. Ancillary tests falls into two categories, one which checks cerebral blood flow and other which checks the bioelectric activity. The former involves angiograms done by conventional method which is cerebral angiography and remains the gold standard or by computed tomography (CT) scan, magnetic resonance imaging (MRI), transcranial Doppler (TCD), and nuclear studies. The bioelectric activity methods include electroencephalography (EEG) and evoked potentials. The meta-analysis showed the use of EEG in 62% cases followed by CT angiogram in 22% cases and TCD in 6% of cases.[7]

The CT angiogram should show absence of blood flow in internal carotid and vertebral arteries to confirm brain death. EEG showing absence of nonartifactual electrical activity of at least 2 μV from baseline for more than half an hour is supportive of brain death. In addition, CT scan may show other reasons of neurological deterioration such as large intracranial bleed with raised intracranial pressure and midline shift. EEG and evoked potentials are affected by sedatives, hypo- or hyperthermia, metabolic derangement, and other local electrical interferences. Also, these tests are often challenging as it involves shifting unstable patients to CT or MRI room and MRI incompatible ECMO circuits.

CONCLUSION

The use of ECMO has been increasing to support critically ill patients, physicians should be familiar with the physiology and pharmacokinetic changes and the impact, it will have on determination of brain death. In ECMO, CO_2 clearance is mainly dependent on the sweep gas flow rate through the oxygenator rather than the mechanical ventilator. The criteria for brainstem testing in patients on ECS are the same as for non-ECS patients with some adaptations for apnea testing in particular adjusting sweep flow to obtain target CO_2 levels as described above. Each unit should have a standardized approach for apnea testing in this patient group to help make timely diagnosis of brain death. This will aid in decision of appropriate withdrawal of ECMO support or facilitation of organ donation. Ancillary tests should be used to confirm brain death when apnea test is not possible.

REFERENCES

1. Kollef MH, Isakow W, Burks AC, Despotovic VN (Eds). The Washington Manual of Critical Care, 3rd edition. Philadelphia: Wolters Kluwer; 2018.
2. Meadows CIS, Toolan M, Slack A. Diagnosis of death using neurological criteria in adult patients on extracorporeal membrane oxygenation: Development of UK guidance. J Intensive Care Soc. 2020;21(1):28-32.
3. Fassoulaki A, Theodoraki K, Melemeni A. Pharmacology of Sedation Agents and Reversal Agents. Digestion. 2010;82: 80-3.
4. The Faculty of intensive Care Medicine. (2018). Supplementary Guidance for the Diagnosis of Death using Neurological Criteria when the patient is supported with extracorporeal membrane oxygenation (ECMO). [online]. Available from: https://www.ficm.ac.uk/standards-and-guidelines/access-standards-and-guidelines [Last accessed December, 2021].
5. Sahu M, Vaswani P, Bipin C, Singh SP, Hadda V. Enigma of apnea test for brain death on ECMO—an ongoing discussion—case study and review of literature. Indian J Thorac Cardiovasc Surg. 2020;37(2):1-4.
6. Madden M, Andrews P, Rector R, Menaker J, Habashi N. Carbogen for Apnea Testing During the Brain Death Declaration Process in Subjects on Extracorporeal Membrane Oxygenation. Respir Care. 2020;65(1):75-81.
7. Migdady I, Stephens RS, Price C, Geocadin RG, Whitman G, Cho SM. The use of apnea test and brain death determination in patients on extracorporeal membrane oxygenation: A systematic review. J Thorac Cardiovasc Surg. 2021;162(3):867-77.

SECTION 21

Data Science and Artificial Intelligence

CHAPTER 120

Artificial Intelligence and Data Science in Critical Care

Aditya Nagori, Ridam Pal, Tavpritesh Sethi

INTRODUCTION

Modern healthcare systems are digitizing at an unprecedented rate.[1] More hospitals are now enabled with electronic record systems and data that can assist medical staff in making decisions for patient care. This rapid digitalization has exponentiated the growth of data science and artificial intelligence (AI) applications in healthcare.[2] Within hospitals, intensive care units (ICUs) generate dense monitoring data where patients are digitally monitored on a minute-to-minute basis. Data science has been famously described by Drew Conway to lie at the intersection of three complementary skills: (1) domain knowledge, (2) programming, and (3) mathematics/statistics **(Fig. 1)**. It is an interdisciplinary science of principled knowledge extraction from complex structured and unstructured data whereas AI helps in data-driven decision making such as classification of critical and noncritical condition tasks.

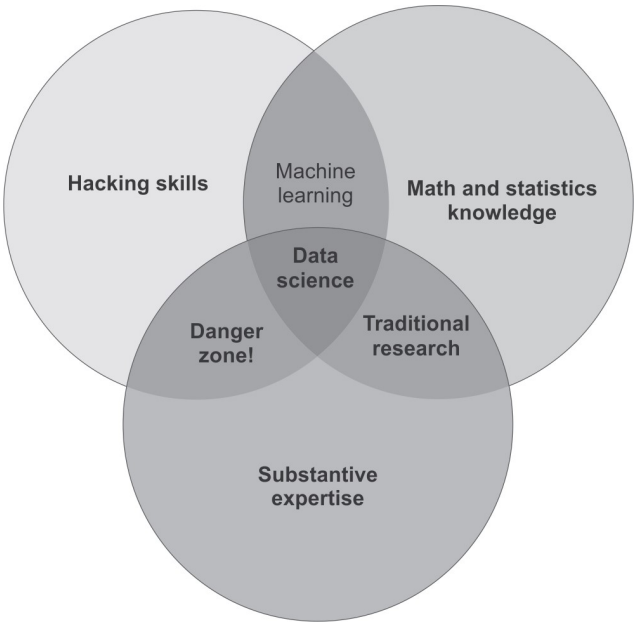


Fig. 1: Drew Conway's diagram for data science. *Hacking* is meant as in the original nonmalicious sense, i.e., the ability to tinker with code. *Substantive expertise* refers to domain knowledge, e.g., the understanding of critical care medicine. *Mathematics* and *statistics* are key components of data science, which in combination with coding have led to the expansive field of machine learning.
Source: The Data Science Venn Diagram—Drew Conway (2010). (Figure reproduced under the Creative Commons Noncommercial License available from Drew Conway's webpage)

ARTIFICIAL INTELLIGENCE

Artificial intelligence, on the other hand, is the fastest-growing branch of computer science and is considered as an *umbrella* term for a variety of algorithms including rule-based systems, statistical modeling, machine learning, natural language processing, and optimization. AI has the promise and potential to generate early and subtle decisions by learning to recognize patterns in a complex multivariate system. These early decisions can mitigate the dire consequences of delayed identification in critical care settings.[3]

Taken together, data science and AI algorithms are revolutionizing the decision-making process in ICUs and current advances are focusing on ensuring patient safety, aid diagnostic support, clinical management, administration, and cost containment.[4] This chapter describes the applications of data science and AI in ICUs on the basis of clinical use cases, data approaches, machine learning approaches, and data types. We also discuss the opportunities, challenges and limitations of data science and AI in ICUs and a roadmap for the adoption of these technologies.

DATA SOURCES IN THE INTENSIVE CARE UNIT

Intensive care units are the most data-rich environments in any hospital with continuous monitoring devices for assessment of patients and routine intervention devices such as infusion pumps, ventilators, resuscitation devices right at the bedside. *Physiological vital information* gets routinely measured by the sensors and displayed on monitors for clinicians to analyze and make decisions.

TABLE 1: Multitude of data sources and their subtypes in an ICU.

Types of data	*Subtypes*
Bedside monitoring	Physiological vital signs, wave-form, alarms, events, ventilator
Blood test	Biochemistry, metabolomics, microbiology, blood gases
Chart	Fluid administration, drug dosage, progress reports, bedside examinations, respiratory care (ventilator)
Imaging	Radiology (X-ray, CT, MRI, ultrasound), echocardiography, pathology)
Text data	Treatment notes, doctor's notes, nurse notes, discharge summaries
Molecular marker	Microarray, microbiota, cytokines profile
Diagnosis	Billing diagnosis, clinician's assessment, clinical score, subphenotypes
Prescriptions/ interventions	Therapy, medications, procedures, surgery
Patient information	Demographics, history, admission discharge, transfer, family, social, and financial

(CT: computed tomography; ICU: intensive care unit; MRI: magnetic resonance imaging)

Further, bedside testing and examinations; blood and urine-based biochemical and microbiology-based biomarkers are routinely done in patients admitted to the ICU. Even more advanced tests such as *omics-based variables* and *microbiota information* are becoming more commonly available at the *ICU bedside with the availability of miniaturized technologies* **(Table 1)**. The variables generally can be classified as static features at the time of admission such as *demographics* and *comorbidities* whereas dynamic variables include data such as monitoring. Further, even the dynamic data are not available at the same sampling rate, i.e., frequency of recording. Together, this heterogeneity of temporal data availability poses specific challenges and solutions for data science and AI approaches for the ICU.

CLASSIFICATION OF DATA SCIENCE AND ARTIFICIAL INTELLIGENCE APPROACHES

In this chapter, we classify these approaches through the lens of complexity and types of algorithms. Further, specialized approaches have been developed to derive value from the heterogeneous types of data discussed in the previous section.

Classification by Complexity

The application of the data science and AI algorithms can be classified into three categories in increasing degree of complexity:

1. Descriptive
2. Predictive
3. Prescriptive

Descriptive

Descriptive analysis is a very important step to explore hypotheses and may be the most important step for gaining insights into developing AI models. Such approaches rely upon standard analyses that describe the statistical properties of data such as measures of central tendency, variability, and visualizations.

Predictive

These approaches are geared towards the development of early warning systems in the ICUs, This step often employs hypotheses generated from descriptive analyses along with domain understanding.[2] The extracted parameters can be used to create cohorts for different disease modeling. The *parameters* and *disease labels* can be used to train machine learning models for useful clinical decision-making. For example, Nemati et al. built an interpretable predictive model for sepsis prediction; they used a set of static and nonstatic features at 1 hour nonoverlapping bins' time-series. The model predicted sepsis with 4–12 hours ahead of onset with AUC 83–85%. Tóth et al. trained and tested a recurrent neural network model on 2.3 million admissions to predict the overnight patient stability with an AUC of 97% prospectively.[5] These examples highlight the pervasive use of AI and data science in ICU and their ability for bettering patient care.

Prescriptive

Prescriptive approaches rely upon discovering the best interventions for a given patient or a class of patients. These approaches generally rely upon the holy grail of machine learning and statistics, i.e., causal learning. *Learning interventions* involve the recommendations for the action that one can take in order to mitigate the risk of a given outcome. The approach makes use of the insights extracted from the descriptive and predictive approaches for making personalized or class-specific interventions. For example, Bertsimas et al. developed a model for specific recommendations to prevent readmissions in ICU.[6]

Classification Based Upon Algorithms

Machine learning (ML) algorithms fall into a subfield of AI which helps computers to learn to perform tasks without being explicitly coded. ML algorithms analyze datasets in a fast and efficient manner to harness patterns that can act as identifiable entities to make decisions. ML algorithms are capable of finding decision rules in multidimensional space by themselves.

We have curated the application data science and AI with respect to different machine learning approaches as follows:

Supervised Approach

A supervised machine learning approach involves learning the mapping between a set of predictors and known outcomes. The mapping is learned in a guided manner or with respect to the labels, for example, mortality prediction, readmission prediction are a few examples where supervised learning is applied. A suitable model is trained on data containing features for predicting known outcomes. Evaluation of the learned models is made through a test set where the prediction is made by the model and subsequently the model prediction is matched with the test outcomes for the accuracy evaluation.

Unsupervised Approach

Unsupervised algorithms do not make use of the known outcome variables; rather they help in finding clusters in the data based on distance matrix among the data points. The number of clusters representing the distribution is chosen based on the variability explained. An unsupervised approach is a potential tool to discover unknown subphenotypes of a disease condition. Identifying the subpopulation of intensive care syndromes is important as it will help better understand the pathophysiology and identify treatment targets.

Reinforcement Learning

The dynamic manifestation of disease conditions in ICU aids the complexity of their detection. Rule-based protocols may not work efficiently in this scenario of dynamic governing factors. Thus, algorithms that can take into account the temporal changes while learning the policies for intervention can aid clinical decision-making. Peine et al. used reinforcement learning (RL) to dynamically optimize the mechanical ventilation in critical care **(Fig. 2)**. The RL employs an agent who acts as the decision-maker; the agent makes use of the data under a certain environment to take

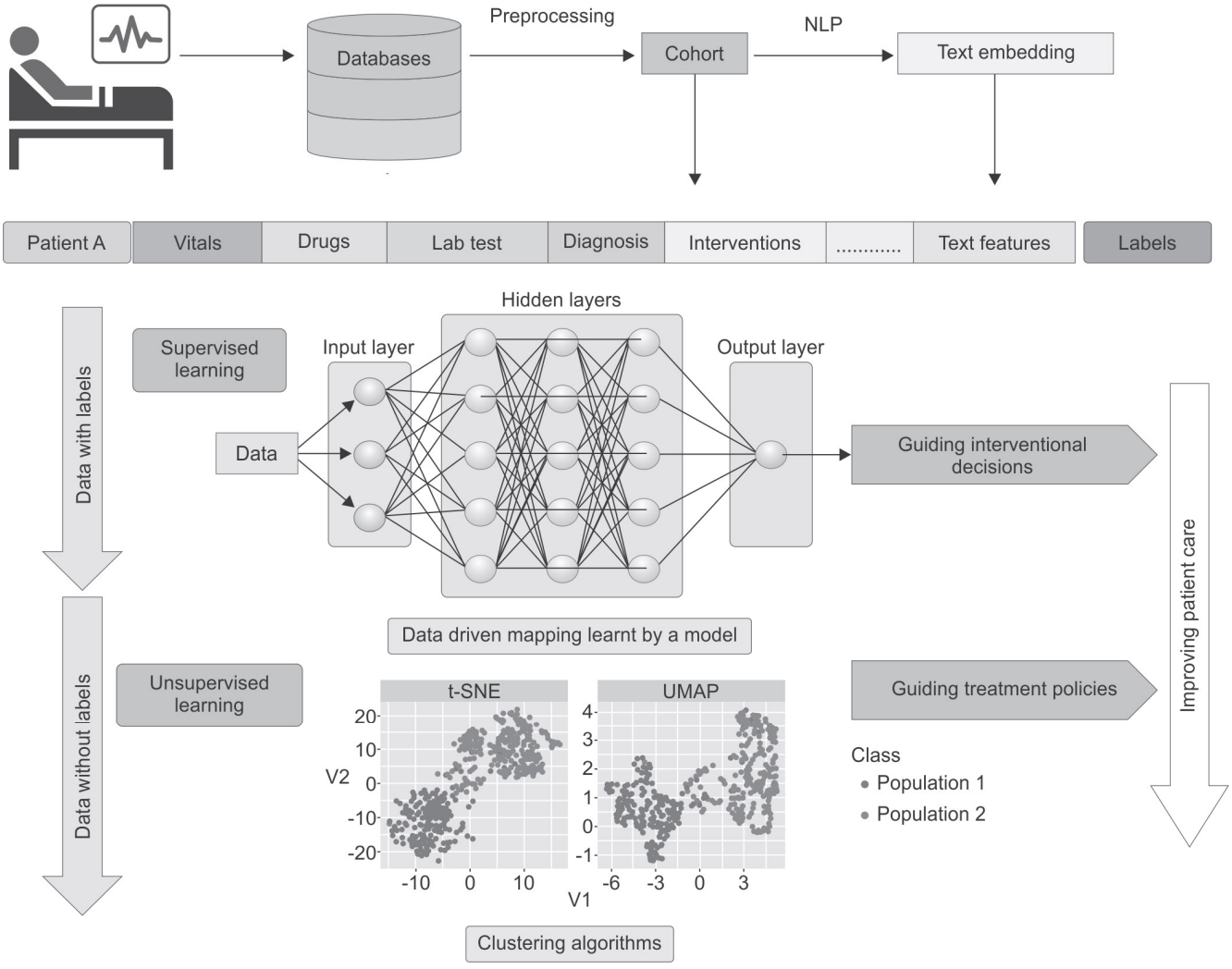


Fig. 2: A general road map of supervised and unsupervised learning in ICU. The ICU databases can be mined for useful data using data mining techniques; in particular natural language, processing algorithms can be used to extract crucial information from text notes. The extracted parameters can be used to create cohorts for different disease modeling. The parameters and disease labels can be used to train machine learning models for useful clinical decision making. (NLP: natural language processing; t-SNE: t-distributed stochastic neighbor embedding; UMAP: uniform manifold approximation and projection)

actions in order to optimize a reward scheme. The agent dynamically analyzes the feedback and improves the policy to optimize the process.[7] This decision-making process is called the *Markov decision process (MDP)* consisting of states representing the environment, action, transition probability, and reward function.[8-10] RL is a very useful technique in ICU; it has been used in optimal drug dosing,[11] the timing for ordering lab tests (Liu et al., 2020).

The parameter can also be used to perform clustering to discover the disease subphenotypes.

Natural Language Processing

Textual data are collated at regular intervals in the critical care setting in the form of treatment charts, physician's notes, nursing notes, discharge summaries, etc. These data are enriched with useful information which can guide to different features for predictive modeling **(Fig. 3)**. The data is substantially present in an unstructured form which needs to be mined/processed to extract useful information. Data preprocessing is a crucial step required for modeling textual data. This includes the removal of stopwords, punctuations, white spaces, tabs, and redundant words for preparing the corpus or input. Language models incorporate the latent semantic space in the form of vectors. Mikolov et al. first coined the idea Word2vec for efficient representation of these vectors using neural networks.[10] This was one of the preliminary language models, built using two-layered neural networks for efficient representation of words in the vector space. Various state-of-the-art (SOTA) language models such as BioBERT, ClinicalBERT, Bio-Clinical BERT[12,13] have been trained on the medical data to capture the attributes of semantic space for predictive modeling and classification. Bio-Clinical BERT has been trained on the discharge summary present in the MIMIC-III data.[14] The transformer models capture the importance of words based on the attention mechanism (provides different weights to inputs based on importance) present in the corpus. In recent decades, this has led to a surge in the development of similar bidirectional transformer models trained on medical corpus.

Clinical Use Cases

Intensive care units are equipped with several electronic sensors to monitor physiological parameters or vitals. These sensors generate a plethora of data that can be used for early warning models to create alarms. Patients under the care are also investigated for the blood gases, biochemical, and microbiological tests. These datasets can be integrated and can be used to research and develop early warning decision support systems. Following is the review of data science and AI algorithms used for diagnosis, monitoring, early prediction of prevalence ICU conditions, readmission, mortality, length of stay prediction tasks.

Early Detection of Critical Outcomes

Prevalent critical illnesses in ICU such as sepsis, shock, respiratory failure, acute kidney injury, multiorgan failure need to be prevented by providing early interventions. Early identification can alert the clinical management to provide early interventions to reduce the chances of secondary organ failure. The goal of clinical management, thus, remains to reduce the incidence of events. For example, Henry et al. reported models on the prediction of septic shock in ICU, and they created an

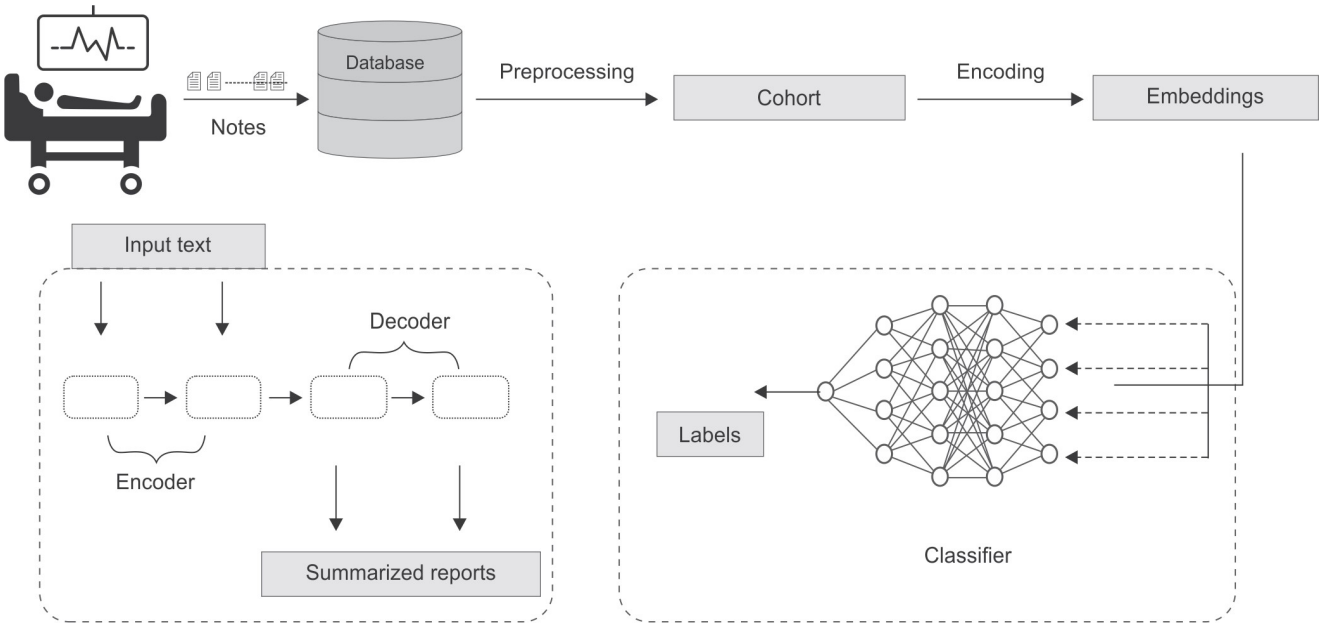


Fig. 3: A generic NLP architecture in a critical care setting for building classification models using textual data (treatment charts, physician's notes, nursing notes, discharge summaries). The other chunk shows how cohorts of data can be summarized into useful information using different kinds of summarization techniques. (NLP: natural language processing)

early warning score using machine learning models built on 54 clinical variables.[15] Hyland et al. used around 117 clinical variables to predict the circulatory shock in ICU. The studies have leveraged the integrated clinical data with state-of-the-art deep learning and machine learning model development for the early prediction of critical outcomes.

Image Classification in Intensive Care Unit

The imaging in ICU is usually done periodically for various different reasons. Intensive care unit-based imaging involves radiology (X-ray, MRI, CT, and ultrasound), echocardiography, and pathology. Radiology-related imaging such as X-ray, MRI, and CT are performed to detect the underlying conditions. Chest-X-rays are the most common imaging in the ICU. Convolutional neural network (CNN) is one of the most advanced techniques used for classification of these chest radiographs. Rajpurkar et al. developed a CNN-based algorithm to detect clinical abnormality in chest radiographs at the performance level of a practicing radiologist **(Fig. 4)**.[16] CNNs are the potential AI tools for image classification and have been reported to surpass practicing radiologists. MRI and CT are performed for comparatively more complex clinical scenarios. Ultrasound is emerging as the most promising technology as it does not require patients to move to another facility and perform seamless imaging for cardiological care at the bedside.

Mortality, Readmission, and Length of Stay

Mortality, readmission, and length of stay prediction are some of the most commonly sought-out questions in ICU setting. Prediction of mortality can help clinical management to prioritize patient care. Readmission is associated with high hospital mortality. Patients who are readmitted to ICU have a higher length of stay.[17] Thus, predicting the readmission is important for reducing mortality and reducing the length of stay. Data science and AI have played an important role in the accurate prediction of mortality, readmission, and LOS. Many studies have reported predicting readmission in ICU using application of data science and AI.[16,18,19] Rajkomar et al. used deep learning models to predict the in-house mortality across sites with AUC of 93–94% and prolonged LOS with an AUC of 85–86% outperforming the clinically used scores.[18] Thus, AI and data science approaches can predict mortality, readmission, and LOS surpassing the known classical methods.

OPPORTUNITIES, CHALLENGES, AND LIMITATIONS

Critical care is one the most important units of a hospital which ubiquitously generates a huge amount of patient data. The data comes from different modalities ranging from charts, signals, text to images. For the human brain to analyze this multidimensional data in real-time is difficult. Data science and AI have the potential to analyze, draw insights, predict, classify, augment and optimize the processes. These great abilities of data science and AI make it a demanding tool in ICU to aid decision making in ICU. The clinical data also poses opportunities for algorithm development and advancing the field of applied data science and AI.

A crucial challenge that resonates across the critical care setting is the contentment of loss of data. Data is produced in huge amounts, yet there has been a constant challenge to store that data. Big-data science approaches need to be incorporated in every healthcare setting for efficient management of storing these data. Integration of these architectures in the ICU setup stays to be an important concern.

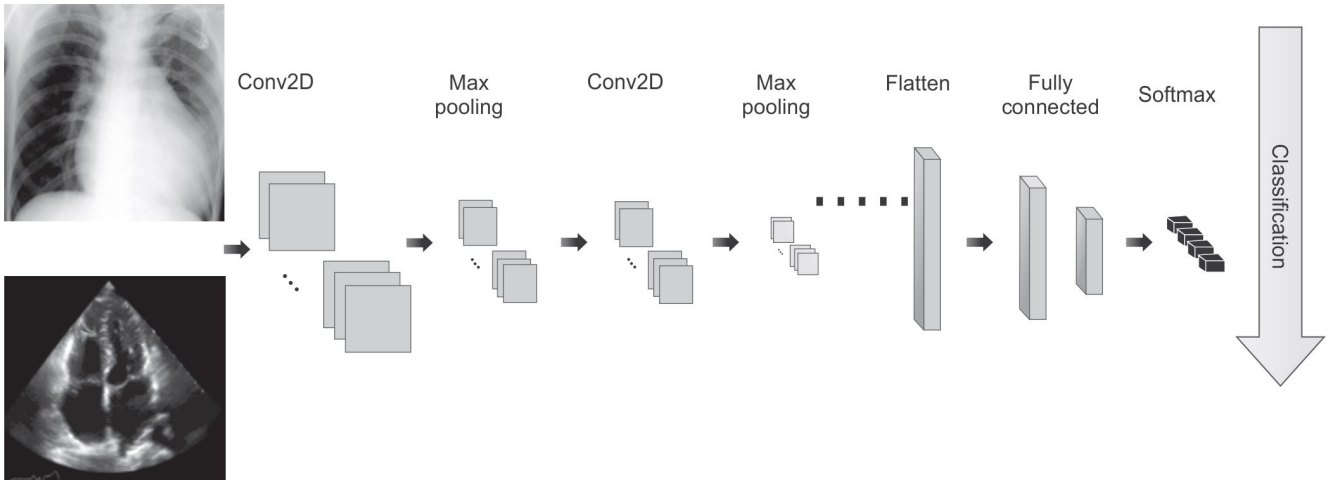


Fig. 4: Most common type of imaging in ICU involves X-rays and ultrasound, a figure showing an AI algorithm, i.e., convolutional neural network (CNN) is used to classify normal and abnormal chest X-rays and ultrasound images. The layers of CNN architecture shown in the figure extract the features from the images; these features get further refined in subsequent layers of the architecture which further helps in discriminating between the classes of images.

Privacy and security concerns are major issue that also needs to be acknowledged while sharing the data for data analysis and model development. However, federated learning and split learning techniques are finding their way to efficient model training without compromising the patient's privacy and data leakages.

Generalizability of models across different critical care poses an important question in the healthcare domain. A study by Tran et al. suggested that approximately 28 thousand papers were published from 2008 to 2018 related to AI in healthcare. Yet, rarely do we observe deployment of these models in healthcare. Most models have contributed to the research sphere but there has been a void while incorporating those techniques in real scenarios which has resulted in less prospective validation of models. The decision-making process should go through prospective validation which is still lacking in many research studies in the literature.[20]

REFERENCES

1. Meskó B, Drobni Z, Bényei É, Gergely B, Győrffy Z. Digital health is a cultural transformation of traditional healthcare. Mhealth. 2017;3:38.
2. Sanchez-Pinto LN, Luo Y, Churpek MM. Big Data and Data Science in Critical Care. Chest. 2018;154(5):1239-48.
3. Herget-Rosenthal S, Saner F, Chawla LS. Approach to Hemodynamic Shock and Vasopressors. Clin J Am Soc Nephrol. 2008;3(2):546-53.
4. Sutton RT, Pincock D, Baumgart DC, Sadowski DC, Fedorak RN, Kroeker KI. An overview of clinical decision support systems: benefits, risks, and strategies for success. NPJ Digit Med. 2020;3:17.
5. Tóth V, Meytlis M, Barnaby DP, Bock KR, Oppenheim MI, Al-Abed Y, et al. Let Sleeping Patients Lie, avoiding unnecessary overnight vitals monitoring using a clinically based deep-learning model. NPJ Digit Med. 2020;3:149.
6. Bertsimas D, Li ML, Paschalidis IC, Wang T. Prescriptive analytics for reducing 30-day hospital readmissions after general surgery. PLoS ONE. 2020;15(9):e0238118.
7. Montague PR. Reinforcement Learning: An Introduction by Sutton RS and Barto AG. Trends Cogn Sci. 1999;3(9):360.
8. Kristensen AR. Dynamic programming and Markov decision processes. Dina Notat. Denmark: Royal Veterinary and Agricultural University.
9. Liu S, See KC, Ngiam KY, Celi LA, Sun X, Feng M. Reinforcement Learning for Clinical Decision Support in Critical Care: Comprehensive Review. J Med Internet Res. 2020;22(7):e18477.
10. Mikolov T, Chen K, Corrado G, Dean J. (2013) Efficient Estimation of Word Representations in Vector Space. [online] Available from https://arxiv.org/pdf/1301.3781.pdf. [Last accessed March, 2022].
11. Nemati S, Ghassemi MM, Clifford GD. Optimal medication dosing from suboptimal clinical examples: a deep reinforcement learning approach. Annu Int Conf IEEE Eng Med Biol Soc. 2016;2016:2978-81.
12. Alsentzer E, Murphy J, Boag W, Weng WH, Jindi D, Naumann T, et al. Publicly Available Clinical BERT Embeddings. In: Proceedings of the 2nd Clinical Natural Language Processing Workshop [Internet]. Minneapolis, Minnesota, USA: Association for Computational Linguistics; 2019. po. 72-8. Also Available online from: https://aclanthology.org/W19-1909.
13. Lee J, Yoon W, Kim S, Kim D, Kim S, So CH, et al. BioBERT: a pre-trained biomedical language representation model for biomedical text mining. Bioinformatics. 2020;36(4):1234-40.
14. Johnson AEW, Pollard TJ, Shen L, Lehman LWH, Feng M, Ghassemi M, et al. MIMIC-III, a freely accessible critical care database. Sci Data. 2016;3:160035.
15. Henry KE, Hager DN, Pronovost PJ, Saria S. A targeted real-time early warning score (TREWScore) for septic shock. Sci Transl Med. 2015;7(299):299ra122.
16. Rajpurkar P, Irvin J, Ball RL, Zhu K, Yang B, Mehta H, et al. Deep learning for chest radiograph diagnosis: A retrospective comparison of the CheXNeXt algorithm to practicing radiologists. PLOS Med. 2018;15(11):e1002686.
17. Kramer AA, Higgins TL, Zimmerman JE. Intensive care unit readmissions in US hospitals: patient characteristics, risk factors, and outcomes. Crit Care Med. 2012;40(1):3-10.
18. Rajkomar A, Oren E, Chen K, Dai AM, Hajaj N, Hardt M, et al. Scalable and accurate deep learning with electronic health records. NPJ Digit Med. 2018;1:18.
19. Rojas JC, Carey KA, Edelson DP, Venable LR, Howell MD, Churpek MM. Predicting Intensive Care Unit Readmission with Machine Learning Using Electronic Health Record Data. Ann Am Thorac Soc. 2018;15(7):846-53.
20. van de Sande D, van Genderen ME, Huiskens J, Gommers D, van Bommel J. Moving from bytes to bedside: a systematic review on the use of artificial intelligence in the intensive care unit. Intensive Care Med. 2021;47(7):750-60.

SECTION

22

Research Methodology

CHAPTER 121

How to Critically Appraise a Critical Care Published Paper?

Amrita Prayag, Prasad Rajhans, Purushotham Godavarthy

INTRODUCTION

With the rapid advances in the field of critical care and overwhelming overload of publications, it is essential for intensivists to be abreast with the vast amount of scientific data and also identify articles relevant to the field of expertise to make informed decisions that could aid and enhance patient care. Practising evidence-based medicine (EBM) in clinical practice entails the integration of clinical skills with the best available scientific evidence in making informed decisions.[1] The essentials of EBM include asking a clinical question, searching for evidence, critically evaluating the evidence for validity and relevance in respect of clinical question, applying the said result in clinical practice, and evaluating the results obtained.[2,3]

CRITICAL APPRAISAL

Critical appraisal is defined as "The process of carefully and systematically examining research to judge its trustworthiness, and its value and relevance in a particular context."[4] It is an important skill to be acquired by intensivists as it helps in understanding the scientific literature using appropriate study design and endpoints and implementing the same in clinical practice. Critical appraisal needs to be carried out meticulously as it helps in understanding the validity, reliability, and potential of the study to change the current practices being followed. It is not a negative dismissal of any research but consists of a balanced assessment of strengths/weaknesses, research process used, and consideration of results including quantitative and qualitative aspects.[5-7]

Why critical appraisal in critical care?

- Critical care being a rapidly evolving subject, there is a need to be updated with the latest developments.
- Inadequacy, out-of-date information in traditional sources of information like textbooks.
- Helps in weeding out irrelevant or weak studies ensuring only requisite information is available.
- Justify the effectiveness of newer medical treatments and technology in the face of limited healthcare resources.

Steps to Critically Evaluate a Published Critical Care Paper

Quick Glance and Initial Assessment—Things to Look For

- *Types of journal*:
  - Indexed journals
  - Peer reviewed
  - Impact factor
- *Timeline*: The research in critical care being rapidly evolving noting the year of publication is important to assess the relevance of a particular topic.
- *Funding*:
  - Declaration of the conflicts of interest by the authors
  - Source of funding
  - Any commercial bias
- *Trial registration*: It is defined as the publication of an internationally agreed-upon set of information about the design, conduct, and administration of any clinical trial on a publicly accessible website managed by a registry conforming to international standards. Registration of clinical trials is an ethical and regulatory requirement before the enrolment of subjects and is. A few clinical registration sites include:
  - The ClinicalTrials.gov run by the National Library of Medicine of the National Institutes of Health (https://clinicaltrials.gov)
  - International Clinical Trials Registry Platform (https://www.who.int/ictrp) run by the World Health Organization.
  - Clinical Trials Registry-India (https://www.ctri.nic.in) run by the Indian Council of Medical Research
- *Ethical considerations*:
  - Disclosure from all the authors that they followed all the standard operating procedures as prescribed ensuring good clinical practice.

- Certificate from the Institutional Review Boards/ Institutional Ethics Committees that the safety, well-being, and rights of the participants were adequately protected.

COMPONENTS OF A RESEARCH PAPER

Abstract

It provides a brief summary of the article and includes the purpose, methods, and results of the study.

Introduction

It provides an introduction of the topic to the reader, unmet needs for the current study, and presents available evidence in the particular subject. Studies being quoted need to be referenced.

Points for Critical Appraisal

- Is the study question relevant and has a scientifically interesting and important aim?
- Does the article attempt to answer your clinical question?
- Does the study add anything new?
- Relevance of the article in the present timeline. Is it a new publication or an earlier one that has influenced later publications?
- Do the authors present a hypothesis?
- If appropriate, was consent obtained from the participants and an ethical approval from the institutional review board?

Methods

This section lays out the study design and procedure followed while conducting the study. The patient, intervention, comparison, and outcomes (PICOs) framework is commonly used to identify components of clinical evidence for systematic reviews **(Table 1)**.

Points for Critical Appraisal

- What type of research question does the study pose?
  - Parameters studied (drug therapy, clinical intervention, etc.)
  - Outcomes of interest from the study.
  - Nature of subjects (group or population of patients)
- Efficacy of intervention—clinical effectiveness (benefits and harms) or cost-effectiveness.
- Frequency of events—incidence or prevalence of disease and other clinical phenomena, risk factors, specific clinical outcomes.
- Selection/inclusion and exclusion criteria/recruitment study site and circumstances.

TABLE 1: Participant, intervention, comparison, outcome, and study framework.

Abbreviation	*Expanded term*	*Description/interpretation*
P	Participant (patient, population or problem)	• What are the characteristics of the patient or problem? • How would a group of patients or problem similar to that in question be described?
I	Intervention, prognostic factor, or exposure	• What do you want to do with this patient (e.g., treat, diagnose, observe)? • What is the main intervention/prognostic factor/exposure under consideration?
C	Comparison	What is the alternative to the intervention (e.g., placebo, different drug, surgery)?
O	Outcome	What are the relevant outcomes (e.g., morbidity, death, complications)?
S	Study design	What should be the best study design or methodology?

Study Designs

Study design either descriptive or interventional may be employed by authors based on research question and clinical setting to ensure transparency and reproducibility **(Flowchart 1 and Table 2)**.[8, 9]

Points for Critical Appraisal

- Is the study design appropriate for the research question and clinical setting?
- Has the inclusion and exclusion criteria been described appropriately?
- In the case of prospective studies, is the description of sample size calculation mentioned?
- Are the endpoints of the study (primary, secondary, and exploratory, if any) mentioned along with exact methods used for the measurement of the variable?
- To address the issue of bias
  - Were proper methods employed in the selection of participant groups?
  - Was blinding used to limit other possible biases?
  - Were proper tools used to limit the influence of confounding variables?

Bias in Study Designs

There could be errors in the final conclusions of the study due to deviations in data collection, analysis, interpretation, or publication called *bias leading* to over or underestimating the true benefits and harms of any intervention. The term

Flowchart 1: Classification of study designs in scientific and clinical research.

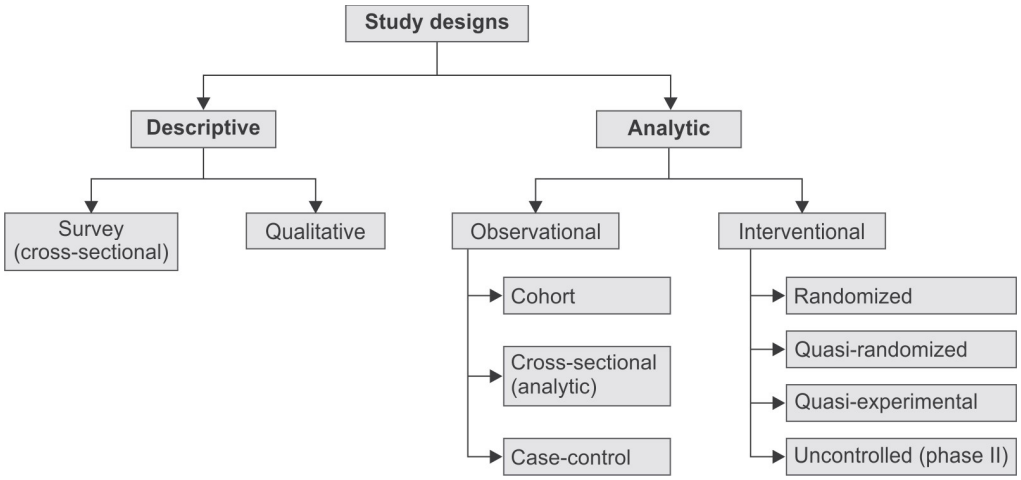


TABLE 2: Clinical research reporting statements and guidelines.

Study design	*Clinical research reporting statement/guideline*
SRs and meta-analyses	Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
Randomized trials	Consolidated Standards of Reporting Trials (CONSORT)
Observational studies	Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)
Qualitative research	Standards for Reporting Qualitative Research (SRQR)
	Consolidated Criteria for Reporting Qualitative Research (COREQ)
Case reports	Consensus-based Clinical Case Reporting Guideline Development (CARE)
Study protocols	Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)
	PRISMA-P
Diagnostic/ prognostic studies	Standards for Reporting Diagnostic Accuracy Studies (STARD)
	Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD)
Quality improvement studies	Standards for Quality Improvement Reporting Excellence (SQUIRE)
Clinical practice guidelines	Appraisal of Guidelines for Research and Evaluation (AGREE)
	Reporting Tool for Practice Guidelines in Health Care (RIGHT)

Bias means either predisposition towards or prejudice and could be due to systematic deviation of the results of a study from the truth. Internal validity refers to reliability or accuracy of the published results and indicates that the study design, implementation, and analysis of the study data have minimized or eliminated bias and the study outcomes indicate a true association between exposure and outcome. External validity helps in identifying if these results could be generalized to other groups or the general population. Every published study has some degree of bias, a key component of critical appraisal is to identify and assess the impact of these bias on the conclusions of the study and check if authors have taken adequate steps to reduce the incidence of these.

Various types of bias include—selection bias, allocation bias, confounding bias, performance bias, method bias, and attrition bias.[10-12] Readymade scales and critical-appraisal checklists are available and may be used in assessment of risk of these bias. The commonly used tools include the new version of the Cochrane risk-of-bias tool, RoB 2 used in the assessment of risk of bias in randomized trials, and ROBINS-I tool for non-randomized studies of interventions. Both these tools include a fixed set of bias domains, which are intended to cover all issues that might lead to a risk of bias.

Selection bias: Selection bias occurs if there are systemic differences between baseline characteristics among that study population that are compared.

Classification bias: Classification bias results due to the improper, incomplete, or ambiguous recording of the study parameters. In clinical trials, blinding prevents differential classification bias.

Confounding bias: Confounding bias results when a casual association is made between the outcomes of study and a factor which is not related to the outcomes, and occurs if the factor is associated with a range of other characteristics that do increase the outcomes risk.

Randomization

In randomized control trials (RCTs), the allocation of patients to a specific intervention group is done by randomization

which is the process of assigning patients by chance to groups that receive different treatments. Randomization reduces selection bias and plays a crucial role in increasing the quality of evidence-based studies. Adequate randomization involves both generations of an allocation sequence and the concealment of allocation.

Blinding

Blinding refers to the process of keeping participants, health-care providers, and data analyzers unaware of the assigned intervention after inclusion and randomization of participants in the trial. This helps in the prevention of selection bias and ensures participants behavior and reporting will not be affected by their assigned group affiliations.

Points for Critical Appraisal

- Was randomization carried out?
- What was the type of randomization and how was it done?
- Were adequate precautions taken to prevent allocation concealment?
- Is there a description of patient characteristics and are the patients in the control and interventional group similar?
- Was blinding carried out and how?
- How many patients were followed up until the end of study and how many were lost to follow-up and what were the reasons?

Statistical Analysis

Statistical analysis is used for analyzing quantitative research data and entails investigating trends, patterns, and relationships using the said data. Various statistical tools like sample size calculation, tests for distribution pattern of study data, and level of significance are used for data analysis *p* value used in many studies merely indicates if the null hypothesis has been accepted or rejected, in contrast, confidence interval (CI) provides information on the direction and strength of the effect. It also provides information related to the precision, power, sample size, and effect size and could be used to test hypotheses.[13-15] An *interim analysis* is the analysis of the data when the study is still ongoing usually before the recruitment for the study is complete. It provides an opportunity to re-estimate the sample size and modify the trial design. It provides the researcher's option to stop the trial for efficacy or futility or continue the trial as originally planned. Intention to treat (ITT) analysis in RCTs is inclusion of all participants who were enrolled and randomized to treatment in the statistical analysis irrespective of what treatment was received or not. This method allows researchers to draw accurate conclusions regarding the effectiveness of an intervention and preserves the benefits of randomization.[16, 17]

Results

This section highlights the findings of the study without any reasoning or explanations **(Table 3)**. The following needs to be followed clearly:

- Only statistical data should be presented without any explanations, reasoning.
- Concise numerical data of all subjects participating in the study including those excluded, dropped out, or withdrawn from the study should be mentioned and reason justified.
- The actual value of the statistical data including the mean with standard deviation/error or median with interquartile range should be presented.
- Statistical data should be depicted in tables, figures, and graphs as appropriate to improve study clarity.

Points for Critical Appraisal

- Has the baseline demographic data of the subjects included in the study been described and is the data between groups similar?
- Are the statistical tests appropriate for the study design and clinical question?
- Were the results presented within the paper and are the results statistically significant?
- Is there any evidence of fishing the data, i.e., changing statistical tests to ensure significance?

Discussion and Conclusion

This section is used to present the outcomes of the obtained results and consists of the following:

- Comparison of the study results with previously published literature highlighting any similarities and differences.
- Any novelty in the findings and impact in patient management.
- Requirement of larger studies for further evaluation or confirmation of the obtained result.
- Highlights and limitations of the present study
- Scope for future research.

References

Referencing is an integral part of scientific research, writing, and publication. Referencing could guide the readers, reviewers, and editors in tracing the original source of information, help to expand and spread the web of knowledge and more importantly give due credit to the original source of work. References provide an overview of the quality of literature search carried out for writing the article.

Points for Critical Appraisal

Points for critical appraisal are as follows:

- Have the references been cited in an appropriate format?

TABLE 3: Commonly used graphical representation in the clinical research papers.

Graph or plot	*Description*
Pie chart	Depicts the groups of data as proportions as part of a whole dataset
Bar/column graph	Depicts the variation of a variable between several groups as bars (horizontal) or columns (vertical)
Histogram	Column graph with no gaps, labeled by using the midpoint, start, or end of an interval
Box and whisker plot	Used for the comparison of values between two or more groups Box-represents 25th or 75th percentile of the cohort Horizontal line—represents median value of the cohort Whiskers—shows the maximum and minimum values
Stem and leaf plot	Depicts a frequency distribution by putting the data in order and retaining at least two significant digits. Data divided into two parts—(1) stem (depicted on the left) and (2) leaf (depicted on the right)
ROC curve	Graphical plot that illustrates the diagnostic ability of a binary classifier system as its discrimination threshold is varied. It is created by plotting true-positive rates against false-positive rates and is commonly used in the studies of diagnostic accuracy
Line graph	Depicts relationship between an independent variable (X-axis) and a dependable variable (Y-axis) which are usually continuous
KM curve	A line graph which represents time-to-event data (overall survival) with X-axis plotting time and Y-axis plotting the event
Scatterplot	Depicts relationship between two variables and their change in a consistent way
Waterfall plot	Special type of bar graph two-dimensional (2D) used to represent the response rate in individual patients (arranged from best to worst)
Spider plot	Depicts multivariate data as equiangular spokes (radii) with each spoke representing one of the variables and the length of the spoke being proportional to the magnitude of the data point relative to the magnitude of the variable across all data points
Forest plot	A graphical display to summarize the results of meta-analyses • Measured effect of each study is depicted as a solid square • Size of the square is proportional to the weight of the study • Horizontal line through each represents 95% CI around the point estimate of that individual study • Diamond represents the weighted pooled effect • Dashed line passing through a diamond is an overall point estimate • Edges of the diamond represent 95% CI around this estimate • Solid vertical lines represent the unity (line of no effect)

(CI: confidence interval; KM: Kaplan-Meier curve; ROC curve: receiver operating characteristic curve)

- Have the authors acknowledged the study limitations and highlighted any conflict of interests.
- Has any insignificant data been dressed up to portray significance?
- Have the authors elucidated the effects of intervention or exposure undertaken in terms of likely benefit or harm to individual patients?
- Does the statistical significance shown in the study match clinical significance?
- Does the conclusion mentioned in the study match the collected data and statistical analysis?

Tools for Critical Appraisal

Several useful resources are available to assess the transparency of the scientific research papers, they are as follows:

- Consolidated Standard for Reporting Trial 2010 for randomized trials—http://www.consort-statement.org
- Sign checklists—http://www.sign.ac.uk/ methodology/checklists.html
- BMJ series of articles—http://www.bmj.com/about-bmj/resources-readers/publications/how-read-paper.
- Equator network for health research—http://www.equator-network.org
- Strobe statement for observational studies—http://www.strobe-statement.org/index.php?id=strobe-home
- Care for case reports—http://www.care-statement.org
- PRISMA statement for metaanalytical studies and systematic reviews—http://www. prisma-statement.org
- Agree—http://www.agreetrust.org
- CASP—http://www.caspuk.net
- http://www.delfini.org

CONCLUSION

Critical appraisal of published scientific literature is an important skill to be mastered by the critical care physicians

to access the validity, reliability, and applicability before using their findings to inform decision-making.

REFERENCES

1. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: What it is and what it isn't. BMJ. 1996;312(7023):71-2.
2. Masic I, Miokovic M, Muhamedagic B. Evidence based medicine-new approaches and challenges. Acta Inform Med. 2008;16(4):219-25.
3. Manjali JJ, Gupta T. Critical appraisal of a clinical research paper: What one needs to know. Cancer Res Stat Treat. 2020;3(3):545-51.
4. Burls A. (2009). What is Critical Appraisal? [online] Available from http://www.bandolier.org.uk/painres/download/whatis/What_is_critical_appraisal.pdf. [Last accessed on March, 2022].
5. Hill A, Spittlehouse C. What is critical appraisal? London: Hayward Medical Communications; 2001.
6. Macinnes A, Lamont T. Critical Appraisal of a Research Paper. Scott Univ Med J. 2014;3(1):10-7.
7. du Prel JB, Röhrig B, Blettner M. Critical appraisal of scientific articles: Part 1 of a series on evaluation of scientific publications. Dtsch Arztebl Int. 2009;106(7):100-5.
8. Umesh G, Karippacheril JG, Magazine R. Critical appraisal of published literature. Indian J Anaesth. 2016;60(9):670-3.
9. Darling HS. Basics of statistics-2: Types of clinical studies. Cancer Res Stat Treat. 2020;3(1):100-9.
10. Šimundić AM. Bias in research. Biochem Med (Zagreb). 2013;23(1):12-5.
11. Gluud LL. Bias in Clinical Intervention Research. Am J Epidemiol. 2006;163(6):493-501.
12. Gurusamy KS, Gluud C, Nikolova D, Davidson BR. Assessment of risk of bias in randomized clinical trials in surgery. Br J Surg. 2009;96(4):342-9.
13. Darling HS. Basics of statistics-3: Sample size calculation. Cancer Res Stat Treat. 2020;3(2):317-22.
14. du Prel JB, Hommel G, Röhrig B, Blettner M. Confidence interval or P-value?: Part 4 of a series on evaluation of scientific publications. Dtsch Arztebl Int. 2009;106(19):335-9.
15. Schulz KF, Altman DG, Moher D. CONSORT Group. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332.
16. Lachin JM. Statistical considerations in the intent-to-treat principle. Control Clin Trials. 2000;21(3):167-89.
17. Smith VA, Coffman CJ, Hudgens MG. Interpreting the Results of Intention-to-Treat, Per-Protocol, and As-Treated Analyses of Clinical Trials. JAMA. 2021;326(5):433-4.

CHAPTER 122

Platform Trials

Anirban Hom Choudhuri, Deepika Jain, Ripon Choudhary

INTRODUCTION

Every clinical trial crosses three functional landmarks: (1) first when the trial is designed, (2) next when the trial is conducted as per the design, and (3) finally when the data is analyzed according to a prespecified plan. The road is simple but very rigid as there are no options to alter the course midway.

Platform trials are a type of clinical trial that provides the opportunity for a change of course midway during the trial and evaluate multiple interventions. The comparison can be done simultaneously against a common control or multiple controls in the various phases within the same master protocol. That is why they are also referred to as "multi arm-multi stage" (MAMS) trials. Since they do not conform to the conventional design of a randomized controlled trial (RCT) and offer scope for "within trial" adaptations, they also fall under the broad heading of adaptive clinical trials.

Food and Drug Administration (FDA) defines platform trials as "a trial designed to study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm."[1]

CONCEPT OF "MASTER PROTOCOL" AND DESIGN OF PLATFORM TRIAL

To comprehend the attributes of the platform trial, one has to understand the concept of "master protocol." A master protocol as defined by FDA is "a protocol designed with multiple substudies which may have different objectives and involves coordinated efforts to evaluate one or more investigational drugs in one or more disease subtypes within the overall trial structure."[1] The master protocol trial can be designed either by following the traditional facets such as frequentist decision rules, fixed sample size, allocation ratios, etc., or adopt innovative research techniques.

Master Protocol and Different Trials

Three types of clinical trials can be designed in this manner in conformation to the "master protocol." They are—(1) basket trials, (2) umbrella trials, and (3) platform trials.

Basket Trials

In a *basket trial*, a treatment or a combination of treatments is evaluated for multiple diseases with a common marker connected to the therapeutic goal **(Fig. 1)**. For example, there is a type of enzyme called *tropomyosin receptor kinase* (TRK) which has three subtypes that undergoes variable fusion to produce cancer. A study was undertaken to evaluate the safety and efficacy of larotrectinib, which is a highly selective TRK inhibitor in adults, children, and adolescents who had tumors with such enzyme fusions.[2] So a basket trial was designed whereby patients with TRK fusion-positive cancers were enrolled under three protocols—(1) a phase 1 study involving adults, (2) a phase 1–2 study involving children, or (3) a phase 2 study involving adolescents and adults. Thus the same (basket) trial established the safety and efficacy of the drug in different disease subtypes in the different age groups.

Umbrella Trials

A trial is called an *umbrella trial* when a single treatment either alone or in combination with other treatments is evaluated for a single disease or multiple diseases or in multiple subtypes of the same disease in different patient

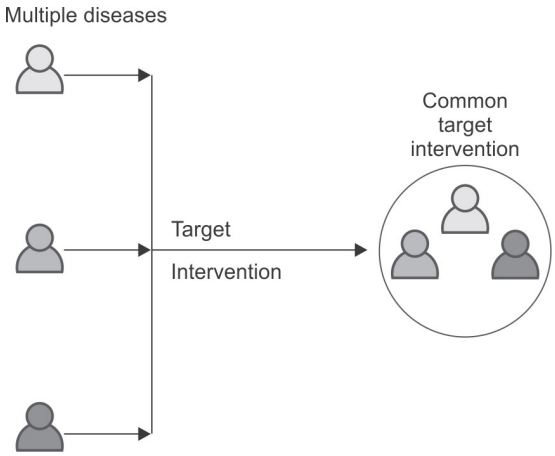


Fig. 1: Basket trial (evaluates a single targeted intervention on multiple diseases with a common molecular alternation).

subgroups **(Fig. 2)**. For example, in *TOGETHER trial* the effect of early treatment with hydroxychloroquine or lopinavir, or ritonavir on the risk of hospitalization in the patients with COVID-19 was evaluated. Here patients were randomized to hydroxychloroquine, lopinavir-ritonavir, and placebo groups in 1:1:1 ratio which was stratified according to the site, age (50 years vs. <50 years), time of onset of symptoms (5 days vs. <5 days). Therefore, the same trial evaluated different disease subtypes of COVID-19 with different investigational treatments.[3]

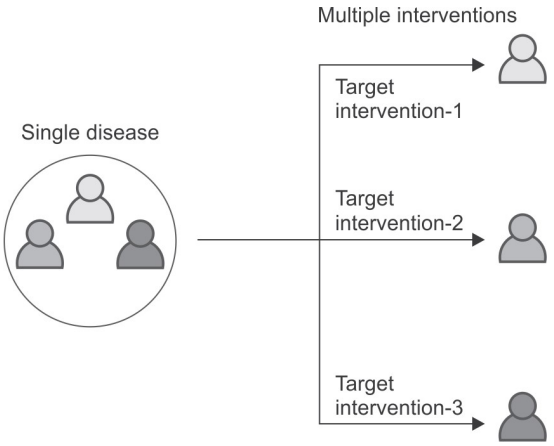


Fig. 2: Umbrella trial (evaluates multiple interventions for a single disease stratified into subgroups by molecular alternations).

Platform Trial

A trial is called a *platform trial* when multiple investigational treatments or treatment combinations are evaluated in the context of a single disease or within several substudies for different disease subtypes. Further, drugs or drug combinations are allowed to enter or leave the trial and the trial can run perpetually. If the new treatment is found to be better than the control, this can become the new control for the next stage and serve as a reference within the same trial structure **(Fig. 3)**. Many textbooks, therefore, consider platform trials as an adaptive form of umbrella trial rather than a distinct category **(Fig. 4)**.

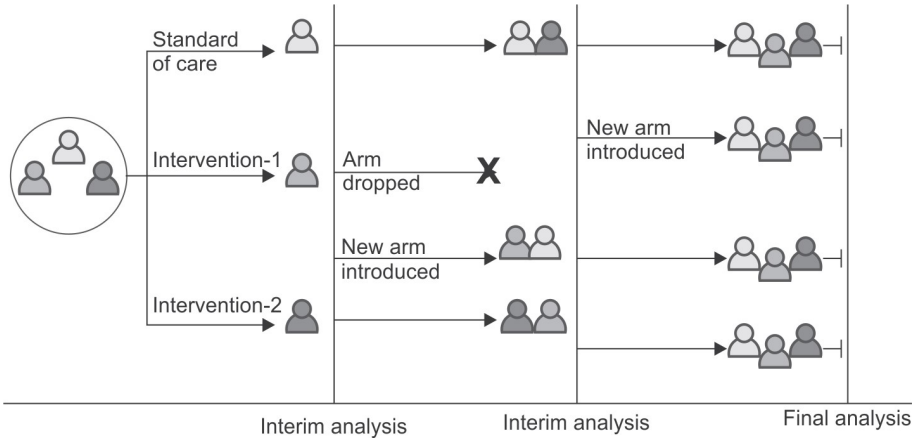


Fig. 3: Platform trial (evaluates several interventions against a common control with the flexibility to allow adding and dropping of interventions in light of new information/interim data analysis).

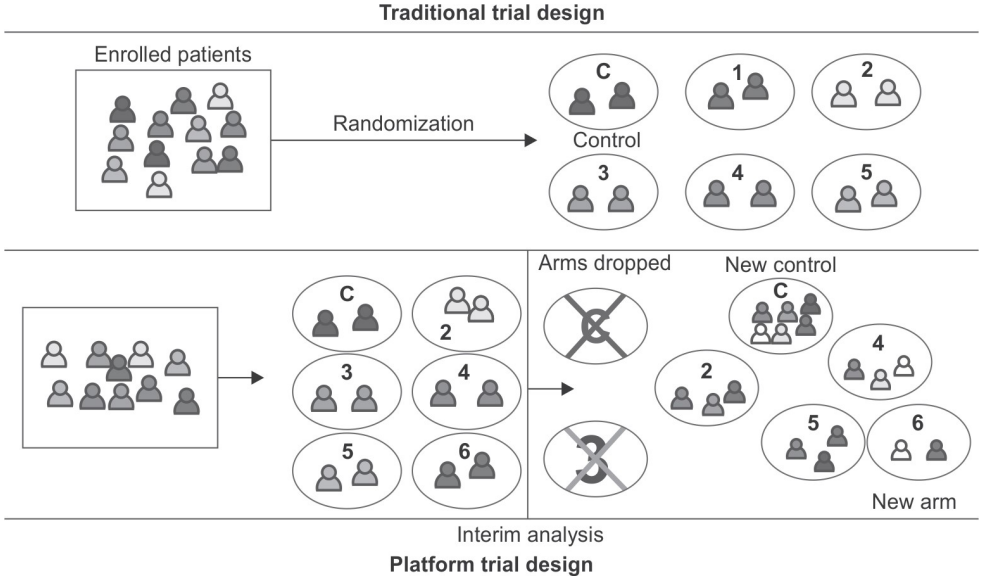


Fig. 4: The adaptive randomization in a platform trial in contrast to the traditional designs.

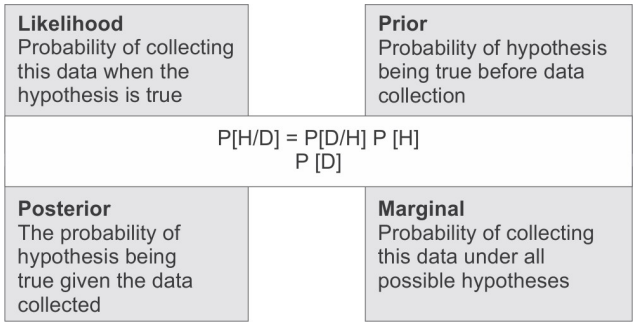


Fig. 5: Bayes' theorem, which is a mathematical way to calculate conditional probability. It gives the actual probability of an event given the evidence.

Traditional Trial Designs

Traditional trial designs use proportionate randomization to allocate patients into various treatment groups. Platform trials on the other hand follow adaptive randomization, wherein patients are randomized into groups with better responses after an interim analysis. This gives the patients entering the trial at a later stage a better chance to be in the treatment group with a higher response even before a final analysis is conducted. The flexibility to drop and add new arms help drop treatments that clearly are inferior to others and add new interventions that appear as beneficial.

APPLICATION OF BAYESIAN INTERFERENCE MODEL IN PLATFORM TRIALS

Most platform trials use Bayesian inference models where Bayes' theorem shown in **Figure 5** is used for updating the probability for a hypothesis becoming true. This assumes importance when more information becomes available during the course of trial and the frequentist methods fail to elucidate details. The Bayesian model is most appropriate for trials evaluating dose, efficacy, toxicity, diagnosis, and pharmacokinetics/pharmacodynamics characteristics. This is common for most platform trials.

IMPORTANCE OF PLATFORM TRIALS IN CRITICAL CARE MEDICINE

The trials in critical care are fraught with both advantages and challenges. A major advantage is in the presence of a controlled intensive care unit (ICU) environment that facilitates meticulous protocol adherence and outcome assessment. The challenges lie in the heterogeneity of patient's characteristics, pre-ICU illness trajectories, and multiple comorbidities. The predicted treatment effect can influence the observed event rate in the presence of such factors and the trials may become interpreted as statistically inconsequential while clinical benefits are discernible. The opposite might happen too. If the trials become so inadvertently powered due to over-optimistic assumption of the baseline event rate, there might be an overestimation of the treatment effect. This was noticed in the famous early goal-directed therapy (EGDT) of Rivers et al., where a baseline mortality rate of 44.4% in the control group produced an absolute risk reduction of nearly 15%.[4] This was irreproducible in the subsequent studies.

Since platform trials are based on the Bayesian framework, the estimations are continuously assessed with the appearance of additional information in the dataset. This reduces the proportion of "false positive" and "false negative" errors.

Many clinical trials were conducted on critically ill patients during COVID-19 pandemic. Platform trials provided the setting for the conduct of multiple trials akin to the display of multiple movies in the same multiplex. The RECOVERY and REMAP-CAP emerged from the same phase 3 platform trial and brought into light its immense usefulness.[5,6]

SOME EXAMPLES OF PLATFORM TRIALS CONDUCTED DURING COVID-19 PANDEMIC

- AGILE-ACCORD Platform trial: The estimated study completion date is 30 April, 2022.
- The RECOVERY-Respiratory Support Trial (ISRCTN 16912075): The recruitment began on April 6, 2020 and was completed on April 5, 2021 and the results are awaited.
- The CAPE-COVID and the CAPE-COD (Community-Acquired Pneumonia: Evaluation of Corticosteroids) Studies (NCT02517489): The study has now completed recruitment.
- The REMAP-CAP trial (NCT0273570): The Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP, NCT0273570) sought to evaluate multiple interventions to improve outcomes of patients admitted to an ICU with severe CAP, and provide a platform to respond rapidly in the event of a respiratory pandemic. The trial concluded that treatment with a 7 day fixed-dose course of hydrocortisone or shock-dependent dosing of hydrocortisone resulted in 93% and 80% probabilities of superiority with regard to the odds of improvement in organ support free days within 21 days.

GENERAL CONSIDERATIONS TO DESIGN A GOOD PLATFORM TRIAL

- A platform trial may or may not require a control group depending upon whether the trial is exploratory or confirmatory, whether the disease is rare or common, or whether there are ethical obligations to be fulfilled, or whether control group is available or unavailable. For example, when a platform trial is designed to replace a proof-of-concept study (which is often small and with historic control), the platform trial may be conducted

without a control group, particularly where the expected treatment effect is large. But when a platform trial is designed for a confirmatory study the inclusion of a control group to negate the effect of false positivity and ensure hypothesis validity becomes essential.

- Whenever a control group is used in a platform trial, a common control for multiple experimental arms can increase the efficiency of the trial. The choice of the common control is usually a standard of care (SOC) accepted by the *regulatory agencies* and *medical community*. When a platform trial is set up in a perpetual manner and is likely to remain open for many years, SOC can change with the approval of new drugs. So the control arm needs an updation according to the new SOC from time to time.
- If more than one SOC is available, the common control can be chosen. The extent of their choice arms is determined by geographical region, feasibility, budgets, a desired margin of efficacy, and safety profiles of the controls.
- Whenever a new treatment arm is added to the platform trial, data becomes available from the common control arm enrolled prior to the addition of the new treatment arm. This is called *nonconcurrent control*. The baseline characteristics of the experimental treatment may not balance the nonconcurrent control due to potential changes in medical practice, drift in population, etc. So far better or much worse outcomes can occur in the control over a time.
- In situations like COVID-19 pandemic where data is precious, it is justified to use all available information from nonconcurrent control after careful adjustment for heterogeneity over time. Statistical models such as a normal dynamic linear model (NDLM) are useful in such situations.

CONCLUSION

It is well accepted that the conduct of a clinical trial is constrained by labor, costs, and patient recruitment failures. Adaptive designs can avert many of these problems. Platform trials are amongst the most popular and useful adaptive designs. Only it needs to be ensured that the enrolled patients are "true" representatives so that the results can be generalized. A good platform trial opens the gate for many collaborative designs. The *I-SPY 2 study* is a typical example. This platform trial was originally designed to evaluate the efficacy of multiple novel neoadjuvant agents for breast cancer. Then the investigators teamed up with intensivists to launch (I-SPY COVID) using the same platform.[7]

More such innovative exercises can improve the design and consolidate the building blocks of critical care research that have become an integral part of our health care mission.

REFERENCES

1. US Food and Drug Administration. (2018). Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry (Guidance for Industry) [online] Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621817.pdf. [Last accessed March, 2022].
2. Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N Engl J Med. 2018;378(8):731-9.
3. Reis G, Moreira Silva EADS, Medeiros Silva DC, Thabane L, Singh G, Park JJH, et al. Effect of Early Treatment With Hydroxychloroquine or Lopinavir and Ritonavir on Risk of Hospitalization Among Patients With COVID-19: the TOGETHER Randomized Clinical Trial. JAMA Netw Open. 2021;4(4):e216468.
4. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345:1368-77.
5. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in Hospitalized Patients with COVID-19. N Engl J Med. 2021;384(8):693-704.
6. Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, et al. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. JAMA. 2020;324(13):1317-29.
7. Clinical Trials. I-SPY COVID-19 TRIAL: an adaptive platform trial for critically ill patients. [online] Available from: https://clinicaltrials.gov/ct2/show/NCT04488081. [Last Accessed March, 2022].

CHAPTER 123

Bayesian Analysis of Trial Results

Prashant Nasa, Vikas Sikri

INTRODUCTION

Understanding the trial results requires knowledge of the statistical method used for analysis. There are broadly two inferential statistics used in biomedical research: Frequentist and Bayesian. Recently, Bayesian analysis gained significant attention in the field of critical care medicine. Few prominent trials where primary outcome were reported nonsignificant using frequentist statistics, post-hoc analysis using Bayesian methods showed evidence of benefit, contradicting the previous conclusions.[1-3]

The Bayesian method was first described independently by Thomas Bayes and Laplace in the 18th century. However, the practical application of the Bayesian method became popular only in the late 20th century. The complex mathematical calculations with Bayesian statistics became practical with recent computer software, increasing its use considerably in the last two decades.[4] The Bayesian methodology has the concept of Bayes' theorem at its core.

$$P(A/B) = P(B/A) \times P(A)/P(B)$$

- P(A/B) (*posterior probability*): It is the probability of observing event A if B is true.
- P(B/A) (*likelihood*): It is the probability of observing B if A is true, obtained from results of the current trial.
- P(A) (*prior*): The probability of the hypothesis being true before collecting the data.
- P(B) (*marginal*): The probability of collecting this data under all possible hypotheses.

Bayes' theorem represents a conditional probability of parameter of interest, updating the prior belief.

Let us take an example to understand this theorem better: *Suppose the probability of a test being positive is 80% in case the patient has disease. The disease incidence in the population is 1%, and the test false positive rate is 5%. What is the probability of disease in case the test is positive?*

Probability of test positive, if there is disease [P(B/A)] = 0.8.
Probability of test positive, if there is no disease = 0.05
Probability of having disease [P(A)] = 0.01
Probability of not having disease = 0.99
Probability of test positive [P(B)] = [P(B/A)] × [P(A)] + (Probability of test positive, if there is no disease) × (Probability of not having disease) = (0.8 × 0.01) + (0.05 × 0.99) = 0.0575
Probability of disease, if test is positive [P(A/B)]= P(B/A) × P(A)/P(B)= 0.8 × (0.01/0.0575) = 0.14 or 14%

Frequentist statistics are traditionally used for statistical inference of clinical trials. It involves testing the significance of null hypothesis or effect estimates (using odd or risk ratio) and is reported as p-value with confidence intervals. The frequentist definition of *probability* of an event is the limit of its relative frequency in identical, repeatable trials but has nothing to do with the event itself. The probability is empirical but objective and based only on the current data. The frequentist inference is binary (significant vs. nonsignificant) based on an arbitrary p-value of <0.05 (type 1 error). The nonsignificant result based on p-value is commonly misunderstood as a "negative" trial or absence of an effect. p-value only represents the relation between the observed data and the null hypothesis. It cannot estimate the size of the effect or whether the null hypothesis is true. Besides, factors such as the precision of measurement or sample size may also affect the p-value. The American Statistical Association recently acknowledged the pitfall of p-value and and provided recommendations on interpretation of the statistical the statistical significance of p-value in relation to clinical trials interpretation.[5]

Bayesian statistics interprets probability as a degree of belief (prior probability) in the event's occurrence. The probability in the Bayesian inference is subjective and updates prior knowledge based on the new data (referred to as posterior probability) **(Fig. 1)** Bayesian inference updates the prior probability through the likelihood function of data to achieve a "less uncertain" posterior probability.

The Bayesian approach is very similar to the bedside clinical diagnosis. The pre-test probability of a diagnosis based on clinical symptoms or risk factors is revised with the

data results (post-test probability). In contrast to the dichotomous results based on p-value, the main result of Bayesian analysis is posterior distribution. The posterior distribution encompasses all values of the parameter of interest *in posteriori*.[6] The result is presented as mean or median with a range known as a credible interval. The differences between frequentist and Bayesian statistics is provided in **Table 1**.

TERMS USED IN BAYESIAN METHODOLOGY

Prior Distribution

The prior distribution is the distribution of pre-test probabilities of all plausible groups in the study. Sources used to construct the prior distribution include results from previous studies, knowledge from physiology, or expert opinion. Prior distribution based on previous scientific studies is called "informative" prior. Low-informative prior based on expert opinion is subjective, prone to bias, and used when no other prior information is available. Data will have a higher impact on posterior distribution in case of low-informative prior. Prior distribution should be constructed before the data collection; otherwise, if based on an expert opinion, there is a risk of bias.

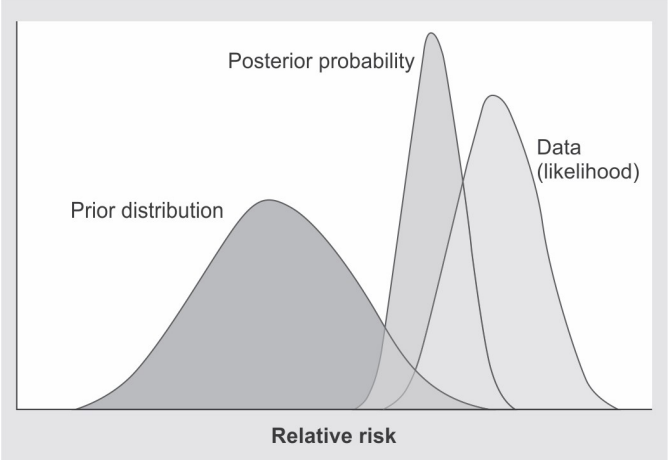


Fig. 1: Posterior distribution narrows the confidence intervals based on data (likelihood) and prior distribution.

Likelihood Function

Likelihood function can be defined as the evidence collected from the experiment. It represents the relationship between outcomes from the data and the parameter of interest. In Bayesian statistics, prior information is updated based on the likelihood function.

Posterior Distribution

The posterior distribution is the main result of Bayesian statistics and essentially a product of prior and likelihood function. It encompasses all probabilities of the parameter of interest. Today's posterior probabilities will become prior for the future experiment. The calculation of posterior distribution is done through Bayes' theorem using softwares such as Bayesian Inference Using Gibbs Sampling (BUGS).

Credible Interval

The posterior distribution is presented as mean or median with credible intervals compared to confidence intervals of frequentist analysis. 95% *credible intervals* are defined as the probability of 0.95 (95% chance) that the true parameter of interest lies within the given intervals. Credible intervals depend on both prior distribution and data results.

Exchangeability of Trials

The trials are presumed exchangeable and "borrow" strength from an informative prior based on the quality of evidence. Bayesian hierarchical modeling based on multiple exchangeable trials can estimate the safety and effectiveness of intervention or parameter.

Likelihood Principle

The likelihood principle is central to Bayesian statistics and states that all information related to the parameter of interest

TABLE 1: Comparison of frequentist and Bayesian statistics.

Variables	***Frequentist analysis***	***Bayesian analysis***
Hypothesis testing	Testing null hypothesis using p-value and significance	Measures the strength of hypothesis using Bayes' theorem
Probability	Objective estimation of a fixed and unknown parameter of interest	Subjective estimation (probability distribution) of random variables (parameter of interest)
Inclusion of prior information	No role in analysis	Yes, use of prior information with distribution
Large sampling	To reject null hypothesis	Not required
Estimated intervals	*Confidence interval*: Range of values in which true mean of the population lies with 95% confidence	*Credible interval*: 95% probability that parameter of interest is within interval limits
Computational effort	Less intensive and easier to calculate	Computational intense
Presentation of results	p-value, confidence intervals, likelihood estimate	Mean, median and mode of posterior probability, density graphs of posterior probability

is obtained from data (likelihood function) and updated with the prior information. The adherence to the principle provides flexibility to study design for:

- Modification of sample size based on efficacy or futility
- Adaptive design of studies
- Multiplicity (checking multiple interventions in one trial)
- Interim analysis for early stopping of trial

Predictive Probability

Predictive probability is a type of posterior probability that predicts the probability of an unobserved outcome (or future outcomes). The distribution of all probabilities related to unobserved outcomes is called predictive distribution. The predictive distribution is used in decisions like early stopping a trial or prediction of a patient clinical outcome.

Sensitivity Analysis

The credibility of the results obtained through frequentist or Bayesian statistics depends on the validity of models, assumptions, or analysis methods. Inclusion (or not) of missing data, distribution of baseline characteristics, and treatment of protocol violation (intention-to-treat vs per-protocol basis) are few examples that may affect the validity of the results. Sensitivity analysis is a method to assess the robustness of the results and determine how they are affected by different assumptions, models, or methods. Besides the above, the Bayesian statistics need sensitivity analysis of prior distribution.

Multiple comparative analyses using an optimistic (intervention will cause benefit), neutral (neither benefit nor harm), null, and pessimistic (intervention will cause harm) prior may be used for global sensitivity analyses in Bayesian approach.[6,7]

STEPS OF BAYESIAN APPROACH[6]

Data Analysis

The mathematical model, prior probability, and design of the study are conceived *a priori*. Simulation software calculates the posterior probability based on Bayes' theorem from the observed data and prior distribution. Sensitivity analysis of the model (goodness of fit) or prior is performed to confirm the validity of the results.

Results

Bayesian statistics are presented as a point estimate of the parameter of interest along with its 95% credible intervals. There were no standard reporting methods of Bayesian studies. Recently, a consensus checklist for reporting Bayesian studies was developed.[8] The core elements to be checked in the statistics section include specification (how it was decided), source, and justification of prior and mathematical model.

ADVANTAGES OF BAYESIAN STATISTICS

Information for Decision-making

Bayesian statistics can identify the degree of strength of the effect, which is missing with frequentist statistics. Incorporation of prior information augments the precision of the information from the current data. Informative prior based on empirical evidence narrows credible intervals.

Adaptive Trial Design

Adaptive trial design works on "flexibility in learning" where trial results modify the trial course within prespecified rules. Bayesian statistics can be used for an interpretation of an adaptive trial. The advantages of adaptive design include[9]:

- Multiple interventions can be tested simultaneously.
- Dynamic sample size
- Predefined interim analysis is used to conclude trial rather than on a predefined sample size.
- New interventions can be added in the ongoing trial (perpetual trial)
- Interaction between different domains or treatments can be evaluated.
- Preferred allocation to a particular arm (increased randomization to beneficial treatment).

Efficient Learning and Decision Analysis

The Bayesian analysis approach results of a trial in an efficient manner:

- Continuous (perpetual) learning from the data
- Hierarchical modeling allows progressive strengthening of evidence from data homogeneity.
- Inference on future outcomes using predictive probabilities.
- Estimation of the effect of the parameter of interest.

The decision analysis reviews the learning from the results with the trial objective to decide the optimum course of action. The decision analysis may result in an early stop of trial or continuation of the study with another arm.

Meta-analysis

The flexibility of Bayesian design allows data accumulation from various sources. Rather than treating each study as an independent, Bayesian analysis uses the estimation process through the prior. The conclusions are achieved faster than the conventional frequentist approach in Bayesian meta-analysis.[10]

Postmarket Surveillance

The Bayesian approach is helpful for postmarketing surveillance to determine the directions of use, efficacy, and side effects of a drug or device. Posterior distribution of phase II/III trial (premarket clinical trial) becomes prior distribution for postmarket surveillance study. Surveillance studies can be used to update information if there is exchangeability between the trials.

POTENTIAL CHALLENGES OF BAYESIAN APPROACH

Extensive Preplanning

The trial based on Bayesian statistics needs arduous preplanning on design, conduct, and analysis. Prior information, parameters (or outcomes) of interest, interim analysis, and mathematical model should be identified a priori. Change in prior information or prespecified analysis analysis during or after completion of trial process may produce bias and affect the validity of the results.

Model-building

The mathematical model used to link prior information and data from the trial need extensive research. The model-building involves various steps:

- Probability distributions of prior information
- Multiple sources of prior information and their relationship
- Identification of covariates related to patient outcomes or missing data
- Sensitivity analyses on the model

Laborious Statistics and Computation

Bayesian analysis computation is laborious and needs training and experience. Various computation software have been developed, based on tools such as Markov Chain Monte Carlo (MCMC), e.g., WinBUGS, BRUGS, for sampling to analyze trial data, check model assumptions, assess (using simulation) prior probabilities, and estimate sample size.

Prior Information

Prior information is a core strategy of Bayesian statistics and should be identified *a priori*. The choice of prior information needs statistical and clinical clarification.

APPLICATION OF BAYESIAN STATISTICS

We discuss the Bayesian approach application through two recent randomized controlled trials (RCTs) in critical care medicine.

REMAP-CAP Study on Interleukin-6 Receptor Antagonist in COVID-19

The Randomized Embedded Multifactorial Adaptive Platform (REMAP) trial for community-acquired pneumonia (CAP) is an innovative trial design to study the effect of multiple interventions into one or more domains using Bayesian inferences to develop evidence on multiple treatments.[11]

Interleukin (IL)-6 receptor antagonists tocilizumab and sarilumab, IL-1 receptor antagonist, anakinra; interferon β-1a; were tested against control (no immunomodulation) in a multiarm domain.[12]

The primary outcome was organ (respiratory and cardiovascular) support-free days at day 21.

Statistical Analysis

Prior: Prior distribution for parameter of interest (treatment effect) was defined *a priori*, informative, and classified as neutral. Covariates of the primary model were defined. The information and statistics about prior were part of the publication. Predefined interim analysis was performed. Information about missing outcomes was mentioned.

Statistical analysis: Statistical models, software used for calculation and algorithms (MCMC algorithm), was specified in methods section. The role of the steering committee in the monitoring, interim analysis, and nonconvergence was also mentioned. Odds ratio (OR) > 1 was defined as increased survival or more organ support-free days. Trial conclusion criteria were predefined, >99% posterior probability for effectiveness, <0.25% posterior probability for inferiority. Intervention efficacy: >99% posterior probability for OR > 1; intervention futility: OR > 1.2, posterior probability < 5%, intervention equivalence OR: 0.83–1.2, posterior probability > 90%. Software (R software) used was mentioned in methods.

Discussion: The study was concluded after a predefined interim analysis showing effectiveness in the tocilizumab group. Data was summarized and presented in median adjusted OR with 95% credible intervals for organ support-free days and survival. No modeling for different priors was done as single neutral prior model was used. Sensitivity analysis was performed and mentioned in the appendix.

Post-hoc Bayesian Analysis of ANDROMEDA-SHOCK

The RCT (ANDROMEDA-SHOCK) comparing the peripheral perfusion-targeted resuscitation based on capillary refill time (CRT) versus the lactate-targeted resuscitation did not found any significant difference in 28-day mortality (34.9% vs. 43.4%, P = 0.06). There was an absolute (8.5%) risk difference between the two strategies, favoring CRT-based resuscitation. However, trial was designed to show difference of 15%, final p-value was 0.06 (not <0.05), and null hypothesis could not be rejected.[13] Bayesian post-hoc analysis of ANDROMEDA-SHOCK using a mathematical model of different priors, neutral, null and pessimistic was performed. To avoid bias, model used multiple prior distributions. Using an OR < 1, the CRT group was found to reduce mortality with a probability of >90%, independent of priors. The effect of study data is considered strong if posterior obtained with all prior concur. There was also a higher probability of a lower quartile of SOFA score in the secondary outcome in CRT strategy.[2]

The different inferences from frequentist and Bayesian analysis reflect too much importance on the statistical

significance of the p-value. The dichotomous results based on p-value cannot determine the effect size of the intervention.

CONCLUSION

Bayesian statistics provide a clinically intuitive inference of the trials. There are various advantages of Bayesian statistics over conventional frequentists, including prior knowledge on the subject, estimation of effect size, reduced effect of sample size, and adaptive design. The quality assessment of Bayesian statistics should involve three essential items, prior specified and decided *a priori*, source and justification of the prior, and presentation of results.

REFERENCES

1. Sidebotham D, Popovich I, Lumley T. A Bayesian analysis of mortality outcomes in multicentre clinical trials in critical care. Br J Anaesth. 2021;127(3):487-94.
2. Zampieri FG, Damiani LP, Bakker J, Ospina-Tascón GA, Castro R, Cavalcanti AB, et al. Effects of a resuscitation strategy targeting peripheral perfusion status versus serum lactate levels among patients with septic shock. A Bayesian reanalysis of the ANDROMEDA-SHOCK trial. Am J Respir Crit Care Med. 2020;201(4):423-9.
3. Goligher EC, Tomlinson G, Hajage D, Wijeysundera DN, Fan E, Jüni P, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome and posterior probability of mortality benefit in a post hoc Bayesian analysis of a randomized clinical trial. JAMA. 2018;320(21):2251-9.
4. Verma V, Mishra AK, Narang R. Application of Bayesian Analysis in Medical Diagnosis. J Pract Cardiovasc Sci. 2019;5:136-41.
5. Wasserstein RL, Lazar NA. The ASA's statement on P-values: Context, process, and purpose. Am Stat. 2016;70:129-33.
6. Ferreira D, Barthoulot M, Pottecher J, Torp KD, Diemunsch P, Meyer N, et al. Theory and practical use of Bayesian methods in interpreting clinical trial data: a narrative review. Br J Anaesth. 2020;125(2):201-7.
7. Depaoli S, Winter SD, Visser M. The Importance of prior sensitivity analysis in Bayesian statistics: Demonstrations using an interactive shiny app. Front Psychol. 2020;11:608045.
8. Ferreira D, Barthoulot M, Pottecher J, Torp KD, Diemunsch P, Meyer N. A consensus checklist to help clinicians interpret clinical trial results analysed by Bayesian methods. Br J Anaesth. 2020;125(2):208-15.
9. Pallmann P, Bedding AW, Choodari-Oskooei B, Dimairo M, Flight L, Hampson LV, et al. Adaptive designs in clinical trials: why use them, and how to run and report them. BMC Med. 2018;16:29.
10. Halsey LG. The reign of the p-value is over: what alternative analyses could we employ to fill the power vacuum? Biol Lett. 2019;15:20190174.
11. Angus DC, Berry S, Lewis RJ, Al-Beidh F, Arabi Y, van Bentum-Puijk W, et al. The REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) Study. Rationale and Design. Ann Am Thorac Soc. 2020;17(7):879-91.
12. REMAP-CAP Investigators. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med. 2021;384:1491-1502.
13. Hernández G, Ospina-Tascón GA, Damiani LP, Estenssoro E, Dubin A, Hurtado J, et al. Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: The ANDROMEDA-SHOCK Randomized Clinical Trial. JAMA. 2019;321(7):654-64.

CHAPTER 124

Adaptive Clinical Trial Design

Kushal Rajeev Kalvit, Atul Prabhakar Kulkarni

INTRODUCTION

"Learn as you go along"

Clinical trials have been traditionally conducted following a fixed format, which has three essential steps—(1) designing a trial, (2) conducting the trial as designed, and (3) analyzing the results as per the prespecified statistical plan.[1] The "prespecified" and the fixed components make the trial inflexible which leaves no space for any adjustments. Adaptive clinical trial designs fill this void, allowing flexibility **(Table 1)**. Bauer in 1989, suggested the use of confirmatory adaptive methodology, which allowed mid-trial design modifications in ongoing trials, by using either unblinded internal or external data, without compromising type I error rate.[2] The recently published guidelines by US Food and Drug Administration (FDA) defines an adaptive design as one "that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial."[3] Byrom et al. defined adaptive clinical trials (ACTs) as "the studies that incorporate preplanned, mid-course adjustments to study design based upon accumulating study data,"[4] while Dragalin defined it as "a multistage study design that uses accumulating data to decide how to modify aspects of the study without undermining the validity and integrity of the trial."[5] The most important aspect of ACT design is that all the modifications need to be *prospectively planned* and no *random modifications can be made without specifying* the reason and method of modification beforehand.

TABLE 1: Usual versus adaptive clinical trials—the differences.

Features	*Usual clinical trial*	*Adaptive clinical trial*
Design	Fixed	Flexible
Trial arms	2 or 3	Many arms are possible
Statistical analysis	Usual methods, a simple analysis will suffice	Bayesian predicted probability, complex analysis is required
Interim analysis	May or may not be done	Routinely needed, in fact, is a must, so that changes can be made to adapt to the data
Data Monitoring Committee	Not much active role, except to monitor serious adverse events, record checking	Active participation is mandatory for success, for adapting the design to collected data
Role of regulatory authorities	Well endorsed	Unsure

PRINCIPLES OF ADAPTIVE CLINICAL TRIALS

The basic principle that sets ACT apart from traditional methods is that interim analyses are conducted and prespecified (or a *priori*) adjustments are made based on the analysis of interim data. While interim analyses are carried out in a traditional trial also, they assess for safety or futility of continuing the trial. In an adaptive design trial, "the defining characteristic is that results from interim data analyses are used to modify the ongoing trial without undermining its integrity or validity" or simply put changes can be made to one or many aspects of the trial to make it more efficient and useful while maintaining the validity and integrity of data.[6,7] Despite the attraction of flexibility, adaptive trials are bound by limitations such as logistical issues, computational difficulties, and challenging interpretability of results. The aspects specific to adaptive design trial are discussed here.

What are we Adapting to in an Adaptive Design?

Based on the results of the interim analysis, the researchers can make the following changes to the trial:[8]

- Abandonment of a certain dose due to inefficacy or toxicity. All subsequent patients would then be enrolled in other dosage arms (adaptive dose-finding). For example, adaptive, dose-finding clinical trial of *L-carnitine* in the treatment of septic shock.[9]
- Abandonment of an entire treatment arm and allocating all subsequent patients to other arms or addition of newer

treatment arms in the course of the study (adaptive group sequential). It is also known as *pick-the-winner/drop-the-loser approach*. For example, high dose AmBisome on a high dose fluconazole backbone for cryptococcal meningitis induction therapy.[10]

- Changing the allocation ratio between the treatment arms (adaptive randomization). The DexFEM trial studying low-dose *dexamethasone* in heavy menstrual bleed utilized this approach.[10]
- Identifying subsets of patients who would benefit the most and focusing on allocation of treatment to them (Adaptive treatment-switching or population enrichment). The study of rizatriptan in pediatric migraine patients adopted this strategy of allocating the treatment only to those who were initial nonresponders while the initial responders subsequently received only a placebo.[11]
- Early stoppage of the entire trial due to success or excess risk of one arm over the other.
- Redefining the entire sample size.
- Switching between null and alternative hypotheses, primary and secondary end-points, or single and multiple hypotheses (Adaptive hypothesis).
- Multiple adaptive trial means incorporating multiple adaptive designs in a single study.
- Seamless I/II and II/III studies allow for combining the objectives of Phase I, II, III in a single protocol and movement from one phase to another without stopping patient enrollment. For example, the Matchpoint trial in patients with chronic myeloid leukemia was a phase I/II seamless study to find the dose of ponatinib in addition to conventional chemotherapy.[12]
- Adaptive trial design allows changes in the study protocol and conduct based on biomarker responses to treatments (including genomic markers). For example, the FOCUS4 trial evaluated multiple biomarker responses in colorectal cancer.[13]

There are many types of designs for ACTs mentioned in **Table 2**, the most frequently used design has been the seamless phase II/III design, followed by the adaptive group sequential, biomarker adaptive design, and the adoptive dose-finding design among others.[14]

TRIAL PLANNING

As with any clinical trial, the protocol for conducting the trial should be prepared and documented in a detailed manner. Special attention should be given towards the number and timing of interim analyses, the statistical methods to be used during the mid-trial analyses, the results which may or may not alter the course of the trial, and the algorithm which is to be followed to make changes in the trial conduct. Documentation and adherence to minute details lessen the risk of bias. It is also important to include factors that may lead to deviation from the prescribed algorithm and the same should be discussed with the regulatory committees when the need arises. An integral part of an adaptive trial design is *simulation testing*. Simulation testing allows one to walk through the trial virtually and assess for potential pitfalls or fallacies. One can repeatedly make changes to the design and run simulations to minimize any chance of erroneous conduct or result. Another commonly encountered problem is to acquire funding and approval from the ethical/regulatory committees; as many of them are not familiar or comfortable with an adaptive design. The researchers need

TABLE 2: Types of adaptive trials.[15,16]

Adaptive design type	*Details*	*Advantages*	*Disadvantages*
Dose finding	Dose may increase or decrease depending on the efficacy seen in interim analysis	Avoids under or overdosing the participants	May lead to errors if interim analysis done during an early stage
Response adaptive randomization	Treatment allocation ratios can be changed as per interim analyses	May allow recruitment of more subjects to the most promising study arm that has the best efficacy or fewer side effects, also called "play-the-winner" approach	If interim analysis is done during an early stage of the trial may lead to errors
Sample size reassessment	Change in sample size based on interim analyses	An adequate number of subjects are recruited without under or over recruiting	Adaptations can be misguided if interim analysis is done with a small sample size Increasing sample size may logistically (e.g., cost and time) be challenging
Seamless design	Allows for immediate continuation from one phase to the next phase	Single-trial can do in place or two or more separate trials, increasing efficiency	It may be more challenging methodologically or logistically
Adaptive enrichment	Allows trial eligibility criteria to be modified	Allows targeting the subgroups which may benefit from the intervention	Limited generalizability to the study population, may cause errors if done early with small data

to adopt various strategies such as explaining in a simplified manner, highlighting the advantages of such a design, and appointing an independent statistician with experience in adaptive designs to be a reviewer for the proposal. One can also explain the results of simulation testing to the funding body or ethics committee for a better understanding of the trial.[6]

TRIAL CONDUCT

Once the trial protocol has been developed and funds acquired, the next step is communicating with the study sites. As the groundwork should be done by the staff at all the study sites, appropriate information sheets and training modules should be provided to all associated staff members to avoid violations. The next stakeholder is the study participant. Special patient information sheets for the different types of possible adaptations need to be prepared and all the steps need to be explained to the study participants. The uncertainty of the interim results and subsequent sudden change in the treatment type or dose should be communicated to all participants well in advance to avoid attrition due to consent withdrawal. Lastly, the drug supplier company or pharmacy needs to be prepared for changes in the demands of certain doses or treatment modalities.[17]

INTEGRITY AND VALIDITY OF DATA—THE ACHILLES' HEEL

This is perhaps the most crucial thing for any adaptive design trial and may make or mar the credibility of the study. Preserving the integrity implies that all necessary data during interim analyses gets collected, analyzed, and stored without any leakage of information. All associated personnel need to follow good clinical practice principles for the same. Maintaining the internal validity implies that the trial answers the original research question accurately without aberrations because of multiple interim analyses. These objectives are difficult to achieve in a real-world example but are possible with rigorous protocols, adherence to the same, and adequate training of staff.[18]

There are many important statistical issues in the analysis of adaptive design trials. While interpreting the results, the 95% confidence intervals (CIs) calculated traditionally may not provide adequate coverage as per the design. This problem can be overcome either by running multiple simulations in advance to compute a correct confidence interval that would contain the true effect or by conducting a bootstrap analysis. *p*-values calculated to minimize the type 1 error rate may or may not be adequately calibrated. Simulation testing is the only way to ensure the derivation of the correct *p*-value.[17] Traditionally, we have had a number of Frequentist approaches to distribute the type 1 error rate (alpha) in case of interim analyses. However, many Bayesian approach methods (alpha spending function), as well as hybrid methods (combining both approaches), are now available for estimation and minimization of type 1 error rate in adaptive design trials.[19,20] Treatment effect estimates may be biased in any adaptive design trial given the changing treatment arms and allocation. Many strategies such as using a bias-corrected maximum likelihood estimator, shrinkage approaches, bootstrap analysis, or median unbiased estimator can be utilized to avoid wrong estimates.[21]

PANDEMICS AND OUTBREAKS: PERFECT ARENA FOR ADAPTIVE TRIALS?

Pandemics such as SARS, H1N1 influenza, COVID-19, and outbreaks such as that of Ebola, Zika virus, or Nipah virus pose a unique situation where answers to multiple unknowns are expected in a short time. It has been seen that the current COVID-19 pandemic was flooded with misinformation about multiple treatment options that spread faster than the virus via social media platforms. Traditional randomized controlled trials in such a scenario would take months to years to get us the right answer. Adaptive design trials are a perfect recipe for comparing multiple treatments and/or doses simultaneously in order to find an effective treatment. Newer treatment options can be added to ongoing trials as new evidence gathers and the sample size can be adjusted accordingly. The RECOVERY, REMAP CAP, SOLIDARITY, and ACTT trials are all multiarm multistage (MAMS) trials that have provided valuable evidence for the treatment of COVID-19 infection and continue to recruit and evolve their design as the pandemic ebbs and flows.[22]

BARRIERS TO THE USE OF ADAPTIVE TRIAL DESIGN

Despite their presence for nearly three decades,[23] adaptive trial designs are not commonly used due to multiple reasons like lack of expertise/unfamiliarity among researchers, funder/regulator concerns, and uncertainty regarding the interpretation of its statistical analyses.

The main barriers to implementation of ACT design are as follows:[24]

- More planning is required than the usual simple clinical trial, therefore there is a need for additional planning time.
- ACT design needs the investigators to perform more activities than a normal trial to conduct analysis of various options and simulations.
- ACT demands more clinical and statistical expertise and better software.
- More logistical planning and effective implementation is required, e.g., various doses of drug may need to be available at a short notice.

- More top-down motivational and financial support to upper hierarchical ranks is needed in the organization conducting the trial.

CONCLUSION

Adaptive design clinical trials have revolutionized the field of clinical research methodology. The decade long traditional trials have been reduced to mere months or a year without compromising the validity or credibility of data results. The design and complexities of adaptive trials are constantly evolving to quench our thirst for faster and more robust answers.

REFERENCES

1. Friedman LM, Furberg CD, DeMets DL, Reboussin DM, Granger CB. Fundamentals of Clinical Trials, 4th edition. New York: Springer; 2010. pp. 1-23.
2. Bauer P. Multistage testing with adaptive designs. Biometrie und Informatik in Medizin und Biologie. 1989;20:130-48.
3. US Food and Drug Administration. (2019). Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry. [online]. Available from https://www.google.com/url?sa=t&source=web&rct=j&url=https://www.fda.gov/media/78495/download&ved=2ahUKEwj9y_PdhKbzAhUw3jgGHTrfCbIQFnoECAYQAQ&usg=AOvVaw3XBQFh3nVHmx8eUp_wdJsP&cshid=1632982278143. [Last accessed March, 2022].
4. Byrom B, Mcentegart D. Data without doubt. Good Clin Prac J. 2009;16(4):5.
5. Dragalin V. Adaptive Designs: Terminology and Classification. Drug Inf J. 2006;40(4):425-35.
6. Pallmann P, Bedding AW, Choodari-Oskooei B, Dimairo M, Flight L, Hampson LV, et al. Adaptive designs in clinical trials: why use them, and how to run and report them. BMC Med. 2018;16(1):29.
7. Chow SC. Adaptive clinical trial design. Annu Rev Med. 2014;65:405-15.
8. Todd JA, Evangelou M, Cutler AJ, Pekalski ML, Walker NM, Stevens HE, et al. Regulatory T Cell Responses in Participants with Type 1 Diabetes after a Single Dose of Interleukin-2: a Non-Randomised, Open Label, Adaptive Dose-Finding Trial. PLoS Med. 2016;13(10):e1002139.
9. Lewis RJ, Viele K, Broglio K, Berry SM, Jones AE. An adaptive, phase II, dose-finding clinical trial design to evaluate L-carnitine in the treatment of septic shock based on efficacy and predictive probability of subsequent phase III success. Crit Care Med. 2013;41:1674-8.
10. Molefi M, Chofle AA, Molloy SF, Kalluvya S, Changalucha JM, Cainelli F, et al. AMBITION-cm: intermittent high dose AmBisome on a high dose fluconazole backbone for cryptococcal meningitis induction therapy in sub-Saharan Africa: study protocol for a randomized controlled trial. Trials. 2015;16:276.
11. Ho TW, Pearlman E, Lewis D, Hämäläinen M, Connor K, Michelson D, et al. Rizatriptan Protocol 082 Pediatric Migraine Study Group. Efficacy and tolerability of rizatriptan in pediatric migraineurs: results from a randomized, double-blind, placebo-controlled trial using a novel adaptive enrichment design. Cephalalgia. 2012;32(10):750-65.
12. Copland M, Slade D, Byrne J, Brock K, de Lavallade, Craddock C, et al. FLAG-IDA and Ponatinib in Patients with Blast Phase Chronic Myeloid Leukaemia: Results from the Phase I/II UK Trials Acceleration Programme Matchpoint Trial. Med Blood. 2019;134(Suppl 1):497.
13. Adams R, Brown E, Brown L, Butler R, Falk S, Fisher D, et al. Inhibition of EGFR, HER2, and HER3 signalling in patients with colorectal cancer wild-type for BRAF, PIK3CA, KRAS, and NRAS (FOCUS4-D): a phase 2-3 randomised trial. Lancet Gastroenterol Hepatol. 2018;3(3):162-71.
14. Bothwell LE, Avorn J, Khan NF, Kesselheim AS. Adaptive design clinical trials: a review of the literature and ClinicalTrials.gov. BMJ Open. 2018;8(2):e018320.
15. Park JJ, Thorlund K, Mills EJ. Critical concepts in adaptive clinical trials. Clin Epidemiol. 2018;10:343-51.
16. Lang T. Adaptive Trial Design: Could We Use This Approach to Improve Clinical Trials in the Field of Global Health? Am J Trop Med Hyg. 2011;85(6):967-70.
17. Gallo P. Operational challenges in adaptive design implementation. Pharm Stat. 2006;5(2):119-24.
18. Fleming TR, Sharples K, McCall J, Moore A, Rodgers A, Stewart R. Maintaining confidentiality of interim data to enhance trial integrity and credibility. Clin Trials. 2008;5(2):157-67.
19. Gao P, Liu L, Mehta C. Exact inference for adaptive group sequential designs. Stat Med. 2013;32(23):3991-4005.
20. Chevret S. Bayesian adaptive clinical trials: a dream for statisticians only? Stat Med. 2012;31(11-12):1002-13.
21. Carreras M, Brannath W. Shrinkage estimation in two-stage adaptive designs with midtrial treatment selection. Stat Med. 2013;32(10):1677-90.
22. Noor NM, Pett SL, Esmail H, Crook AM, Vale CL, Sydes MR, et al. Adaptive platform trials using multi-arm, multi-stage protocols: getting fast answers in pandemic settings. F1000Res. 2020;9:1109.
23. Bauer P, Bretz F, Dragalin V, König F, Wassmer G. Twenty-five years of confirmatory adaptive designs: opportunities and pitfalls. Stat Med. 2016;35(3):325-47.
24. Quinlan J, Gaydos B, Maca J, Krams M. Barriers and opportunities for implementation of adaptive designs in pharmaceutical product development. Clin Trials. 2010;7(2):167-73.

CHAPTER 125

The Right End-points for Critical Care Trials

Ram E Rajagopalan, Janarthanan S, Vetriselvan P

INTRODUCTION

As practicing intensivists we rely on clinical studies of new interventions to allow us to administer better care to our patients. Typically we trust large randomized controlled trials (RCTs) to provide us with robust and relevant information. Despite the ideal structure of these RCTs, even when there is strong clinical and experimental rationale for a treatment, we are increasingly encountering studies that are unable to establish their efficacy. While there may be many reasons for these negative studies, in this chapter, we will concentrate on one issue, namely *the selection of outcome measures (end-points) and their appropriate analysis*.

OUTCOMES VERSUS END-POINTS

Though the terms are used interchangeably, *outcomes* are events that are the consequence of an intervention on a given disorder while *end-points* are objective measures of the event. Thus, while mortality is an outcome, its measurement as "28-day mortality" is an end-point. A clearly defined endpoint refines the description of an outcome and standardizes its measurement across literature. This chapter will discuss the rationale, limitations, and optimal utilization of pertinent end-points in clinically-oriented papers, while avoiding excessive emphasis on mathematical or statistical nuance.

SELECTING END-POINTS: GENERAL ISSUES[1]

Clinical End-points

Most of us are interested in pragmatic clinical studies that assess patient-centered outcomes, i.e., the Phase III trials. An outcome that is evaluated in such a trial must ideally be important to the end-user in the routine care of their patients. Such clinical end-points typically include parameters that are easily interpreted by the user and contribute significantly to changes in practice patterns.

Among clinical end-points, some like mortality are objectively determined (*hard end-points*) and are common to any disease process (*patient-oriented* outcome measures).[2] In contrast, other measures may be related to the specific underlying illness (*disease oriented*); e.g., the duration of ventilation or vasopressor therapy. These *soft end-points* may not be objectively determined and would need to be carefully defined.

Surrogate outcomes that use physiological or biochemical end-points may be relevant in early phase trials but are not consistent or reliable markers of clinical response. Some surrogate parameters may be validated measures of clinical outcomes that may be combined with clinical endpoints to add strength to the conclusions (e.g., cardiac troponins or hemoglobin A1c).

Ideal clinical end-points should meet the following criteria:[1]

- *Relevance:* They must be a pertinent measure of how the patient "feels, functions, or survives"[3] and be considered as having significant practical value.
- *Validity:* They must have been shown to measure the outcome of interest accurately.
- *Precision:* They should measure the outcome with the smallest error and with minimal uncertainty.
- *Repeatability:* The end-point should perform reliably with repeated measurements.
- *Feasibility:* They should be easily available, without contributing to additional risk, cost or disruption of patient care; ideally being a part of routine data collected.

In critical care, *mortality is considered the ideal end-point*, but nonmortality end-points too could function as valuable practical adjuncts and are being increasingly considered as relevant.

MORTALITY AS AN END-POINT

There are several reasons why mortality end-points are the *favored primary outcome measure* in late-phase clinical trials which are as follows:[4]

- Mortality is *an easy-to-assimilate, binary outcome* that seems straightforward and precise.

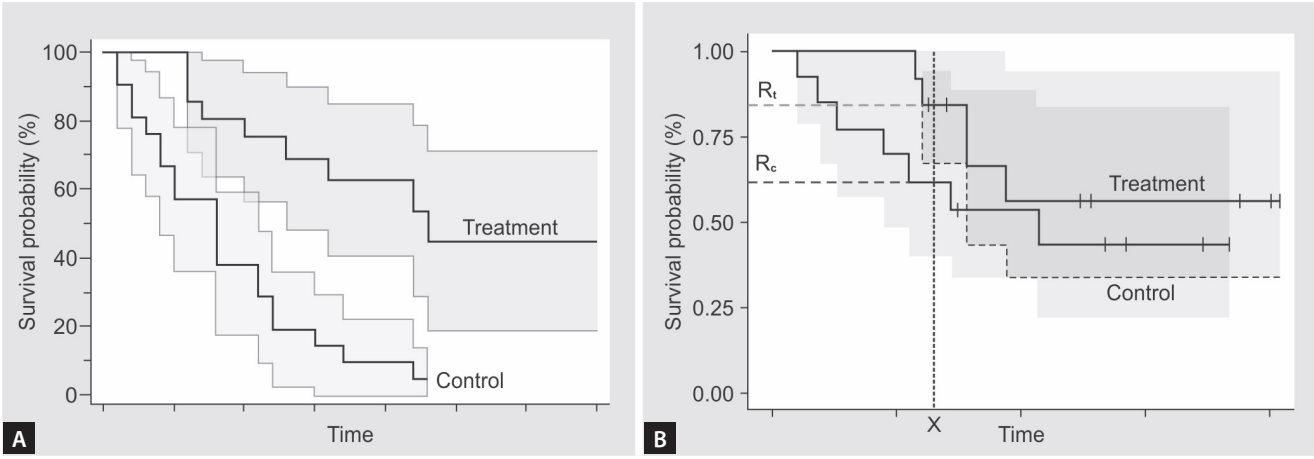
- It is a vital, *patient-centered outcome* that is highly relevant to patients and their relatives.
- It has an *established legacy* in clinical research in the intensive care unit (ICU). Most practitioners have very little confidence in trials that do not report significant mortality end-points. Its importance may have been conflated by the preferences of medical regulatory authorities.[5]

Despite its popularity as an endpoint, there are significant limitations to its performance. In a review of 146 critical care RCTs, studies with mortality as the primary end-point were less likely to support the study hypothesis than those with nonmortality end-points (10% vs. 43–58%).[6] While some of this may actually be due to the inefficacy of studied treatments on mortality (true negative studies), the use of mortality end-points may be intrinsically problematic for the following reasons:

- Clinical studies often show survival benefits that are less than what we anticipate with a successful treatment.[6] A host of confounding factors (covariates) may weaken the advantage of an effective therapy (e.g., the mortality reduction attributable to a successful ventilatory intervention may be offset by death due to sepsis). Understanding this modest impact on survival is essential to setting realistic mortality end-points.
- Despite the impression that mortality is a "hard" end-point that cannot be misidentified, it is often evaluated at fixed time points during treatment. The selection of the ideal time for such evaluation is ambiguous and arbitrary.[5] Thus, a very short evaluation time, say 7 days, may underestimate mortality by not identifying deaths occurring after that interval. We have always assumed that the risk of an outcome, especially mortality, does not increase after the initial duration of critical illness; usually a month—and on this basis we use 28–30-day mortality end-points. The fallacy of this perception is demonstrated, for example, in sepsis where there is excess mortality extending a few years beyond the index event. The arbitrary 28-day mortality end-point will underestimate death in sepsis.

Given the limitations of measuring and interpreting mortality end-points, there are several approaches to improving their performance which are as follows:

- Many RCTs are designed not only with an overestimation of the treatment effect but also the presumption of very poor survival in untreated control patients.[7] Studies based on these presumptions are small, and when executed demonstrate modest, often statistically insignificant, benefits. These "false negative" outcomes can be minimized by setting smaller mortality-reduction goals together with a truthful pre-estimation of mortality in the control arm. *Increasing the sample size of such studies* would be required, but may impose higher study expenditure.
- In contrast to studies that use measurement of mortality at a fixed time interval, one could evaluate the time taken to reach the outcome. This *time-to-event analysis* has the advantage of not requiring to select an arbitrary time for evaluation. These end-points are typically plotted using the Kaplan-Meier "survival-time" estimate. Differences are identified by the slope of "whole" curve *(hazard rates)* in contrast to the fixed-time *risk-rates* **(Figs. 1A and B)**. These analyses incorporate an understanding of data loss ("censoring") and provide more robust assessment of differences in mortality rates.[8,9]
- *Changes in the study design and analysis* may improve the performance of mortality end-points. Among them the *"adaptive platform"* design (e.g., PROWESS-SHOCK[10] trial of drotrecogin α in sepsis), *Bayesian analysis* (e.g.,



Figs. 1A and B: Kaplan–Meier curves plotting the probability of events (% or proportion of survival) over time; (A) Two significantly different curves (no overlap of shaded confidence limits) suggesting that hazard rates are dissimilar (effective treatment); (B) No statistically significant difference between treatment and control (overlapping confidence intervals). It is incorrect to assess mortality risks in treatment and control arms (R_t, R_c) at an arbitrary time interval (X). A statistically significant risk ratio (R_t/R_c) should not be interpreted as treatment benefit.

ANDROMEDA-SHOCK[11] trial), or *cluster-randomized crossover trials*[12] have been suggested. As confounding covariates may attenuate mortality even in studies with very effective treatments, modeling them into the assessment of end-points may be crucial. This may be done a priori, to identify the *attributable mortality*[13] or may use post-hoc *multivariable adjustments* to minimize the confounding effects of preidentified covariates.[6] Detailed discussion of methodology is beyond the scope of this paper.

In summary, mortality end-points are complex in interpretation and are significantly smaller than we often anticipate. Larger trials that use time-to-event analysis are an ideal step toward making them more meaningful.

NONMORTALITY END-POINTS

The power limitations of traditional mortality end-points have renewed interest in nonmortality outcomes as primary or adjunctive measures of therapeutic benefit. Among the more commonly reported nonmortality outcomes in the ICU, the occurrence of organ dysfunction, the need and duration of organ support, and complications rates are often of interest. However, the selection of specific end-points to describe these outcomes remains fraught with methodological concerns that need to be explored.

Incidence/Incidence Rates/Incidence Density

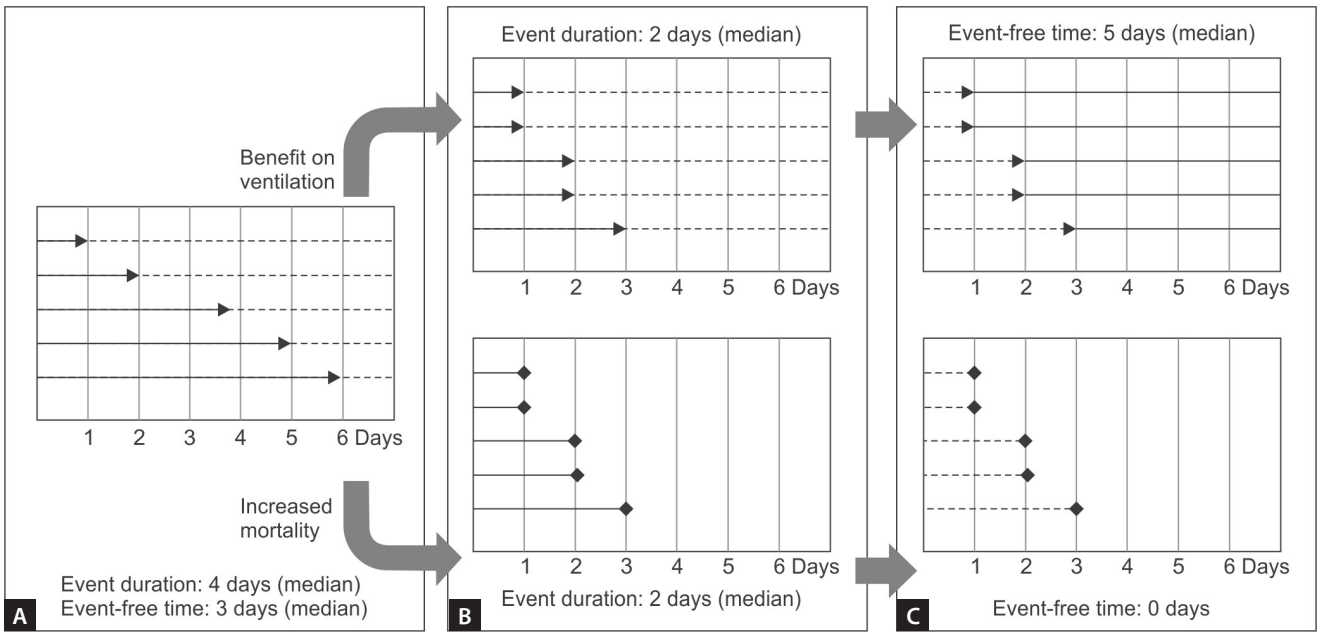
Reporting nonmortality outcomes as simple proportions of the population at risk *(incidence)* would disregard the importance of the duration of illness on their frequency. Consequently, this is usually adjusted for risk-exposure by deriving an *incidence rate* (incidence/number of patient-days), or by including more proximate factors, such as expressing the rates of nosocomial pneumonia per ventilator-day. Incidence rates are also termed *incidence density or exposure-adjusted incidence rates.* While it appears logical to consider treatment-induced changes in incidence density as measurable end-points, an important *drawback* is the nonconstancy of the exposure risk over time, e.g., identical pneumonia incidence rates expressed per 100 ventilator-days may seem equivalent, but may be derived from 100 patients ventilated for 1 day or 10 patients for 10 days. As the risk for pneumonia clearly changes with the duration of ventilation, the two cannot be compared. The limitations of using incidence density ratios instead of time-to-event analysis (see below) have been demonstrated in literature.[14]

Time-to-event Analysis and Event-free Survival

As with mortality end-points, measurement of event rates at fixed time points is erroneous. These events should preferably be measured longitudinally (over time) using time-to-event analysis. Thus, a shortening of days on ventilation or duration of stay in the ICU may be considered markers of effective therapy.

Unfortunately, there is a major shortcoming in event analysis for nonmortality end-points. In the ICU, where death is frequent, the population is a mix of survivors and nonsurvivors. When a treatment effect is measured by the time-to-event, a reduction in duration of nonmortality outcome may demonstrate the benefit of a treatment or it could be caused by accelerated fatality.[15] We use an illustration **(Figs. 2A to C)** to differentiate the two.

The reduction of baseline ventilator days (from a median of 4-days; **Fig. 2A**) with a treatment could either represent



Figs. 2A to C: The limitation of event analysis in high-mortality settings and demonstrates the value of even-free survival (see text for details).

treatment benefit (upper **Fig. 2B**) or a hastened mortality (lower **Fig. 2B**). Both will shorten the duration of ventilation (median 2 days).

The use of *event-free survival* would resolve this dilemma. Prolongation of the length of time a patient remains alive and support-free after the treatment is a better marker of therapeutic success. Effective therapy (upper **Fig. 2C**) shows longer survival free of ventilation ("ventilator-free days" increase to 5 days). Patients who die on ventilation (lower **Fig. 2C**) will have no event-free survival (0 days). Though other methods are available for this distinction, event-free survival is a commonly used end-point.

Continuous/Discrete/Ordinal Scales

Additionally, the end-points that are on a continuous scale [like length of stay (LOS) or duration of ventilation] are preferred over discrete/dichotomous outcome measures (such as the presence or absence of an event), because of higher power. Some end-points cannot be measured on a continuous scale, though progression of severity can be graded on a rank-based (ordinal) scale. Measuring neurological disability in stroke, using the modified Rankin score, is an example. While extreme numerical values can be assigned to each end of the spectrum of disability (0 = no deficit and 6 = death), progression up or down the severity spectrum receive scores that are not linearly related, i.e., each unit change in scale does not represent equivalent progression. Yet these scales, too, provide greater nuance[16] and power[17] than dichotomous end-points. Recently the use of ordinal scales has been advocated for the therapeutic trials in COVID pneumonia where the World Health Organization (WHO) Ordinal score has been used to increase the power of analysis and reduce the duration of studies.[17]

The methods developed above can be applied to most nonmortality end-points in the ICU. A partial list includes:

- Progression and resolution of critical illness (length of ICU stay)
- Development of organ dysfunction [acute kidney injury (AKI), acute respiratory distress syndrome (ARDS), and multiple organ dysfunction syndrome (MODS)]
- Need for organ support (ventilation, dialysis, hemodynamic support)
- Development of complications [infections, shock, pulmonary embolism (PE), cardiovascular events, and stroke]

As an example; LOS[15] is a common measurable outcome in all critically ill patients.

- It is a preferred outcome because of its importance to patients and families. It is a fair correlate of mortality and a good economic determinant.
- It can easily be derived from the ICU charts or electronic records.
- The *end-point of choice should be the hazard rate of ICU-free days*. As a continuous variable, measuring LOS has greater power than analysis of dichotomous outcomes.
- Despite its strengths, care must be taken in standardizing the definitions and in identifying the start and end of ICU stay accurately. For example, a patient who is ready for discharge may face administrative delays in transfer and LOS may be misestimated ("immutable time bias"). These delays may also occur if criteria for admission and discharge are not precisely delineated.[15]

In summary, nonmortality end-points are attractive because their efficacy can be demonstrated even in smaller RCTs. However, they too have limitations that need careful consideration before general use.

COMPOSITE END-POINTS[18,19]

With decreasing mortality in many diseases, very large RCTs are needed to detect new treatment benefits with adequate power. One key approach to reducing trial sizes has been to use composite end-points containing two or more outcome measures (components). The end-points included may be a mix of mortality and nonmortality measures. A composite end-point is attained whenever any one of the component outcomes is seen. Thus, in the composites used for coronary disease, the end-point is reached whenever the first component [death, myocardial infarction (MI) or revascularization procedure] is reached, an approach termed as "time-to-first-event" (TTFE).[18]

As the frequency of such a composite is the sum of individual components, it is an end-point that is more likely to be reached in a clinical trial and could reduce trial size. These components should ideally meet clear prior assumptions:[19]

- Each component must affect the outcome measured in the same direction.
- The relative clinical importance of each component should be identical.
- The frequency of each component must be similarly affected by treatment (equivalent risk reduction).

In most composite end-points, there is seldom similarity in the significance of components (e.g., death and stable MI). Also, if a treatment results in a greater risk reduction of the less important component (unstable angina), it may be misinterpreted as having an equivalent effect on a more serious outcome (death). Several approaches have been taken to improve the value of composite end-points. Instead of the TTFE approach, methods that look at all the components have been suggested.[18] Considering the differential importance of each component, weights can be used to adjust for their relative importance.[18]

With the exception of coronary disease, composite end-points do have widespread use in critical care literature.

CONCLUSION

In conclusion, while mortality continues to remain the preferred end-point in critical care trials, low event rates may confound our ability to draw firm conclusions of benefit or harm in most studies. Attempts to improve their measurement and realistic planning of RCTs will make them more efficient markers of clinical outcome. In such a scenario, nonmortality end-points may be useful adjuncts as long as care is taken to recognize and correct for their limitations. Carefully considered composite endpoints may be used in critical care trials in the future.

REFERENCES

1. McLeod C, Norman R, Litton E, Saville BR, Webb S, Snelling TL. Choosing primary endpoints for clinical trials of health care interventions. Contemp Clin Trials Commun. 2019;16:100486.
2. de Grooth HJ, Parienti JJ and Oudemans-van Straaten HM. Should we rely on trials with disease rather than patient-oriented endpoints? Intensive Care Med. 2017;44(4):464-6.
3. US Department of Health and Human Services F, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER): Multiple Endpoints for Clinical Trials: Guidance for Industry, 2017.
4. Veldhoen RA, Howes D, Maslove DM. Is mortality a useful primary endpoint for critical care trials? Chest. 2019;158(1):206-11.
5. Vincent JL. Endpoints in sepsis trials: More than just 28-day mortality? Crit Care Med. 2004;32(5 Suppl.):S209-213.
6. Harhay MO, Wagner J, Ratcliffe SJ, Bronheim RS, Gopal A, Green S, et al. Outcomes and statistical power in adult critical care. Randomized trials. Am J Respir Crit Care Med. 2014;189(12):1469-78.
7. Latronico N, Metelli M, Turin M, Piva S, Rasulo FA, Minelli C. Quality of reporting of randomized controlled trials published in Intensive Care Medicine from 2001 to 2010. Intensive Care Med. 2013;39(8):1386-95.
8. Schober P, Vetter TR. Survival analysis and interpretation of time-to-event data: The Tortoise and the hare. Anesth Analg. 2018;127(3):792-8.
9. Spruance SL, Reid JE, Grace M, Samore M. Hazard ratio in clinical trials. Antimicrobial agents and chemotherapy. 2004;48(8):2787-92.
10. Ranieri VM, Thompson BT, Barie PS, Dhainaut J-F, Douglas IS, Finfer S, et al. for the PROWESS-SHOCK Study Group. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med. 2012;366(22):2055-64.
11. Zampieri FG, Damiani LP , Bakker J, Ospina-Tasco GA, Castro R, Cavalcanti AB, et al. Effects of a resuscitation strategy targeting peripheral perfusion status versus serum lactate levels among patients with septic shock. A Bayesian reanalysis of the ANDROMEDA-SHOCK Trial. Am J Respir Crit Care Med. 2020;201(4):423-9.
12. Bellomo R, Forbes A, Akram M, Bailey M, Pilcher DV, Cooper DJ. Why we must cluster and cross over. Crit Care Resusc. 2013;15(3):155-7.
13. Shankar-Hari M, Harrison DA, Rowan KM, Rubenfeld GD. Estimating attributable fraction of mortality from sepsis to inform clinical trials. J Crit Care. 2018;45:33-9.
14. Bender R, Beckmann L. Limitations of the incidence density ratio as approximation of the hazard ratio. Trials. 2019;20:485.
15. Harhay MO. (2016). Endpoints in intensive care unit based randomized clinical trials.; Publicly Accessible Penn Dissertations. [online] Available from: https://repository.upenn.edu/edissertations/2326. [Last accessed March, 2022].
16. Saver JL. Novel end point analytic techniques and interpreting shifts across the entire range of outcome scales in acute stroke trials. Stroke. 2007;38(11):3055-62.
17. Dodd LE, Follmann D, Wang J, Koenig F, Korn LL, Schoergenhofer C, et al. Endpoints for randomized controlled clinical trials for COVID-19 treatments. Clin Trials. 2020;17(5):472-82.
18. Armstrong PW, Westerhout CM. Composite end points in clinical research; A time for reappraisal. Circulation. 2017;135:2299-307.
19. McCoy CE. Understanding the use of composite endpoints in clinical trials. West J Emerg Med. 2018;19(4):631-4.

SECTION

23

COVID-19 Related Issues

126

CHAPTER

Pathophysiology of Happy Hypoxia in COVID

Abhinav Gupta, Vikas Gulia

INTRODUCTION

A phenomenon has emerged in the recent coronavirus disease 2019 (COVID-19) pandemic related to profound hypoxemia with minimal dyspnea, which is out of proportion to the extent of radiographic abnormality and change in lung compliance. This has been referred to as happy hypoxia (hypoxemia) or silent hypoxia. There is no consensus definition of happy hypoxia. It has been reported to affect as many as one-third of patients with COVID-19 lung injury if defined as the absence of dyspnea in patients rapidly developing respiratory failure.[1]

It is important to differentiate oxygenation and CO_2 clearance separately.

- Hypoxemia: Generally, it occurs due to:
  - *Ventilation–perfusion (V/Q) mismatch*: Hypoxemia due to perfusion of an *inadequately* ventilated part of lung or inadequate blood flowing to areas of the lung with excess ventilation. Increasing the concentration of inhaled oxygen generally improves this condition.
  - *Shunt physiology*: Blood flows from the right ventricle to the left ventricle without ever coming into contact with oxygenated alveoli at all. This could be either an anatomic abnormality (e.g., ventricular septal defect) or complete dysfunction of parts of the lung (e.g., mucus plugging of one lobe of the lung). A hallmark of shunt physiology is that it is poorly responsive to increased levels of oxygen. Therefore, any patient who is desaturating despite high concentrations of inhaled oxygen likely has a shunt.
- CO_2 clearance and dead space:

$$CO_2 \text{ level} \sim \frac{(CO_2 \text{ production rate due to metabolism})}{(\text{respiratory rate})\,(\text{tidal volume} - \text{dead space})}$$

  Dead space air does not participate in CO_2 clearance. This can be a:
  - "Micro" level dead space—less effective CO_2 clearance. For example, scarred alveoli due to acute respiratory distress syndrome (ARDS) become inefficient at CO_2 clearance.
  - "Macro" level dead space—gas still goes in and out of lung tissue, but no CO_2 clearance occurs. For example, pulmonary embolism.
- The work of breathing is related to the drive to clear CO_2. Factors influencing work of breathing include:
  - *Dead space*: Increasing the dead space means that the patient must inhale and exhale *more* gas every minute to maintain the same CO_2 level.
  - *Lung compliance*: If the lungs have more elastic recoil impeding inflation, this will increase the work of breathing.
  - *Airway resistance*: Airflow obstruction, such as asthma, may increase the work of breathing.

LUNG INJURY IN COVID-19

Direct viral infection due to COVID-19 infection and secondary immune system—mediated inflammation lead to alveolar epithelial and capillary endothelial damage with interstitial edema and alveolar fluid filling. Autopsy data has revealed typical features of ARDS, including exudative and proliferative phases of diffuse alveolar damage, hyaline membranes, edema, atypical pneumocyte hyperplasia, alveolar hemorrhage, infarction, endothelial-cell injury, and capillary congestion with microthrombosis and dilation.[2] However, there is systemic vascular pathology differing from ARDS in COVID-19 patients which includes a greater extent of vascular abnormalities, including macrothrombosis and microthrombosis, endothelial-cell injury, vascular dilation, and aberrant angiogenesis.[3]

PATHOPHYSIOLOGY OF HAPPY HYPOXEMIA

Pathophysiology of refractory hypoxemia with a normal work of breathing involves:

- *Intrapulmonary shunting and impaired diffusion capacity*: The infection leads to interstitial edema, and subsequent loss of surfactant and superimposed pressure leading to alveolar collapse. As a result, there is intrapulmonary shunting due to perfusion of nonaerated lung with a substantial fraction of the cardiac output (Q).

The tidal volume increases during the disease course leading to rising negative inspiratory intrathoracic pressure and in combination with increased lung permeability due to inflammation, this will eventually result in progressive edema, alveolar flooding, and patient self-inflicted lung injury (P-SILI).[4] The increased edema will further enhance lung weight, alveolar collapse, and dependent atelectasis, resulting in progressively increasing shunt fraction and further decline of oxygenation which cannot completely be corrected by increasing fraction of inspired oxygen (F_iO_2).[5] This is reflected by marked increase in alveolar-arterial oxygen pressure [$P(A\text{-}a)O_2$] gradient caused by arterial hypoxemia due to V/Q mismatch and thus persistence of pulmonary arterial blood flow to nonventilated alveoli. Loss of alveolar epithelial cells and a procoagulant state cause the denuded basement membrane to be covered with debris, consisting of fibrin, dead cells, and complement activation products, collectively referred to as hyaline membranes.[5]

- *Relatively preserved lung compliance*: Gas exchange abnormalities in some patients with COVID-19 occur earlier than increases in mechanical loads. During the initial phase of ventilation in COVID-19, there is no increased airway resistance, and there is presumably no increased anatomical or physiological dead-space ventilation. The breathing effort also remains rather low because lung compliance is normal in many patients without preexisting lung disease. As recently shown by Gattinoni et al. in a cohort of 16 critically ill patients, relatively normal values for respiratory system compliance (50.2 ± 14.3 mL/cm H_2O) correlated with increased shunt fraction 0.50 ± 0.11.[6] Relatively high compliance indicates a well-preserved lung gas volume and explains in part the absence of dyspnea early in the course of illness. On the basis of these observations, Gattinoni and colleagues[7] proposed high-compliance phenotype [termed "L type" for low elastance, low recruitability with positive end-expiratory pressure (PEEP), and greater perfusion to regions of low alveolar volume (VA) in relation to cardiac output (Q) rather than shunt formation] combined with vasoplegia [i.e., the absence of hypoxic pulmonary vasoconstriction (HPV)] as a partial explanation for silent hypoxemia. Two explanations have been advanced to explain higher compliance early in COVID-19 lung injury with severe hypoxemia. The first is the focality and limited extent of lung injury on computed tomography (CT) images (often peripheral and basilar ground glass opacities) in many patients early in the disease course. A second explanation is that the gas exchange abnormalities arise primarily from a vascularly mediated injury, leading to a low alveolar V/Q ratio rather than to shunt creation and to less reduction in aeration and lung density. However, autopsy studies[8] do not support these explanations and may simply represent an earlier stage in the evolution of lung injury.
- *Dysfunctional hypoxemic vasoconstriction*: Pulmonary vascular regulation has been postulated to be impaired in patients with COVID-19 to account for a degree of hypoxemia that is out of proportion to the extent of radiographic abnormality and compliance change. The key physiological response to minimizing arterial hypoxemia arising from V/Q mismatch and shunt formation is HPV, and its possible impairment in COVID-19 has been hypothesized. Impairment in HPV and vasoplegia could play a role in increasing the severity of hypoxemia in COVID-19 lung injury. CT and dual-energy CT perfusion imaging have revealed enlarged vessels and enhanced perfusion, particularly in ground glass opacity areas, supporting the idea of dysregulated perfusion. The persistence of high pulmonary blood flow to nonaerated lung alveoli appears to be caused by the relative failure of the HPV mechanism (constriction of small intrapulmonary arteries in response to alveolar hypoxia) during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, as recently illustrated by Lang et al. using dual-energy CT.[9] Vasoplegia also seems to be influential in the loss of lung perfusion regulation, possibly induced by shear stress on the interfaces between lung structures, as part of the P-SILI spectrum. Diminished levels of angiotensin-converting enzyme 2 (ACE2) lead to an increase in angiotensin II (Ang II) mediating pulmonary vasoconstriction through agonism at Ang II-receptor. Liu et al. revealed that serum Ang II levels were linearly associated with viral load and lung injury in COVID-19.[10]

The factors mentioned could potentially be causes of disproportional hypoxia. There could be a pure divorce between oxygenation and CO_2 clearance.

Rapid Deterioration

Hypoxemia-driven tachypnea, hyperpnea, and altered oxygenation predict clinical deterioration induced by either disease severity or host response. As the disease progresses, the more consolidated air spaces do not inflate as easily at higher transpulmonary pressures. The volume loss is proportionally greater at higher lung volumes. This loss of volume reduces total lung compliance and increases the work of breathing. There is also evidence that the dynamic compliance of the remaining ventilated lung is reduced in SARS-CoV-2 pneumonia (as seen in pneumococcal pneumonia) most possibly by a reduction in surfactant activity, further increasing the work of breathing.[11] Physiological dead space is also increasing due to reduced blood flow caused by intravascular thrombi. Importantly, the anxiety experienced by COVID-19 patients also affects the cortical feedback to the respiratory centers. Consequently, as the disease progresses, dyspnea becomes increasingly apparent.[12]

POSSIBLE UNIQUE DIFFERENCE IN VENTILATORY CONTROL AND DYSPNEA PERCEPTION IN COVID-19 LUNG INJURY

SARS-CoV-2 could possibly have a direct effect on peripheral oxygen sensing and response (ACE2 receptors in the carotid body); therefore a direct, virally mediated effect at the level of the carotid bodies could potentially limit the ventilatory response to hypoxia and could decrease or abolish the sense of dyspnea within the midbrain and higher cortical sensory areas.[13] Other coronaviruses have been shown in animal models to affect medullary brain stem nuclei involved in respiration via the transmission of virus directly along afferent nerves arising in the lung, nasopharynx, and other peripheral mechanoreceptors and chemoreceptors.[14]

Older patients and patients with diabetes could have blunted hypoxic responses, and these two high-risk groups may experience less dyspnea when very hypoxemic.[15]

Importantly, silent hypoxemia in COVID-19 should not be compared with states of chronic stable hypoxemia, such as high-altitude residence or congenital cardiac disease. Despite a decreased arterial oxygen content, these individuals develop compensations that allow adequate O_2 delivery and use, including polycythemia, higher perfusion, greater gas exchange efficiency in the lungs and tissues, and more efficient oxygen use at the cellular level. These adaptations, some driven by hypoxia-inducible factor (HIF)–mediated gene upregulation, take considerably more time to evolve than the few days that patients are ill with COVID-19. Relatively asymptomatic patients with COVID-19 and with hypoxemia can have a high rate of rapid respiratory decompensation and greater mortality.[16] Compensatory hyperventilation causes increased stress on less-compliant lung regions with large tidal-volume efforts contributing to further lung injury (P-SILI).[17]

CONCLUSION

This uncommon presentation, never before reported in ARDS, may simply reflect individuals whose pattern of lung injury leads to a decrease in the work of breathing (less reduction in compliance) or whose unique combination of physiological responses maximizes hypoxemia (low HPV) while blunting the ventilatory response (low hypoxic ventilatory response) and dyspnea for any degree of lung injury. Patients with silent hypoxemia have a high risk for rapid deterioration. Despite possible physiological explanations for silent hypoxemia, this state of relative repose does not preclude ongoing lung injury and systemic inflammation that can lead to respiratory failure despite close monitoring and supportive care.

REFERENCES

1. Swenson KE, Ruoss SJ, Swenson ER. The pathophysiology and dangers of silent hypoxemia in COVID-19 lung injury. Ann Am Thorac Soc. 2021;18(7):1098-105.
2. Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. Lancet Infect Dis. 2020;20:1135-40.
3. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. N Engl J Med. 2020;383:120-8.
4. Komorowski M, Aberegg SK. Using applied lung physiology to understand COVID-19 patterns. Br J Anaesth. 2020;125(3):250-3.
5. Mason RJ. Pathogenesis of COVID-19 from a cell biologic perspective. Eur Respir J. 2020;55(4):2000607.
6. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. Covid-19 does not lead to a "typical" acute respiratory distress syndrome. Am J Respir Crit Care Med. 2020;201(10):1299-300.
7. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. 2020;46(6):1099-102.
8. Pernazza A, Mancini M, Rullo E, Bassi M, De Giacomo T, Rocca CD, et al. Early histologic findings of pulmonary SARS-CoV-2 infection detected in a surgical specimen. Virchows Arch. 2020;477(5):743-8.
9. Lang M, Som A, Mendoza DP, Flores EJ, Reid N, Carey D, et al. Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. Lancet Infect Dis. 2020;20(12):1365-6.
10. Liu W, Hualan L. COVID-19: Attacks the 1-Beta chain of hemoglobin and captures the porphyrin to inhibit human Heme metabolism. ChemRxiv. 2020.
11. Light RB. Pulmonary pathophysiology of pneumococcal pneumonia. Semin Respir Infect. 1999;14(3):218-26.
12. Worsham CM, Banzett RB, Schwartzstein RM. Air hunger and psychological trauma in ventilated patients with COVID-19: an urgent problem. Ann Am Thorac Soc. 2020;17:926-7.
13. Villadiego J, Ram´ırez-Lorca R, Cala F, Labandeira-Garc´ıa JL, Esteban M, Toledo-Aral JJ, et al. Is carotid body infection responsible for silent hypoxemia in COVID-19 patients? Function (Oxf). 2020;2(1):zqaa032.
14. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol. 2020;92(6):552-5.
15. Tobin MJ, Laghi F, Jubran A. Why COVID-19 silent hypoxemia is baffling to physicians. Am J Respir Crit Care Med. 2020;202:356-60.
16. Xie J, Covassin N, Fan Z, Singh P, Gao W, Li G, et al. Association between hypoxemia and mortality in patients with COVID-19. Mayo Clin Proc. 2020;95(6):1138-47.
17. Li HL, Chen L, Brochard L. Protecting lungs during spontaneous breathing: what can we do? J Thorac Dis. 2017;9(9):2777-81.

CHAPTER 127

Hypoxemia and Cardiorespiratory Compensation in COVID-19

Amit Kumar Mandal, Alok Sahoo, Swagata Tripathy

INTRODUCTION

Coronavirus infection disease 2019 (COVID-19) pandemic brought innumerable patients with significant hypoxemia. Hypoxemia can be life-threatening, and human physiology compensates for it variably. Cardiovascular response to acute hypoxemia comprises increased cardiac output and a neurogenic redistribution of peripheral blood flow, with preferential oxygen delivery to the central nervous system and myocardium. Presentation of hypoxemia has been conventional in most cases of COVID-19, though a significant proportion has been "silent"—the true extent of silent hypoxemia is unknown, as there is no consensus definition. The present chapter deals with the possible causes, cardiorespiratory compensations, and clinical implications of hypoxemia in the management of COVID-19.

HYPOXEMIA LUNG INJURY

Hypoxemia[1-3] has been the cardinal reason for hospital admission in COVID-19 positive patients and the leading predictor of admission to the intensive care unit, mechanical ventilation, and death.[4,5] Elderly patients are especially vulnerable for severe hypoxemia, with mortality in the range of 40–80%.[2,4,6,7]

Intrapulmonary shunt and ventilation-perfusion mismatch are the chief gas exchange abnormalities causing hypoxemia in COVID-19, as in other viral pneumonia, bacterial pneumoniae,[8] and acute respiratory distress syndrome **(Fig. 1)**.[9]

Specific pathophysiologic characteristics may be more indicative of COVID-19 than others, including substantial endothelial damage and micro- or macroemboli formation.[10] Unique shunt physiology appears in COVID pneumonia: An increase in minute ventilation decreases carbon dioxide (CO_2) more than it increases oxygenation. Reduction in CO_2 restricts respiratory drive and the expected dyspnea **(Table 1)**.[11] Whether hypoxemia or systemic inflammation in COVID-19 contributes to microvascular injury, hypercoagulable state, and other organ dysfunctions, such as

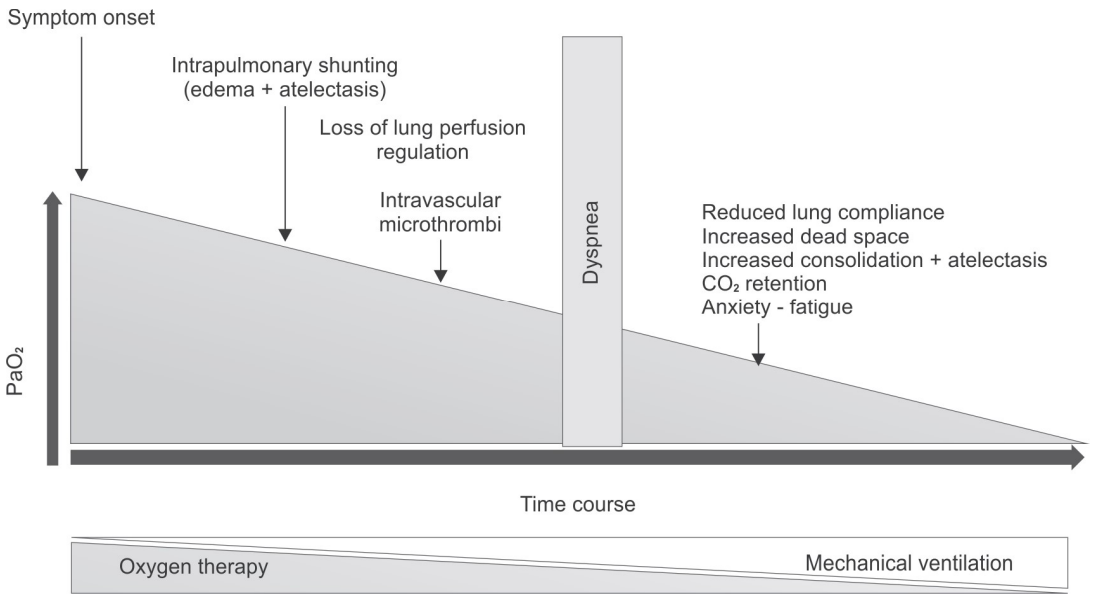


Fig. 1: Possible mechanisms of hypoxemia in COVID-19.[28]

TABLE 1: Response to arterial hypoxemia.[11]

Response to arterial hypoxemia				
Chemoreceptors	***Sense primarily***	***Ventilatory response***		***Limitations***
Peripheral	Hypoxemia (also CO_2 and pH)	• Increase TV • Increase RR • Increase alveolar ventilation	• Increase PaO_2 • Increase pH	• Shunt • VQ mismatch • Respiratory muscle work • Interpersonal variability
Central	CO_2 and pH (also hypoxemia)		Decreases $PaCO_2$	
In COVID pneumonia				
Presentation		***Ventilatory response***	*Limits respiratory drive and dyspnea*	
• Shunt • VQ mismatch	Decrease PaO_2	$PaCO_2$ is normal or reduced		

(RR: respiratory rate; TV: tidal volume)

lung damage through an exacerbation of local inflammatory response[12] (as shown in nonventilated lung regions and other organs in non-COVID-19 disease) is unknown **(Table 1)**.

VARIATION IN HYPOXEMIA AND BREATHLESSNESS

In a retrospective study,[13] patients admitted to the hospital with dyspnea, or silent hypoxia had a similar clinical course. Hypoxia if untreated can increase morbidity and mortality; hence pulse oximetry is recommended in every COVID-19 patient, irrespective of symptoms.

- CO_2 retention is more strongly correlated with breathlessness in lung disease than hypoxemia.[14]
- Mild hyperventilation can significantly reduce arterial CO_2 and decrease respiratory drive mediated by carotid and central chemoreceptors **(Table 1)**.[15] Minimal effects observed in CO_2 excretion compared to O_2 uptake with intrapulmonary shunt and $\dot{V}/\dot{Q}$ mismatch.[16]
- Breathlessness will be limited to patients who increase breathing and lower arterial partial pressure of CO_2.[17] As observed in high altitude, individuals have arterial hypoxemia; still, they demonstrate limited subjective breathlessness due to an unnoticed increase in the respiratory rate that washes out enough arterial CO_2 to mitigate the sensation of dyspnea.[18]
- Ventilatory response to hypoxemia[19] is largely mediated by the carotid chemoreceptors. Brainstem and cerebrocortex mediate hypoxic ventilatory decline and are highly variable: wherein some patients, the respiratory rate and tidal volume, increased when exposed to hypoxia, others may have little response[20] or exhibit decreased minute ventilation despite significant hypoxemia.[20,21] Sustained COVID-19-induced hypoxemia for 15 minutes can lead to hypoxic ventilatory decline.
- A healthy adaptation to hypoxia during ascent to high altitude overcomes this hypoxic ventilatory decline,[18] but in chronic mountain sickness, this adaptation fails, resulting in worsening hypoxemia, polycythemia, and congestive heart failure.[22]
- Responses to hypoxia and hypercapnia reduce with age 40–50% reduction in the hypoxic and hypercapnic ventilatory responses between young (22–30 years) and older (64–73 years) subjects.[23,24]
- Hypoxic ventilatory responses vary with ethnicity[20] and are blunted by chronic hypoxia, as in chronic obstructive pulmonary disease (COPD), sleep apnea, and obesity[25,26] placing such patients at a higher risk of profound hypoxemia at the time of clinical presentation.
- Silent hypoxemia in COVID-19 should not be compared with states of chronic stable hypoxemia, such as high-altitude residence or congenital cardiac disease, as these individuals develop compensations that allow adequate O_2 delivery and use, including polycythemia, greater gas exchange efficiency in the lungs and tissues, and more efficient oxygen use at the cellular level. These adaptations, some driven by HIF (hypoxia-inducible factor)-mediated gene upregulation, take considerably more time to evolve than the few days that patients are ill with COVID-19.[27]

HYPOXEMIA IN COVID-19 LUNG INJURY AND NON-COVID-19 ARDS

COVID-19 lung injury and published reports for or against the hypothesis are given in **Tables 2 to 4**.

CARDIOVASCULAR RESPONSE TO HYPOXEMIA

Cardiovascular response to hypoxemia is shown in **Figure 2**.

Cardiovascular response to acute hypoxemia:[11]

- Increased cardiac output, mediated predominantly by increased heart rate with moderate augmentation of blood pressure

TABLE 2: Vascular regulation.

COVID-19-induced lung injury		***Non-COVID-19-induced ARDS***
Hypothesis	Vasoplegia and impaired HPV (hypoxic pulmonary vasoconstriction)	Intact vascular responsiveness
Published reports	*For*: • Imaging: Vascular engorgement and increased perfusion in diseased lung areas[29,30] • Mildly elevated PA pressure by echocardiography and PA catheterization[31-33] • ACE-2 expression in lung vasculature[34] *Against*: • Almitrine and inhaled pulmonary vasodilators-beneficial use argues against global vasoplegia[35,36] • No direct evidence of HPV impairment	• *Hypoxemia in ARDS*: – Improved with Almitrine and inhaled pulmonary vasodilators[37,38] – Worsened by systemic vasodilators[37,38] • Mildly elevated PA pressure and PVR, by PA catheterization[39,40] • Direct evidence of HPV responsiveness[41]
Conclusion: Limited data with need for further investigation.		

(ACE-2: angiotensin-converting enzyme 2; ARDS: acute respiratory distress syndrome; PA: pulmonary artery; PVR: pulmonary vascular resistance)

TABLE 3: Lung compliance.

COVID-19 induced lung injury		***Non-COVID-19 induced ARDS***
Hypothesis	Compliance minimally reduced	Compliance greatly reduced
Published reports	C_{ST} range, 20–90 mL/cm H_2O[1,42-44]	C_{ST} range, 10–78 mL/cm H_2O[45,46]
Conclusion: Minimal and clinically nonsignificant differences in observed values considering the wide range of compliance seen in non-COVID-19 ARDS.		

(ARDS: acute respiratory distress syndrome)

TABLE 4: Oxygen and dyspnea.

COVID-19-induced lung injury		***Non-COVID-19-induced ARDS***
Hypothesis	Impaired central and peripheral O_2 sensing and dyspnea perception secondary to direct viral effects	Preserved O_2 sensing at both peripheral and central chemoreceptors and intact dyspnea perception
Published reports	• Viral access in brain stem and cortex in humans[47] • Viral brain stem access in animals[48] • Carotid body and brain express ACE-2[49,50] • No reported dyspnea in 9–34% of patients[1,42]	0–27% of patients with no reported dyspnea in SARS and H1N1 influenza ARDS[51-54]
Conclusion: Limited data with need for further investigation because of ACE-2 expression in brain and chemoreceptors and documented viral presence in these sites.		

(ACE-2: angiotensin-converting enzyme 2; ARDS: acute respiratory distress syndrome; COVID-19: coronavirus disease; SARS: severe acute respiratory syndrome)

- Limited by age and cardiovascular disease
- Cognitive function is preserved till late due to increased cerebral blood flow holding cerebral oxygenation.[55,56]

LIMITS OF CARDIOVASCULAR COMPENSATION IN PROFOUND HYPOXEMIA

Decreased tolerance of physical exertion or even regular activity is a sensitive indicator of the adequacy of early cardiovascular response to hypoxemia. A critical threshold is reached when oxygen delivery is reduced to <25% of normal and there is no difference in critical O_2 delivery threshold in septic and non-septic patients.[57] This point of failure of cardiovascular compensation[11] is characterized by one following:

- Worsening acidosis or serum lactate
- Decreased mixed venous oxygenation
- Increased requirements for vasopressors despite adequate fluid resuscitation
- Increase in blood pressure fluctuations to changes in body position
- Bradycardia, arrhythmias, ischemic changes on electrocardiogram (ECG), and heart rate variability

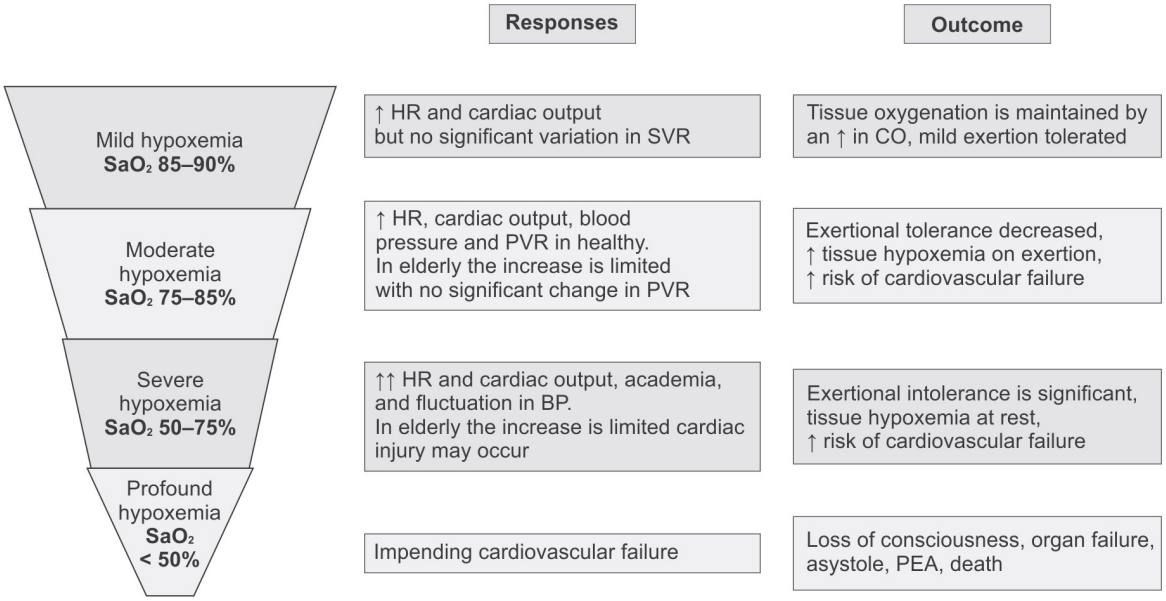


Fig. 2: Cardiovascular compensation of different hypoxemia[11] mild (85–90% SpO_2), moderate (75–85% SpO_2), severe (50–75% SpO_2), and profound (<50% SpO_2) hypoxemia.
(CO: cardiac output; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance)

- Increased troponin levels or decreased myocardial contractility.

COVID-19 can cause cardiac complications; dysfunction of the right ventricle (RV) in particular is common and often associated with a poor prognosis.[58] Echocardiographic studies reveal right ventricular dysfunction in up to 40% of patients. RV dysfunction in COVID-19 causes increased pulmonary vascular hydraulic load and reduced RV contractility, which precipitates the acute uncoupling of the RV from the pulmonary circulation. Protective ventilation strategy in ARDS should be rigorously applied to reduce the risk of ventilator-induced lung injury and RV dysfunction.[59]

CONCLUSION

Hypoxemia in any patient can be life-threatening. Acute hypoxemia begets specific compensatory changes in the cardiorespiratory physiology to protect the body from its harmful effects. Although a "silent" response to hypoxemia is not unknown, COVID-19 is unique in having a more significant proportion of patients presenting with this partial compensation, which, if left unrecognized or undertreated, may be fatal. While the uniqueness of COVID-19 is still being studied, it is pertinent that relatively asymptomatic patients with COVID-19 and hypoxemia can decompensate to rapid cardiorespiratory failure with a high mortality.[60]

REFERENCES

1. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in critically ill patients in the Seattle region-case series. N Engl J Med. 2020;382:2012-22.
2. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA. 2020;323:1574-81.
3. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8:475-81.
4. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180:1-11.
5. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: Prospective cohort study. BMJ. 2020;369:m1966.
6. Gold JAW, Wong KK, Szablewski CM, Patel PR, Rossow J, da Silva J, et al. Characteristics and clinical outcomes of adult patients hospitalized with COVID-19-Georgia, March 2020. MMWR Morb Mortal Wkly Rep. 2020;69:545-50.
7. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020;323:2052-9.
8. Light RB. Pulmonary pathophysiology of pneumococcal pneumonia. Semin Respir Infect. 1999;14:218-26.
9. Radermacher P, Maggiore SM, Mercat A. Fifty years of research in ARDS. Gas exchange in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2017;196:964-84.
10. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med. 2020;383:120-8.

11. Bickler PE, Feiner JR, Lipnick MS, McKleroy W. "Silent" Presentation of Hypoxemia and Cardiorespiratory Compensation in COVID-19. Anesthesiology. 2021;134(2):262-9.
12. Eltzschig HK, Carmeliet P. Hypoxia and inflammation. N Engl J Med. 2011;364:656-65.
13. Bhatnagar S, Sirohiya P, Elavarasi A, Sagiraju HKR, Baruah M, Gupta N, et al. (2021). Silent Hypoxia in Coronavirus disease-2019: Is it more dangerous? A retrospective cohort study. [online] Available from https://www.medrxiv.org/content/10.1101/2021.08.26.21262668v1.
14. Kobayashi S, Nishimura M, Yamomoto M, Akiyama Y, Miyamoto K, Kawamaki Y. Relationship between breathlessness and hypoxic and hypercapnic ventilatory response in patients with COPD. Eur Respir J. 1996;9:2340-5.
15. Forster HV, Smith CA. Contributions of central and peripheral chemoreceptors to the ventilatory response to CO_2/H+. J Appl Physiol (1985). 2010;108:989-94.
16. Petersson J, Glenny RW. Gas exchange and ventilation-perfusion relationships in the lung. Eur Respir J. 2014;44:1023-41.
17. Prabhakar N. O_2 and CO_2 detection by the carotid and aortic bodies. In: Zufall F, Munger S (Eds). Chemosensory Transduction. Philadelphia: Elsevier; 2016. pp. 321-38.
18. Sato M, Severinghaus JW, Bickler P. Time course of augmentation and depression of hypoxic ventilatory responses at altitude. J Appl Physiol (1985). 1994;77:313-6.
19. Bisgard GE, Neubauer JA. Peripheral and central effects of hypoxia. In: Dempsey J, Pack A (Eds). Regulation of Breathing. New York: Marcel Dekker; 1995. pp. 617-68.
20. Powell FL, Milsom WK, Mitchell GS. Time domains of the hypoxic ventilatory response. Respir Physiol. 1998;112:123-34.
21. Robbins PA. Hypoxic ventilatory decline: Site of action. J Appl Physiol (1985). 1995;79:373-4.
22. Wilkins MR, Ghofrani HA, Weissmann N, Aldashev A, Zhao L. Pathophysiology and treatment of high-altitude pulmonary vascular disease. Circulation. 2015;131:582-90.
23. Kronenberg RS, Drage CW: Attenuation of the ventilatory and heart rate responses to hypoxia and hypercapnia with aging in normal men. J Clin Invest. 1973;52:1812-9.
24. Peterson DD, Pack AI, Silage DA, Fishman AP. Effects of aging on ventilatory and occlusion pressure responses to hypoxia and hypercapnia. Am Rev Respir Dis. 1981;124:387-91.
25. Zwillich CW, Sutton FD, Pierson DJ, Greagh EM, Weil JV. Decreased hypoxic ventilatory drive in the obesity-hypoventilation syndrome. Am J Med. 1975;59:343-8.
26. Garay SM, Rapoport D, Sorkin B, Epstein H, Feinberg I, Goldring RM. Regulation of ventilation in the obstructive sleep apnea syndrome. Am Rev Respir Dis. 1981;124:451-7.
27. Swenson KE, Ruoss SJ, Swenson ER. The pathophysiology and dangers of silent hypoxemia in COVID-19 lung injury. Annals ATS. 2021;18(7):1098-105.
28. Dhont S, Derom E, Braeckel EV, Depuydt P, Lambrecht BN. The pathophysiology of 'happy' hypoxemia in COVID-19. Respir Res. 2020;21:198.
29. Lang M, Som A, Carey D, Reid N, Mendoza DP, Flores EJ, et al. Pulmonary vascular manifestations of COVID-19 pneumonia. Radiol Cardiothorac Imaging. 2020;2:e200-77.
30. Patel BV, Arachchillage DJ, Ridge CA, Bianchi P, Doyle JF, Garfield B, et al. Pulmonary angiopathy in severe COVID-19: physiologic, imaging, and hematologic observations. Am J Respir Crit Care Med. 2020;202:690-9.
31. Evrard B, Goudelin M, Montmagnon N, Fedou AL, Lafon T, Vignon P. Cardiovascular phenotypes in ventilated patients with COVID-19 acute respiratory distress syndrome. Crit Care. 2020;24:236.
32. Pagnesi M, Baldetti L, Beneduce A, Calvo F, Gramegna M, Pazzanese V, et al. Pulmonary hypertension and right ventricular involvement in hospitalised patients with COVID-19. Heart. 2020;106:1324-31.
33. Caravita S, Baratto C, Di Marco F, Calabrese A, Balestrieri G, Russo F, et al. Haemodynamic characteristics of COVID-19 patients with acute respiratory distress syndrome requiring mechanical ventilation: an invasive assessment using right heart catheterization. Eur J Heart Fail. 2020;22:2228-37.
34. Wiener RS, Cao YX, Hinds A, Ramirez MI, Williams MC. Angiotensin converting enzyme 2 is primarily epithelial and is developmentally regulated in the mouse lung. J Cell Biochem. 2007;101:1278-91.
35. Bendjelid K, Giraud R, Von Düring S. Treating hypoxemic COVID-19 "ARDS" patients with almitrine: the earlier the better? Anaesth Crit Care Pain Med. 2020;39:451-2.
36. Fan E, Beitler JR, Brochard L, Calfee CS, Ferguson ND, Slutsky AS, et al. COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted? Lancet Respir Med. 2020;8:816-21.
37. Mélot C, Naeije R, Mols P, Hallemans R, Lejeune P, Jaspar N. Pulmonary vascular tone improves pulmonary gas exchange in the adult respiratory distress syndrome. Am Rev Respir Dis. 1987;136:1232-6.
38. Reyes A, Roca J, Rodriguez-Roisin R, Torres A, Ussetti P, Wagner PD. Effect of almitrine on ventilation-perfusion distribution in adult respiratory distress syndrome. Am Rev Respir Dis. 1988;137:1062-7.
39. Squara P, Dhainaut JF, Artigas A, Carlet J, Group ECAW. Hemodynamic profile in severe ARDS: results of the European Collaborative ARDS Study. Intensive Care Med. 1998;24:1018-28.
40. Bull TM, Clark B, McFann K, Moss M, National Institutes of Health/National Heart, Lung, and Blood Institute ARDS Network. Pulmonary vascular dysfunction is associated with poor outcomes in patients with acute lung injury. Am J Respir Crit Care Med. 2010;182:1123-8.
41. Benzing A, Mols G, Brieschal T, Geiger K. Hypoxic pulmonary vasoconstriction in nonventilated lung areas contributes to differences in hemodynamic and gas exchange responses to inhalation of nitric oxide. Anesthesiology. 1997;86:1254-61.
42. Ziehr DR, Alladina J, Petri CR, Maley JH, Moskowitz A, Medoff BD, et al. Respiratory pathophysiology of mechanically ventilated patients with COVID-19: a cohort study. Am J Respir Crit Care Med. 2020;201:1560-4.
43. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 does not lead to a "typical" acute respiratory distress syndrome. Am J Respir Crit Care Med. 2020;201:1299-300.
44. Ramin S, Charbit J, Dagod G, Girard M, Jaber S, Capdevila X. Transpulmonary pressure in SARS-CoV-2-associated acute respiratory distress syndrome: a single-center observational study. Crit Care. 2020;24:408.

45. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al.; PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368:2159-68.
46. Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med. 2006;354:1775-86.
47. Matschke J, Lütgehetmann M, Hagel C, Sperhake JP, Schröder AS, Edler C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. Lancet Neurol. 2020;19:919-29.
48. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol. 2020;92:552-5.
49. Villadiego J, Ramírez-Lorca R, Cala F, Labandeira-García JL, Esteban M, Toledo-Aral JJ, et al. Is carotid body infection responsible for silent hypoxemia in COVID-19 patients? Function (Oxf). 2021;2:zqaa032.
50. Kabbani N, Olds JL. Does COVID19 infect the brain? If so, smokers might be at a higher risk. Mol Pharmacol. 2020;97:351-3.
51. Xiao Z, Li Y, Chen R, Li S, Zhong S, Zhong N. Aretrospective study of 78 patients with severe acute respiratory syndrome. Chin Med J (Engl). 2003;116:805-10.
52. Sheng WH, Chiang BL, Chang SC, Ho HN, Wang JT, Chen YC, et al. Clinical manifestations and inflammatory cytokine responses in patients with severe acute respiratory syndrome. J Formos Med Assoc. 2005;104:715-23.
53. Chen CY, Lee CH, Liu CY, Wang JH, Wang LM, Perng RP. Clinical features and outcomes of severe acute respiratory syndrome and predictive factors for acute respiratory distress syndrome. J Chin Med Assoc. 2005;68:4-10.
54. Siau C, Law J, Tee A, Poulose V, Raghuram J. Severe refractory hypoxaemia in H1N1 (2009) intensive care patients: initial experience in an Asian regional hospital. Singapore Med J. 2010;51:490-5.
55. Schober A, Feiner JR, Bickler PE, Rollins MD. Effects of changes in arterial carbon dioxide and oxygen partial pressures on cerebral oximeter performance. Anesthesiology. 2018;128:97-108.
56. Lefferts WK, Hughes WE, White CN, Brutsaert TD, Heffernan KS. Effect of acute nitrate supplementation on neurovascular coupling and cognitive performance in hypoxia. Appl Physiol Nutr Metab. 2016;41:133-41.
57. Ronco JJ, Fenwick JC, Tweeddale MG, Wiggs BR, Phang PT, Cooper DJ, et al. Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. JAMA. 1993;270:1724-30.
58. Bonnemain J, Ltaief Z, Liaudet L. The right ventricle in COVID-19. J Clin Med. 2021;10:2535.
59. Guérin C, Albert RK, Beitler J, Gattinoni L, Jaber S, Marini JJ, et al. Prone position in ARDS patients: Why, when, how and for whom. Intensiv Care Med. 2020;46:2385-96.
60. Xie J, Covassin N, Fan Z, Singh P, Gao W, Li G, et al. Association between hypoxemia and mortality in patients with COVID-19. Mayo Clin Proc. 2020;95:1138-47.

CHAPTER

128

Coronavirus Disease-associated Fungemia

Shivaprakash M Rudramurthy, Arunaloke Chakrabarti

INTRODUCTION

Candida species is most commonly encountered pathogen in fungemia cases admitted to the intensive care units (ICUs).[1,2] In the pre-coronavirus disease (COVID) era, the incidence of candidemia in these settings varied between 1 and 34/1,000 ICU admission depending upon geographic region and type of ICU's. Overall mortality of the candidemia cases may go up to 60%.[2,3] In critically ill patients admitted to ICU, multiple factors such as prolonged ICU stay, central venous catheter (CVC), broad-spectrum antibiotics, mechanical ventilation, surgery, anastomotic leakage, and acute necrotic pancreatitis are considered important risk factors for acquiring candidemia.[1] Though *C. albicans* is the most common pathogen in developed countries, nonalbicans *Candida* with the species resistant to azoles and echinocandins have emerged in many countries in both developed and developing world. Since 2009, emergence of multidrug resistant *C. auris* pandemic has multiplied the challenge in managing ICU admitted patients.[4,5]

In the early part of COVID-19 pandemic, low (<1%) incidence of secondary fungal infection was reported due to strict infection control practices.[6] However, since second half of 2020 secondary fungal infections including candidemia is increasingly reported due to indiscriminate use of antibiotics, glucocorticoids, immunomodulators, and lapse of infection control.[7] Rarely, fungemia due to *Cryptococcus* spp.,[8] *Trichosporon* spp.,[9] and *Saccharomyces cerevisiae* (after use of probiotics) have been reported. The present chapter describes the epidemiology, diagnosis, management, and prevention of COVID-associated fungemia with specific reference to the critically ill patients admitted to ICU.

EPIDEMIOLOGY

Majority of the reported cases of COVID-19-associated candidemia (CAC) are from patients admitted to ICU's. The incidence varies ranging from 0.7 to 23.5% among different countries including Spain (0.7%), India (2.5%), Iran (5.0%), Italy (8.0%), United Kingdom (12.6%), and China (23.5%).[10,11,12-17] Low incidence in certain centers in Spain was possibly due to practice of antimicrobial stewardship even during pandemic period, as was observed in an university hospital where antimicrobial consumption was similar during baseline and pandemic period.[18] However, in another hospital in the same country, an overwhelming incidence of candidemia in critically ill COVID patients was noted in 4 months (10.8%) compared with previous 7 years (1.07–2.19 candidemia/1,000 patients admitted to the ICU).[19] Similarly, 10 times increase in frequency of candidemia was reported during pandemic period in two Brazil hospitals.[20] The candidemia rate at 1.15–1.43 cases/1,000 patient days on March 16, 2020 rose to 10.23–11.83 cases/1,000 patient days on August 31, 2020 in those two hospitals. The overall mortality also rose to 72.7% from 17.7 to 22.0%. Indiscriminate uses of antibiotics and steroid were considered responsible for the rise of number of CAC cases.[20] Similar rise in number of CAC was noted in United Kingdom (12% vs. 6.9% $p = 0.0336$).[15] They mentioned that the increased rate of invasive candidiasis observed during the COVID-19 pandemic was not directly associated with the COVID-19 itself, but possibly related to medical therapies of those patients.[15] In Italy also, the number of CAC cases was significantly higher during COVID-19 pandemic period compared to historic pre-COVID cohort (10.97 vs. 1.48 cases per 10,000 persons-day follow-up, $p \leq 0.001$). The same study reported ICU stay and immunosuppression were significantly associated with CAC cases.[21] Similar rise in CAC cases was noted in patients admitted to ICU in the United States of America (USA),[22] Turkey,[23] and Columbia.[24] In Turkey, candidemia incidence was higher in COVID-19 patients (2.16/1,000 patient-days) than non-COVID-19 patients during pandemic period (1.06/1,000 patient-days) ($p < 0.001$), and candidemia developed 2 weeks earlier in COVID-19 groups and CAC patients had higher mortality (92.5% vs. 79.4%, $p < 0.005$). CAC cases had higher rate of corticosteroid use (63.8% vs. 9.9%; $p < 0.001$).[23] A study from United States showed 50–80% of CAC cases were healthcare-associated, while comparing the candidemia

cases during pandemic, prepandemic periods, and non-COVID-associated candidemia during pandemic period.[25] In India, 2.5% (15/596) of candidemia cases were reported from critically ill COVID-19 patients at New Delhi.[10]

In general, the time to develop fungemia in COVID-19 patients admitted to ICU varied from 5 to 53 days with overall mortality of ~45%.[11] Although the mortality in these patients depends on the comorbid conditions of individual patient, implicated *Candida* species can also be related to mortality rate, as high mortality has been associated with *C. glabrata* (100%), *C. auris* (60%), and *C. albicans* (42%).[11]

Available studies reporting COVID 19-associated fungemia in ICU settings indicates that *C. albicans* is still the most common agent in developed countries followed by *C. auris, C. glabrata, C. parapsilosis, C. tropicalis,* and *S. cerevisiae*.[11] Fungemia due to *Cryptococcus* spp. and *Trichosporon* spp. have also been reported in these group of patients.[8,9] *S. cerevisiae* fungemia has been linked to probiotic use.[26] Fungemia due to more than one species of yeast in the same patient is not uncommon. However, there is no difference in the antifungal susceptibility noted in the *Candida* species isolated from COVID-19 and non-COVID-19 patients.[23]

The re-emergence of multidrug resistant *C. auris* in COVID-19 patients has been reported in many countries. In India, the fungus was isolated in majority (10 cases) of candidemia cases with the high case-fatality rate of 60%.[10] In Columbia, six of 20 cases of fungemia were due to *C. auris*.[24] *C. auris* candidemia developed early (9 days vs. 17.7 days) and had higher mortality (47.1% vs. 60%).[24]

RISK FACTORS FOR COVID 19-ASSOCIATED CANDIDEMIA

Like the risk factors of candidemia in ICUs in pre-COVID period, the risk factors in CAC included prolonged stay in the ICU, indwelling CVCs, mechanical ventilation, diabetes mellitus, abdominal surgery, parenteral nutrition, and receipt of broad-spectrum antibiotics. Long stay of the COVID 19 patients in the ICU on mechanical ventilation leads to high rate of bacterial superinfection, and use of multiple antibiotics in those patients increase the chance of acquiring candidemia.[1,2] In addition to the classical risk factors, COVID-19 patients may be at higher risk of acquiring the yeast infections due the inflammatory response elicited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), such as induction of diabetes mellitus. Use of mechanical ventilation, extracorporeal membrane oxygenation (ECMO), and corticosteroids in COVID-19 patients are considered as specific risk for CAC.[11,15,27] COVID-19 can cause sepsis or septic shock-like syndrome resulting in damage to the epithelial cell leading to translocation of the commensal *Candida* spp. from the gut or respiratory tract into the blood stream. Indirect evidence of fungal translocation through mucosal barrier damage has been established by measurement of serum beta-d-glucan (BDG) and correlating it with severity of sepsis and septic shock.[28]

Patients with severe respiratory failure needs ECMO. High numbers of vascular catheters used in the ECMO procedure and increased tendency of clotting predispose the colonizing *Candida* species to adhere to the catheters and acts as a source of dissemination leading to fungemia.[11] Corticosteroids may cause immunosuppression by decreasing the inflammatory cytokines production such as interleukin-1 (IL-1), IL-6, tumor necrosis factor (TNF), and leukotrienes by macrophages. In multivariate logistic regression analysis, corticosteroid use was identified as one of the independent risk factors for mortality in candidemia patients.[23]

Hyperglycemic state in COVID-19 patients is induced by the virus itself, poor glycemic control of diabetic patients, COVID-19 infection-related stress, and corticosteroid therapy. COVID-19 damages the pancreatic beta-cells expressing angiotensin-converting enzyme-2 receptors leading to acute diabetes directly or indirectly.[29] The corticosteroid therapy in acute respiratory distress syndrome (ARDS) of severe COVID 19 patients also deranges the sugar level. The hyperglycemic state is a risk factor for CAC. In a review of CAC, diabetes was risk factor in 35% (15/43) patients.[11] Immunomodulators such as tocilizumab may also lead to CAC.[30] Recently, Moser et al. have demonstrated attenuated monocyte CD80 upregulation and rescinded release of IL-6, TNF, IL-1a, and IL-1b in COVID-19 patients increase susceptibility for *C. albicans* infection.[31] A case of cryptococcal fungemia suggests nosocomial acquisition or reactivation of the latent or asymptomatic infection due to stress related to COVID-19.[8]

DIAGNOSIS

The salient features of the available diagnostic tests for CAC are summarized in **Table 1**. The gold standard for the diagnosis of fungemia in COVID-19 is by blood cultures, though the procedure has low-sensitivity and long turn-around time. The sensitivity may improve with the culture of high volume of blood (40 mL of blood in two sets of blood culture). The isolated yeast can be identified using various automated phenotypic identification systems, but some yeasts like *C. auris* may be misidentified by those methods. Recently, real-time-based system (AurisID, OLM diagnostics) claims identification of *C. auris* within 60–90 minutes.[32] In general, turn-around time of yeast identification has grossly improved with the introduction of the matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) in routine diagnostic laboratories, though the initial cost of the MALDI-TOF limits its wide use in developing countries.[33,34] MALDI-TOF can also rapidly identify the yeast directly in >50% of the signal-positive blood culture bottles.[34]

TABLE 1: Salient features of diagnostic tests of invasive candidiasis.

Diagnostic test	*Specimen*	*Advantages*	*Disadvantages*
Fungal culture	Blood	Enables species identification and susceptibility	Slow (median 2–3 days) and low sensitivity (may improve with high volume of blood)
MALDI-TOF	Isolate or signal-positive blood bottle	• Identification within few minutes • Identification from signal-positive bottle in >50% cases • Future scope of susceptibility testing	Initial cost of the instrument is high
T2 *Candida*	Blood	Identification within 4–6 hours	Only five yeast can be identified, cannot perform susceptibility, high cost
BDG	Serum or plasma (EDTA)	• Improves sensitivity • Can be used to stop empirical therapy due to high negative predictive value	Panfungal marker and not specific for *Candida*; many source of false positivity; high cost
Mannan antigen and anti-mannan antibody	Serum or plasma (EDTA)	• Increase diagnostic sensitivity • Commercial test available	False positivity in heavy colonization; low sensitivity in nonalbicans *Candida* species
PCR	Blood (EDTA)	Rapid and some tests are commercially available	Commercial tests are expensive; may not detect all *Candida* species

(BDG: beta-d-glucan; EDTA: ethylenediaminetetraacetic acid; MALDI-TOF: matrix-assisted laser desorption ionization-time-of-flight; PCR: polymerase chain reaction)

Detection of 1,3 BDG in serum is one of the important diagnostic tests available for the diagnosis of invasive candidiasis. Though BDG is panfungal marker and can be positive in many fungal infections, the rise in level of BDG in blood is high in invasive candidiasis and pneumocystis infection.[35] The performance of BDG test for the diagnosis of invasive candidiasis has good sensitivity and specificity of 65–85% and 75–85%, respectively among critically ill patients.[35,36] The performance of the test is better when the values of two consecutive tests are considered. Caution should be taken while interpretating BDG results especially in the setting of COVID-19 as bacterial sepsis or septic shock during SARS-CoV-2 infection may lead to translocation of *Candida* from the gut giving false positive results.[28] It is pertinent here to mention that BDG has a good negative predictive value for invasive candidiasis that may help to discontinue the empirical antifungal agents at the earliest.[37,38] Recently, new format for BDG testing (Fungitell STAT assay, associates of Cape Cod) has been developed that can be applied to test single-patient sample instead of waiting for the grouping of samples for batch testing. The new test format could be valuable as the turn-around time is as low as 1 hour.[39]

Commercial assays for detection of mannan antigen and antibodies against the mannan and *C. albicans* germ tube are available. They are used in few laboratories of European countries, as the tests are not Food and Drug Administration (FDA) approved. In a recent meta-analysis on detection of mannan and antimannan antibody for diagnosis of invasive candidiasis, the sensitivity and specificity were found to be 58% and 93% and 59% and 86%, respectively. The sensitivity and specificity increase to 83% and 86%, respectively when combination of mannan and antimannan antibody tests are used.[40] In a situation, where BDG assay is not available, use of the mannan and antimannan tests may help in early diagnosis of invasive candidiasis.

T2 *Candida* that amplify and detect Candidal deoxyribonucleic acid (DNA) directly from the whole blood by super-magnetic particles and T2 magnetic resonance is cleared by FDA for the diagnosis of invasive candidiasis. It can detect *C. albicans/C. tropicalis*, *C. glabrata/C. krusei*, and *C. parapsilosis* within a mean time of 4–5 hours with sensitivity and specificity of 91% and 98%, respectively. Cost, nonavailability of isolate for susceptibility tests, and nonavailability in Indian market are the main limitations.[41] Commercial and in-house polymerase chain reaction (PCR) assays are available for detection of DNA in the whole blood or blood fractions, but the interpretation of these test results are difficult due to heterogeneity of the assays.[42] The meta-analysis of the blood PCR in proven and probable invasive candidiasis has shown the sensitivity and specificity of 95% (95% CI, 82–98%) and 92% (95% CI, 87–98%), respectively.[43]

MANAGEMENT

Considering the high mortality of CAC due to delay in the initiation of antifungals in ICU settings, it is essential to initiate the empirical antifungal treatment based on local epidemiology in patients with worsening sepsis.[19] Sincere attempt should be made to diagnose the CAC to achieve maximum clinical success. There is no difference in the management of the CAC or non-COVID candidemia in ICU settings. For the management of CAC, it is recommended to follow the updated guideline by the Infectious Diseases

Society of America.[44] An echinocandin (caspofungin, anidulafungin, and micafungin) is recommended as initial treatment for critically ill patient with candidemia admitted to ICU. However, in a multicenter study of 25 hospitals in Asian countries during pre-COVID era, echinocandin nonsusceptible yeast including *Cryptococcus, Trichosporon, Rhodotorula,* and *Malassezia* were isolated from blood or bone-marrow culture in 8.1% of 2,155 yeast isolates. The echinocandin nonsusceptible yeasts isolates were more (8.6%) in India, Singapore, and Thailand hospitals.[45] The authors concluded that an operational algorithm for management of candidemia is essential in centers where non-*Candida* yeast is common.[45] Lipid preparation of amphotericin B may be prescribed for pending identification and susceptibility of isolated yeast.

Fluconazole (IV/oral) is the alternative if the patients are not critically ill, and are unlikely to have fluconazole resistant *Candida* species. Treatment needs to be guided by the antifungal susceptibility whenever possible and transition from echinocandin to fluconazole should be done in stable patients if the implicated *Candida* species is susceptible to fluconazole and have negative blood cultures after antifungal initiation. Lipid formulation of amphotericin is a good alternative especially when the above antifungals are not available or exhibits resistance to those antifungals by antifungal susceptibility testing. The duration of the treatment should be guided by the follow-up blood culture every day or every alternate day. Therapy should continue at least for 2 weeks after first negative blood culture.[44] The association of longer CVC dwell duration for the increase in the incidence of CAC provides the insight to consider the vascular catheter management in these cases.[22] Hence, wherever feasible source control in the form of removal of CVC should be done to improve the outcome of CAC patients. During intra-abdominal *Candida* infections blood culture is positive in about 5–20% cases.[46] Source control by drainage and/or debridement should be considered in those patients.[44]

PREVENTION

Early diagnosis, monitoring for *Candida* infections especially for antifungal resistant infections such as *C. auris,* is key to reduce mortality associated with CAC.[47] Based on the comparison of the COVID-19 and pre-COVID-19 candidemia cases, Seagle et al. attribute that at least part of increase in the incidence of CAC may be due to the changes in the health delivery and infection control practices during this pandemic.[25] The outbreaks of *C. auris* infections in the ICUs have also been related to unnecessary use of azoles and changes in routine infection control practices such as limited availability or reuse of gloves and gowns, and changes in cleaning and disinfection practices during the COVID-19 pandemic.[47,15] In addition, occurrence of cases of *C. auris* without any links to known cases or healthcare indicate an increase in undetected transmission. Hence, Centers for Disease Control and Prevention (CDC), USA suggests screening for *C. auris* colonization as an important part of containment efforts.[47] Active surveillance for invasive *Candida* infection and understanding the local epidemiology can minimize the deleterious effect of CAC.[15] Generally, epidemiological vigilance in the form of screening for *Candida* colonization, optimizing early diagnosis and treatment, and implementing strict infection control practice in the ICUs are recommended to decrease the burden.[19,48]

Strengthening the antifungal stewardship program and adopting the strategies such as discontinuation of antifungals with negative mycological results, assessment of impact of antifungal use in terms of efficacy, safety, drug interactions, and resistance emergence are to be considered in any ICU settings as part of preventive strategies for the development of fungemia.[49,50] Reducing the duration of the CVC dwell is also an important strategy to reduce such infections.

CONCLUSION

- In the early part of COVID-19 pandemic, low (<1%) incidence of fungemia was reported.[6] However, during the second half of 2020, rise in COVID-19-associated fungemia was noted in patients with comorbidities, and due to indiscriminate use of antibiotics, glucocorticoids, and lapse of infection control.[7]
- *Candida* spp. are major etiological agents of fungemia, rarely *Trichosporon* spp., *Cryptococcus* spp., and *Saccharomyces cerevisiae* (after use of probiotics) have been isolated.[26,9,47]
- Along with the rise of CAC cases, drug-resistant *C. auris* has re-emerged as important pathogen in several ICUs.[51,10,52]
- The incidence of CAC varied among countries and even regions of a country: Spain (0.7%), India (2.5%), Iran (5.0%), Italy (8.0%), United Kingdom (12.6%), and China (23.5%).[11]
- Low incidence in some centers in Spain was due to practice antimicrobial stewardship even in the pandemic period.[18]
- In contrast, majority of the centers in several countries reported rise of CAC cases up to ten times due to indiscriminate use of antibiotics and steroid therapy in COVID-19 patients with rise of overall mortality.[20] Additionally, ICU stay and immunosuppression were considered significant risk factors for CAC during pandemic period.[21]
- 50–80% of CAC was healthcare-associated, as noted while comparing the candidemia cases during pandemic, prepandemic periods, and non-COVID-associated candidemia during pandemic period.[25]
- Diagnosis of candidemia may improve with the culture of high volume of blood.[1] T2 magnetic resonance nanoparticle-based technique improves the diagnosis of

CAC by improving turn-around time for diagnosis. But, T2 *Candida* can detect only five *Candida* spp. (*C. albicans, C. tropicalis, C. parapsilosis, C. glabrata, and C. krusei*), cannot perform antifungal susceptibility testing, and test is expensive and not available in Indian market.[41]

- Matrix-assisted laser desorption ionization-time-of-flight technique, available in many centers now, has improved the turn-around time (few minutes only) for identification of yeast.[33] Auris ID (Olm diagnostic) kit can identify *C. auris* within 1–1.5 hours.[32]
- Beta-D-glucan test can improve the sensitivity of diagnosis of CAC. The test is more commonly used to stop empiric therapy (when the test is negative) due to high negative predictive value.[37] New kit Fungitell STAT assay (associates of Cape Cod) can perform BDG test in single-patient with turn-around time only 1 hour.[39]
- Though several molecular diagnostic kits have been developed for detection of *Candida* DNA directly from blood or after DNA extraction; the tests await multicenter standardization.[53]
- Like earlier recommendation for ICU-acquired candidemia, echinocandin is recommended as the first-line therapy in CAC. Fluconazole and amphotericin B are recommended as alternate therapy. However, it is desirable to perform antifungal susceptibility testing for optimal antifungal therapy.[11,44]

REFERENCES

1. Kullberg BJ, Arendrup MC. Invasive Candidiasis. N Engl J Med. 2015;373(15):1445-56.
2. Chakrabarti A, Sood P, Rudramurthy SM, Chen S, Kaur H, Capoor M, et al. Incidence, characteristics and outcome of ICU-acquired candidemia in India. Intensive Care Med. 2015;41(2):285-95.
3. Mazzanti S, Brescini L, Morroni G, Orsetti E, Pocognoli A, Donati A, et al. Candidemia in intensive care units over nine years at a large Italian university hospital: Comparison with other wards. PLoS One. 2021;16(5):e0252165.
4. Rudramurthy SM, Chakrabarti A, Paul RA, Sood P, Kaur H, Capoor MR, et al. Candida auris candidaemia in Indian ICUs: Analysis of risk factors. J Antimicrob Chemother. 2017;72(6):1794-801.
5. Cortegiani A, Misseri G, Giarratano A, Bassetti M, Eyre D. The global challenge of *Candida auris* in the intensive care unit. Crit Care. 2019;23(1):150.
6. Ripa M, Galli L, Poli A, Oltolini C, Spagnuolo V, Mastrangelo A, et al. Secondary infections in patients hospitalized with COVID-19: incidence and predictive factors. Clin Microbiol Infect. 2021;27(3):451–7.
7. Seaton RA, Gibbons CL, Cooper L, Malcolm W, McKinney R, Dundas S, et al. Survey of antibiotic and antifungal prescribing in patients with suspected and confirmed COVID-19 in Scottish hospitals. J Infect. 2020;81(6):952–60.
8. Thyagarajan RV, Mondy KE, Rose DT. *Cryptococcus neoformans* blood stream infection in severe COVID-19 pneumonia. IDCases. 2021;26:e01274.
9. Ali GA, Husain A, Salah H, Goravey W. *Trichosporon asahii* fungemia and COVID-19 co-infection: An emerging fungal pathogen; case report and review of the literature. IDCases 2021;25:e01244.
10. Chowdhary A, Tarai B, Singh A, Sharma A. Multidrug-Resistant *Candida auris* Infections in Critically Ill Coronavirus Disease Patients, India, April–July 2020. Emerg Infect Dis. 2020;26(11):2694-6.
11. Arastehfar A, Carvalho A, Nguyen MH, Hedayati MT, Netea MG, Perlin DS, et al. COVID-19-associated candidiasis (Cac): An underestimated complication in the absence of immunological predispositions? J Fungi. 2020;6(4):211.
12. Garcia-Vidal C, Sanjuan G, Moreno-García E, Puerta-Alcalde P, Garcia-Pouton N, Chumbita M, et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clin Microbiol Infect. 2021;27(1):83-8.
13. Salehi M, Ahmadikia K, Mahmoudi S, Kalantari S, Jamalimoghadamsiahkali S, Izadi A, et al. Oropharyngeal candidiasis in hospitalised COVID-19 patients from Iran: Species identification and antifungal susceptibility pattern. Mycoses. 2020;63(8):771-8.
14. Antinori S, Bonazzetti C, Gubertini G, Capetti A, Pagani C, Morena V, et al. Tocilizumab for cytokine storm syndrome in COVID-19 pneumonia: an increased risk for candidemia? Autoimmun Rev. 2020;19(7):102564.
15. White PL, Dhillon R, Healy B, Wise MP, Backs M. Candidemia in Coronavirus Disease 2019: A Link to Disease Pathology or Increased Clinical Pressures? Clin Infect Dis. 2020.
16. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13.
17. Bishburg E, Okoh A, Nagarakanti SR, Lindner M, Migliore C, Patel P. Fungemia in COVID-19 ICU patients, a single medical center experience. J Med Virol. 2021;93(5):2810–4.
18. Guisado-Gil AB, Infante-Domínguez C, Peñalva G, Praena J, Roca C, Navarro-Amuedo MD, et al. Impact of the COVID-19 pandemic on antimicrobial consumption and hospital-acquired candidemia and multidrug-resistant bloodstream infections. Antibiotics. 2020;9(11):816.
19. Agrifoglio A, Cachafeiro L, Figueira JC, Añón JM, García de Lorenzo A. Critically ill patients with COVID-19 and candidaemia: We must keep this in mind. J Mycol Med. 2020;30(4):101012.
20. Riche CVW, Cassol R, Pasqualotto AC. Is the Frequency of Candidemia Increasing in COVID-19 Patients Receiving Corticosteroids? J Fungi. 2020;6(4):286.
21. Mastrangelo A, Germinario BN, Ferrante M, Frangi C, Li Voti R, Muccini C, et al. Candidemia in Coronavirus Disease 2019 (COVID-19) Patients: Incidence and Characteristics in a Prospective Cohort Compared With Historical Non–COVID-19 Controls. Clin Infect Dis. 2021;73(9):e2838-9.
22. Macauley P, Epelbaum O. Epidemiology and Mycology of Candidaemia in non-oncological medical intensive care unit patients in a tertiary center in the United States: Overall analysis and comparison between non-COVID-19 and COVID-19 cases. Mycoses. 2021;64(6):634-40.
23. Kayaaslan B, Eser F, Kaya Kalem A, Bilgic Z, Asilturk D, Hasanoglu I, et al. Characteristics of candidemia in COVID-19

patients; increased incidence, earlier occurrence and higher mortality rates compared to non-COVID-19 patients. Mycoses. 2021;64(9):1083-91.
24. Rodriguez JY, Le Pape P, Lopez O, Esquea K, Labiosa AL, Alvarez-Moreno C. *Candida auris*: A Latent Threat to Critically Ill Patients With Coronavirus Disease 2019. Clin Infect Dis. 2021;73(9):e2836-7.
25. Seagle EE, Jackson BR, Lockhart SR, Georgacopoulos O, Nunnally NS, Roland J, et al. The landscape of candidemia during the Coronavirus Disease 2019 (COVID-19) Pandemic. Clin Infect Dis. 2022;74(5):802-11.
26. Ventoulis I, Sarmourli T, Amoiridou P, Mantzana P, Exindari M, Gioula G, et al. Bloodstream infection by saccharomyces cerevisiae in two COVID-19 patients after receiving supplementation of *Saccharomyces* in the ICU. J Fungi. 2020;6(3):98.
27. White PL, Dhillon R, Cordey A, Hughes H, Faggian F, Soni S, et al. A National Strategy to Diagnose Coronavirus Disease 2019–Associated Invasive Fungal Disease in the Intensive Care Unit. Clin Infect Dis. 2021;73(7):e1634-44.
28. Prattes J, Raggam RB, Vanstraelen K, Rabensteiner J, Hoegenauer C, Krause R, et al. Chemotherapy-induced intestinal mucosal barrier damage: a cause of falsely elevated serum 1,3-Beta-D-glucan levels? J Clin Microbiol. 2016;54(3):798-801.
29. Rudramurthy SM, Hoenigl M, Meis JF, Cornely OA, Muthu V, Gangneux JP, et al. ECMM/ISHAM recommendations for clinical management of {COVID}-19 associated mucormycosis in low- and middle-income countries. Mycoses. 2021;64(9):1028-37.
30. Segrelles-Calvo G, Araújo GR de S, Llopis-Pastor E, Carrillo J, Hernández-Hernández M, Rey L, et al. *Candida spp.* co-infection in COVID-19 patients with severe pneumonia: Prevalence study and associated risk factors. Respir Med. 2021;188:106619.
31. Moser D, Biere K, Han B, Hoerl M, Schelling G, Choukér A, et al. COVID-19 Impairs Immune Response to *Candida albicans*. Front Immunol. 2021;12:640644.
32. Mulet Bayona JV, Salvador García C, Tormo Palop N, Gimeno Cardona C. Validation and implementation of a commercial real-time PCR assay for direct detection of *Candida auris* from surveillance samples. Mycoses. 2021;64(6):612–5.
33. Peng Y, Zhang Q, Xu C, Shi W. MALDI-TOF MS for the rapid identification and drug susceptibility testing of filamentous fungi. Exp Ther Med. 2019;18(6):4865-73.
34. Das S, Tawde Y, Singh S, Chakrabarti A, Ray P, Rudramurthy SM, et al. Identification and broth-microdilution antifungal susceptibility testing of yeast directly from automated blood cultures. Future Microbiol. 2020;15:1453-64.
35. Onishi A, Sugiyama D, Kogata Y, Saegusa J, Sugimoto T, Kawano S, et al. Diagnostic accuracy of serum 1,3-β-D-glucan for Pneumocystis jiroveci pneumonia, invasive candidiasis, and invasive aspergillosis: systematic review and meta-analysis. J Clin Microbiol. 2012;50(1):7-15.
36. Karageorgopoulos DE, Vouloumanou EK, Ntziora F, Michalopoulos A, Rafailidis PI, Falagas ME. β-D-Glucan Assay for the Diagnosis of Invasive Fungal Infections: a meta-analysis. Clin Infect Dis. 2011;52(6):750-70.
37. Bassetti M, Azoulay E, Kullberg BJ, Ruhnke M, Shoham S, Vazquez J, et al. EORTC/MSGERC Definitions of Invasive Fungal Diseases: Summary of Activities of the Intensive Care Unit Working Group. Clin Infect Dis. 2021;72(Suppl 2):S121–7.
38. Posteraro B, Tumbarello M, De Pascale G, Liberto E, Vallecoccia MS, De Carolis E, et al. (1,3)-β-d-Glucan-based antifungal treatment in critically ill adults at high risk of candidaemia: an observational study. J Antimicrob Chemother. 2016;71(8):2262-9.
39. D'Ordine RL, Garcia KA, Roy J, Zhang Y, Markley B, Finkelman MA. Performance characteristics of Fungitell STAT™, a rapid (1→3)-β-D-glucan single patient sample in vitro diagnostic assay. Med Mycol. 2021;59(1):41-9.
40. Mikulska M, Calandra T, Sanguinetti M, Poulain D, Viscoli C. The use of mannan antigen and anti-mannan antibodies in the diagnosis of invasive candidiasis: recommendations from the Third European Conference on Infections in Leukemia. Crit Care. 2010;14(6):R22.
41. Monday LM, Parraga Acosta T, Alangaden G. T2Candida for the Diagnosis and Management of Invasive *Candida* Infections. J Fungi. 2021;7(3):178.
42. Clancy CJ, Nguyen MH. Diagnosing invasive candidiasis. J Clin Microbiol. 2018;56(5): e01909-17.
43. Avni T, Leibovici L, Paul M. PCR Diagnosis of Invasive Candidiasis: systematic review and meta-analysis. J Clin Microbiol. 2011;49(2):665-70.
44. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62(4):e1-50.
45. Lin S, Lu PL, Tan BH, Chakrabarti A, Wu U, Yang JH, et al. The epidemiology of non-Candida yeast isolated from blood: The Asia Surveillance Study. Mycoses. 2019;62(2):112-20.
46. Vergidis P, Clancy CJ, Shields RK, Park SY, Wildfeuer BN, Simmons RL, et al. Intra-abdominal candidiasis: the importance of early source control and antifungal treatment. PLoS One. 2016;11(4):e0153247.
47. Center for Disease Control. (2021). Fungal disease and COVID 19 2021. [online] Available from: https://www.cdc.gov/fungal/covid-fungal.html [Last accessed March, 2022].
48. Gangneux JP, Bougnoux ME, Dannaoui E, Cornet M, Zahar JR. Invasive fungal diseases during COVID-19: We should be prepared. J Mycol Med. 2020;30(2):100971.
49. Bienvenu AL, Bleyzac N, Richard JC, Leboucher G. No time for pending confirmation of invasive fungal disease in critically ill COVID-19 patients-think empirical treatment. Crit Care. 2020;24(1):588.
50. Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, et al. Bacterial and Fungal Coinfection in Individuals with Coronavirus: a rapid review to support COVID-19 Antimicrobial Prescribing. Clin Infect Dis. 2020;71(9):2459-68.
51. Hanson BM, Dinh AQ, Tran TT, Arenas S, Pronty D, Gershengorn HB, et al. Candida auris invasive infections during a COVID-19 case surge. Antimicrob Agents Chemother. 2021;65(10):e0114621.
52. Rajni E, Singh A, Tarai B, Jain K, Shankar R, Pawar K, et al. A high frequency of *Candida auris* blood stream infections in COVID-19 patients admitted to intensive care units, North-western India: a case control study. Open Forum Infect Dis. 2021;8(12):ofab452.
53. Camp I, Spettel K, Willinger B. Molecular Methods for the Diagnosis of Invasive Candidiasis. J Fungi. 2020;6(3):101.

CHAPTER 129

COVID-19-associated Pulmonary Aspergillosis

Avinash Agrawal, Manoj Goel, Vikas Kesarwani

INTRODUCTION

Patients with corona virus-19 (COVID-19) infection and associated adult respiratory distress syndrome (ARDS) are at higher risk for secondary infections. Invasive pulmonary aspergillosis (IPA) is emerging as a serious secondary infection with reportedly a higher mortality of 16% and 25% compared with patients without evidence for aspergillosis.[1,2] COVID-19-associated pulmonary aspergillosis (CAPA) is acknowledged as an additional contributing factor to mortality.[1] Various baseline poor prognostic factors associated with CAPA contribute to the negative effects on survival,[3] which might be further compromised by azole-resistant CAPA.[4,5] A prospective study which included 108 critically ill patients with ARDS from COVID pneumonia reported a higher 30-day mortality in a cohort with superimposed aspergillosis versus without aspergillosis (44% vs. 19%).[1] Obtaining a diagnosis of CAPA has a few challenges in intensive care. Aerosol generating procedures including bronchoscopy are restricted in hospitals during COVID-19 pandemic to reduce exposure to healthcare workers. While bronchoscopy *per se* in mechanically ventilated patients in ICU has higher patient morbidity. Diagnosing CAPA in ICU requires clinical suspicion followed by diagnostic procedures to obtain respiratory tract samples. Detection of *Aspergillus* in upper airway specimen does not discern between colonization versus invasive disease, whereas testing of galactomannan (GM) in serum is not widely available and has a low sensitivity.[6] Due to difficulty in confirming an early proven diagnosis and also high mortality in patients with CAPA, it is important for clinicians to have high clinical suspicion of superinfection with invasive aspergillosis in seriously ill COVID-19 patients as a timely antifungal therapy might be life-saving.

RISK FACTORS

Severe acute respiratory syndrome (SARS) caused by COVID-19 infection itself could be the main risk factor for CAPA.[7] Advanced age, multiple comorbidities, and immunosuppression with diseases such as hematological malignancies with or without severe lymphopenia are risk factors for invasive mold disease.[8] Prolonged and large doses of corticosteroids and anti-interleukin (IL-6)-directed therapy in COVID-19 patients themselves are additional risk factor of superinfections **(Box 1)**.

BOX 1: Possible risk factors for COVID-19-associated pulmonary aspergillosis.

- COVID-19 infection per se
- ARDS
- COVID-19 patient on mechanical ventilation >5 days
- EORTC/MSG host/risk factors
- Preexisting comorbid conditions, e.g., diabetes and hematological malignancy
- High dose/prolonged used of corticosteroids
- Anti-IL-6 therapy
- Lymphopenia
- Advanced age
- Structural lung disease

(ARDS: adult respiratory distress syndrome; COVID-19: coronavirus disease 2019; EORTC: European Organization for the Research and Treatment of Cancer; IL-6: interleukin-6; MSG: Mycoses Study Group)

PATHOGENESIS

Viral pneumonia is known to increase patients' susceptibility to bacterial and fungal superinfections such as IPA due to multiple factors. Respiratory viruses lead to immune dysfunction or dysregulation, or both, locally or systemically, and cause direct damage to the airway epithelium as well as impair ciliary clearance enabling *Aspergillus* to invade tissue.[9] CAPA involves a continuum of a complex disease process beginning with *Aspergillus* respiratory tract colonization, tissue invasion, and angioinvasion.[10] A combination of determinants was suggested to contribute to the *Aspergillus* angioinvasion results from a combination of determinants which involve predisposing factors, such as European Organization for the Research and Treatment of Cancer/Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) host factors,[11] various comorbidities

and direct injury to the host cells caused by SARS-CoV-2. The COVID-19-induced immune dysregulation, including both hyperinflammation and immune paralysis, reduction of T-cells, and concomitant immunomodulatory therapy, such as corticosteroids and IL-6 inhibitors are the other contributory factors. Presence of severe lymphopenia has also been shown to predict the risk of invasive mold disease.[6]

DIAGNOSIS OF COVID-19-ASSOCIATED PULMONARY ASPERGILLOSIS

Diagnosis of aspergillosis in immunocompromised patients is done through revised EORTC/MSG 2020 criteria, with proven, probable, and possible diagnosis **(Box 2)**.[11] Proven CAPA is based on histopathological, cytopathologic, or direct microscopic examination of specimen obtained by biopsy or fine needle aspiration or by culture of sterile material obtained from biopsy material. Probable CAPA is considered in presence of at least one each of a host factor, typical imaging findings, and mycological evidence. Possible CAPA is a probable case without mycological evidence. These diagnostic criteria were predominantly applicable for patients with known malignancies and immunocompromised. The Asp-ICU study group, developed diagnostic criteria for such infections in critically ill patients, where specific host risk factor (such as neutropenia and hematological malignancy) and specific radiological signs (halo sign, air-crescent sign, or a cavity) were generalized so that the diagnosis can be done in other critically ill patients too.[12] This Asp-ICU algorithm proposes the "putative diagnosis" with lower respiratory tract specimen, which is positive for *Aspergillus* as the entry criterion, with compatible clinical signs and symptoms with abnormal imaging along with either host risk factors or semiquantitative culture of *Aspergillus*. If any one out of four is not met, it is labeled as colonization. To further increase the sensitivity, the modified AspICU was introduced in 2018 by Schauwvlieghe et al, where in along with first-three AspICU criteria (positive lower respiratory tract sample, compatible signs and symptoms, and abnormal imaging) mycological criteria were added.[13]

The diagnosis of pulmonary *Aspergillus* in COVID-19 patients (CAPA), is challenging due to various reasons such as myriad computed tomography (CT) findings associated with COVID-19 pneumonia, differentiating from other secondary infections, e.g., mucormycosis, clinicians reticence in performing aerosol generating procedures such as bronchoscopic alveolar lavage (BAL) and questions around various diagnostic techniques such as biomarkers with varied sensitivity profiles. More invasive procedures like lung biopsy are not routinely performed in critically ill patients, due to various coexisting comorbid and pathological conditions like coagulopathy. There are two distinct forms of CAPA, invasive *Aspergillus*-associated tracheobronchitis (IATB), and parenchymal. A regular and repeated sampling of both serum and respiratory specimens may be needed in a patient who is suspected of CAPA to establish a proven diagnosis. The incidence of probable/proven CAPA is around 5% and possible CAPA is around 15%.[14] **Table 1** summarizes various procedures/specimens for diagnosing CAPA and **Box 3** highlights the approach to diagnose or refute the diagnosis of invasive aspergillosis in COVID-19.

BOX 2: Case definition of COVID-19-associated pulmonary aspergillosis (CAPA).[7]

- *Proven CAPA*: Histology confirmed
- *Probable CAPA*: Bronchoscopic BAL + clinical and/or radiological features
- *Possible CAPA*: Nonbronchoscopic lavage BAL + clinical and/or radiological features

(BAL: bronchoscopic alveolar lavage)

Imaging

The high-resolution CT (HRCT) chest imaging findings suggestive of invasive aspergillosis in COVID-19 include well-circumscribed dense airspace opacities with or without a halo sign, air crescent sign, cavity, or wedge-shaped and segmental or lobar consolidation **(Fig. 1)**. There may also be nodular, ground glass opacities, and cavitating nodules or consolidation.[15]

Nondirected Bronchoalveolar Lavage

As bronchoalveolar lavage poses challenges such as aerosolization, nondirected bronchoalveolar (NBL) obtained through deep bronchial suction with a closed suction system can be used as an alternative at regular intervals along with serum for biomarkers like GM.[7]

Bronchoscopy and Bronchoalveolar Lavage

Bronchoscopy forms the most valuable tool for the diagnosis which provides simultaneous visualization of the airways along with provision of bronchoalveolar (BAL) sample. Visible tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar in trachea and/or bronchi should be sampled with bronchoscopic biopsy or brush specimens, which establish the diagnosis of IATB.[7,10]

Fungal Biomarkers

Galactomannan is a polysaccharide, which forms major constituent of *Aspergillus* cell wall. The enzyme immunoassay (EIA) is done in serum and BAL as interpreted as GM optical density index (ODI), which is a ratio relative to threshold control provided by manufacturer. Its cut off to be considered as positive test, as cleared by FDA is ≥0.5 in serum and BAL.[16] But to increases the diagnostic certainty, EORTC/MSG has proposed threshold OD index of ≥1 in serum or plasma

TABLE 1: Diagnostic procedures and samples for CAPA.

Diagnostic procedure/sample	*Strengths*	*Limitations*
CT scan of chest	Appearance of new airspace opacities especially nodules with halo signs and peripheral patchy consolidation	• Imaging findings are nonspecific • Standard CT imaging is not recommended to refute or diagnose CAPA[10]
Serum	• Easy to obtain • Highly diagnostic for IPA [galactomannan, (1–3)-β-D-glucan (BDG) lateral flow assay, and PCR]	• Variable results in non-neutropenic patients BDG not pathogen specific • Commonly negative in CAPA, including proven cases • Screening of critically ill COVID-19 patients for serum GM or BDG is not recommended[10]
Sputum	Easy to obtain in most non-ventilated patients if patient has productive cough	• Less representative of lower respiratory tract than is BAL • Not validated for biomarker detection • Often positive in patients with COVID-19 but likely represent upper airway colonization
Tracheal aspirate	Easy to obtain in patients who are intubated	• Less representative of lower respiratory tract than is BAL • Not validated for biomarker detection • Often positive in patients with COVID-19 but likely represent upper airway colonization • Detection of *Aspergillus* in sputum and tracheal aspirate is considered insufficient evidence to support CAPA diagnosis, but warrants further diagnostics through bronchoscopy and BAL[10]
Non-bronchoscopic lavage or mini BAL	• Validated for diagnosis of ventilator-associated pneumonia • Suggested as alternative to BAL to diagnose CAPA	• Not fully validated for IPA diagnosis • Not fully validated for *Aspergillus* antigen and PCR detection • Sampling not targeted like BAL
Bronchoscopy with bronchoalveolar lavage (BAL)	• Well validated for the diagnosis of IPA • Validated specimen for *Aspergillus* antigen test (e.g., enzyme immunoassay and lateral flow assay) and PCR • Targeted sampling possible • Maximum efforts are recommended to perform a bronchoscopy for inspection of the airways and BAL to diagnose CAPA in patients with proven or high likelihood of COVID-19 in the ICU[10] • Bronchoscopic mucosal biopsy when plaques are visible in trachea or bronchi to diagnose invasive *Aspergillus* tracheobronchitis (IATB)	Risk of nosocomial transmission and SARS-CoV-2 infection of healthcare workers
Lung biopsy	Diagnostic for proven IPA	High risk of complications

(BDG: 1,3-β-d-glucan; CT: computed tomography; CAPA: COVID-19-associated pulmonary aspergillosis; GM: galactomannan; IPA: invasive pulmonary aspergillosis; PCR: polymerase chain reaction; SARS: severe acute respiratory syndrome)

BOX 3: Optimal approach toward diagnosing or refuting COVID-19-associated pulmonary aspergillosis (CAPA).[10]

- Initiate CAPA diagnostic work-up is in patients with:
  - Unexplained acute respiratory deterioration without other plausible explanation
  - A positive *Aspergillus* culture from the respiratory tract
  - Computed tomography (CT) scan showing new nodule/cavitation/consolidation
- Standard CT imaging does not refute or diagnose CAPA
- Routine screening of critically ill COVID-19 patients for serum GM or BDG is not recommended
- Detection of *Aspergillus* in sputum and tracheal aspirate is considered insufficient evidence to support CAPA diagnosis, but warrants further diagnostics through bronchoscopy and BAL
- Perform a bronchoscopy for inspection of the airways and bronchoalveolar lavage (BAL) to diagnose CAPA
- Perform bronchoscopic mucosal brushing or biopsy of visible plaques in the airways

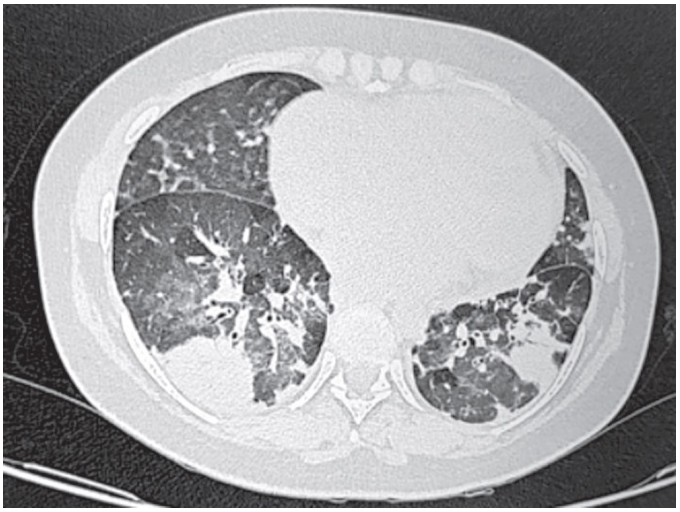


Fig. 1: HRCT of a COVID-19 patient showing new appearance of bilateral patchy peripheral consolidation with background of focal areas of ground glass opacities and septal thickening highly suggestive of CAPA. (CAPA: COVID-19-associated pulmonary aspergillosis; HRCT: high-resolution computed tomography)

and BAL.[11] 1,3-beta-D-glucan, the pan fungal marker is measures through Fungitell assay which was cleared by FDA which measures serum endotoxin assays. Although precise-cut offs for diagnosis of invasive aspergillosis is not yet established, this can be useful in predicting invasive fungal disease and to differentiate from infections such as mucormycosis. This assay is positive in candidal infections, *Pneumocystis jirovecii,* and false positive results can be seen with albumin, intravenous immunoglobulin, and infections with certain bacteria containing beta-glucans in cell wall like *Pseudomonas aeruginosa*. The predictive value of these tests depends upon the host risk factors and clinical presentation with relatively low < 50% positive predictive values (PPV) and high > 90% negative predictive values. BAL fluid GM assay provides additional sensitivity so that the PPV can increase up to 70%. The sensitivity of assay decreases in patients on antifungal drugs, and false positive results can be noted in few ongoing antimicrobial therapies such as piperacillin-tazobactam and amoxicillin-clavulanate. Important drawbacks of sputum and non-BAL are inability to visualize the airways which is very important in suspecting the diagnosis of CAPA and the lack of validation of biomarkers for these specimens.[10]

Molecular Assays

Aspergillus polymerase chain reaction (PCR) can be performed on serum, plasma, whole blood, or BAL fluid and the diagnostic accuracy (sensitivity 84% and specificity 76%, respectively), can be improved with two consecutive positive PCR reports.[7]

Histopathology

All the respiratory specimens are stained with calcofluor white with 10% potassium hydroxide to detect for fungal elements visualized as narrow, septated hyaline hyphae with dichotomous acute angle (45°) branching. Other fungi such as *Fusarium* and *Scedosporium* which have similar appearance need to be excluded. This infection needs to be differentiated from *Mucorales*, which are nonseptate hyphae with right angle-branching.

Assays Under Development

Lateral flow device (LFD) detects a mannoprotein produced by actively growing *Aspergillus* species. This can take place through enzyme-linked immunosorbent assay (ELISA) test or point of care testing and studies indicate better performance.[17,18] Technologies relying on the production of secondary metabolites in breath with thermal desorption-gas chromatography/mass spectrometry are under development for quick results to aid the clinician.

INDICATIONS OF ANTIFUNGAL THERAPY

Proven COVID-19-associated Pulmonary Aspergillosis

Definitive antifungal therapy must be initiated immediately when invasive aspergillosis is proven in a critically ill COVID patient by histopathological and/or direct microscopic detection of *Aspergillus* into tissues, or positive *Aspergillus* culture or microscopy, or PCR from material that was obtained by a sterile aspiration or biopsy from a pulmonary site. However, diagnosing a proven CAPA is practically invariably impossible in a critically ill COVID-19 patient, and should not delay the use of antifungal treatment.

Probable COVID-19-associated Pulmonary Aspergillosis

The diagnosis of probable pulmonary CAPA is based on a pulmonary infiltrate or nodules, or cavitating infiltrate on imaging, combined with mycological evidence. The antifungal treatment should be initiated on the basis of high probability of CAPA.

Possible COVID-19-associated Pulmonary Aspergillosis

In view of the challenges that are related to the diagnosis of CAPA, the antifungal therapy should not be delayed in possible CAPA that is likely if there is radiological evidence of pulmonary infiltrate or nodules, or cavitating infiltrate in combination with mycological evidence (e.g., microscopy, culture, or GM) obtained via nonbronchoscopic lavage.

WHEN TO INITIATE ANTIFUNGAL THERAPY

Any of the following clinical findings should trigger investigations for CAPA and initiate antifungal treatment if strong suspicion for the possible CAPA even in the absence of proven diagnosis:

- Persistent fever for >3 days or occurrence of a new fever after a period of defervescence of longer than 48 hours while appropriate antibiotic therapy is being administered, and there is no other obvious cause.
- Clinical worsening, e.g., increasing tachypnea or oxygen requirement, hemoptysis; and pleural rub or chest pain despite receiving all supportive treatment recommended for critically ill patients with COVID-19.[13]

However, the onset CAPA can be variable and patients can present during the ICU admission or after. An approach to treat CAPA is outlined in **Box 4**.

BOX 4: How to treat COVID-19-associated pulmonary aspergillosis (CAPA).[10]

- Do not administer prophylactic antifungal therapy
- Initiate antifungal therapy in patients with positive BAL *Aspergillus* culture, GM and/or *Aspergillus* PCR
- Consider empirical therapy if plaques are visible in trachea and/or bronchi
- Consider empirical therapy for CAPA in patients in whom a BAL has been performed and BAL GM/PCR results are pending in possible CAPA
- Consider discontinuation of empirical antifungal therapy in patients with a negative BAL GM
- Do not necessarily stop concomitant dexamethasone or corticosteroid therapy in CAPA patients

(BAL: bronchoalveolar lavage; GM: galactomannan; PCR: polymerase chain reaction)

ANTIFUNGAL THERAPY

There are multiple specific caveats to the treatment for CAPA. A robust data to compare the effectiveness of antifungal drugs for CAPA is still lacking, but there is also no data to suggest that treatment would be different than that for patients without COVID-19 **(Table 2)**. The 2020 ECMM/ISHAM consensus criteria for research and clinical guidance[7] have recommended the antifungal treatment path for the management of CAPA **(Box 5)**, which highlights that:

- *Voriconazole or isavuconazole*: It is recommended as first-line treatment for possible, probable, and proven CAPA.
- *Liposomal amphotericin B*: Primary alternative option for treatment of IPA in the ICU.
- *Posaconazole or echinocandins*: Alternative second-line options.
- *Echinocandins*: Not to be used as monotherapy, but can indeed be used for salvage therapy.
- *New antifungal classes under development (fosmanogepix, ibrexafungerp, olorofim, and rezafungin)*: It might be future options.[19]
- At present, no antifungal drug is licensed for prophylactic use against *Aspergillus*.

Systemic antifungal therapy alone might not be sufficient to effectively treat endobronchial fungus invasion. Inhaled

TABLE 2: Antifungal drugs for CAPA.

Antifungal drug	*Dose*	*Remarks*
Voriconazole	Loading dose 6 mg/kg twice a day for two doses, followed by 4 mg/kg twice a day	• It has been the foundational drug for treatment of invasive aspergillosis • Being metabolized via CYP2C19, CYP2C9, and CYP3A4, frequently associated with major drug–drug interactions in the ICU setting • It might show interactions with remdesivir, which is also a substrate for CYP3A4, although overall effect is not yet fully understood[21]
Isavuconazole	Loading dose 200 mg three times a day for six doses, followed by 200 mg once a day, 12–24 hours after the last loading dose	• It has similar clinical activity to voriconazole • Less hepatotoxicity and neurotoxicity and decreased risk of corrected QT-interval prolongation as compared to voriconazole
Liposomal amphotericin B	Initial dose of liposomal amphotericin B is 3 mg/kg per day	• The primary alternative option for treatment of IPA in the ICU • Renal toxicity is particular concern as SARS-CoV-2 has shown renal tropism and is a frequent cause of kidney injury[22]
Echinocandins	*Salvage therapy:* Caspofungin 70 mg loading dose on the first day followed by 50 mg/day. If body weight is more than 80 kg, then 70 mg loading dose on the first day followed by 70 mg/day	Not recommended for use as monotherapy in primary invasive aspergillosis; 59 but, in combination with an azole, might have some therapeutic advantage in critically ill patients
Posaconazole	*Loading dose:* 300 mg oral/intravenous twice a day on the first day followed by maintenance dose: 300 mg oral/intravenous once a day, starting on the second day	• Has excellent in-vitro *Aspergillus* activity • Has been successfully used as salvage treatment in patients without COVID-19[23]
Itraconazole	Loading dose 200 mg thrice daily for 3 days followed by 200 twice a day	It shows excellent in vitro *Aspergillus* activity but does not have robust comparative data with established regimens

(CAPA: COVID-19-associated pulmonary aspergillosis; IPA: invasive pulmonary aspergillosis; SARS: severe acute respiratory syndrome)

BOX 5: Recommended antifungal treatment path for COVID-19-associated pulmonary aspergillosis (CAPA).[7]

Azole sensitive:
- *First line*: Either voriconazole or isavuconazole
- *Second line*: Liposomal amphotericin B

Azole resistant:
- *Suspected*: Voriconazole plus echinocandin or isavuconazole plus echinocandin
- *Suspected or proven*: Liposomal amphotericin B

(liposomal) amphotericin B has been recommended by the Infectious Diseases Society of (IDSA) as adjunctive therapy in IATB.[20]

Duration of Antifungal Therapy

The optimal duration of therapy for CAPA is unknown, but an expert panel suggests 6–12 weeks.[7] In immunocompromised patients, longer duration might be necessary. It seems reasonable to follow-up with lung CT imaging to document the resolution of infiltrates before stopping antifungal treatment. Serial measurements of the serum GM for therapeutic response might be limited by its poor sensitivity in non-neutropenic patients, and attaining follow-up respiratory samples may not be practically viable. Clinical and radiological correlation might help to determine treatment duration.

Concomitant Corticosteroid and Immunomodulatory Therapy

The risk factors for CAPA include use of corticosteroids and tocilizumab.[1] Immune-modulation has become a cornerstone of treatment of COVID-19 in the ICU, with inclusion of combinations of corticosteroids and anti-IL-6 in critically ill patients. It is established that dampening the immune response improves outcome in critically ill COVID-19 and may subsequently reduce the risk for IPA by limiting damage to the epithelium, endothelium, and the tissue. There is no sufficient data to support stopping or continuing dexamethasone or other immune modulatory agents in the context of risk for CAPA, however, these immunomodulatory treatments do reduce the overall mortality in the population at risk for CAPA.[10] But discontinuation or tapering of concomitant corticosteroid therapy could be considered in patients who do not respond to antifungal therapy.

CONCLUSION

COVID-19-associated pulmonary aspergillosis results from the fungal invasion of airway epithelium resulting from direct damage by SARS COV-2 virus. CAPA is proposed to be defined as possible, probable, or proven on the basis of sample validity and thus diagnostic certainty. CAPA is associated with worsening of the course of COVID-19 and increased mortality. Additionally, CAPA caused by azole-resistant *Aspergillus* is also a significant challenge. Bronchoscopy with BAL is the most useful investigation for diagnosing CAPA and must be performed if feasible in high risk patients. Use of voriconazole or isavuconazole is recommended as first-line treatment for possible, probable, and proven CAPA; however, liposomal amphotericin B is the drug of choice if azole resistance is a concern. Corticosteroids may not necessarily be stopped if indicated for the management of COVID-19 infection. Future studies are needed to elucidate the role of host factors, and address an array of diagnosis and management concerns.

REFERENCES

1. Bartoletti M, Pascale R, Cricca M, Rinaldi M, Maccaro A, Bussini L, et al. Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: A prospective study. Clin Infect Dis. 2021;73(11):e3606-14.
2. White PL, Dhillon R, Cordey A, Hughes H, Faggian F, Soni S, et al. A national strategy to diagnose COVID-19 associated invasive fungal disease in the ICU. Clin Infect Dis. 2021;73(7):e1634-44.
3. Koehler P, Salmanton-García J, Gräfe SK, Koehler FC, Mellinghoff SC, Seidel D, et al. Baseline predictors influencing the prognosis of invasive aspergillosis in adults. Mycoses. 2019;62:651-8.
4. Mohamed A, Hassan T, Trzos-Grzybowska M, Thomas J, Quinn A, O'Sullivan M, et al. Multi-triazole resistant Aspergillus fumigatus and SARS-CoV-2 co-infection: a lethal combination. Med Mycol Case Rep. 2021;31:11-4.
5. Ghelfenstein-Ferreira T, Saade A, Alanio A, Bretagne S, de Castro RA, Samia Hamane, et al. Recovery of a triazole-resistant Aspergillus fumigatus in respiratory specimen of COVID-19 patient in ICU—a case report. Med Mycol Case Rep. 2021;31:15-8.
6. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis. 2020;71:762-8.
7. Koehler P, Bassetti M, Chakrabarti A, Chen SCA, Colombo AL, Hoenigl M, et al. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. Lancet Infect Dis. 2021;21:e149-62.
8. Stanzani M, Vianelli N, Cavo M, Kontoyiannis DP, Lewis RE. Development and internal validation of a model for predicting 60-day risk of invasive mould disease in patients with haematological malignancies. J Infect. 2019;78:484-90.
9. Herold S, Becker C, Ridge KM, Budinger GR. Influenza virus induced lung injury: pathogenesis and implications for treatment. Eur Respir J. 2015;45:1463-78.
10. Verweij PE, Brüggemann RJM, Azoulay E, Bassetti M, Blot S, Buil JB, et al. Taskforce report on the diagnosis and clinical management of COVID-19 associated pulmonary aspergillosis. Intensive Care Med. 2021;47(8):819-34.
11. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, et al. Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis. 2020;71(6):1367-76.

12. Blot SI, Taccone FS, Van den Abeele AM, Bulpa P, Meersseman W, Brusselaers N, et al. A Clinical Algorithm to Diagnose Invasive Pulmonary Aspergillosis in Critically Ill Patients. Am J Respir Crit Care Med. 2012;186(1):56-64.
13. Schauwvlieghe AFAD, Rijnders BJA, Philips N, Verwijs R, Vanderbeke L, Tienen CV, et al. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. Lancet Respir Med. 2018;6:782-92.
14. Borman AM, Palmer MD, Fraser M, Patterson Z, Mann C, Oliver D, et al. COVID-19-Associated Invasive Aspergillosis: Data from the UK National Mycology Reference Laboratory. J Clin Microbiol. 2020;59(1):e02136-20.
15. Koehler P, Cornely OA, Böttiger BW, Dusse F, Eichenauer DA, Fuchs F, et al. COVID-19 associated pulmonary aspergillosis. Mycoses. 2020;63(6):528-34.
16. Lahmer T, Kriescher S, Herner A, Rothe K, Spinner CD, Schneider J, et al. Invasive pulmonary aspergillosis in critically ill patients with severe COVID-19 pneumonia: Results from the prospective AspCOVID-19 study. PLoS One 2021;16(3):e0238825.
17. White PL, Parr C, Thornton C, Barnes RA. Evaluation of real-time PCR, galactomannan enzyme-linked immunosorbent assay (ELISA), and a novel lateral-flow device for diagnosis of invasive aspergillosis. J Clin Microbiol. 2013;51(5):1510-6.
18. Mercier T, Dunbar A, Veldhuizen V, Holtappels M, Schauwvlieghe A, Maertens J, et al. Point of care aspergillus testing in intensive care patients. Crit Care. 2020;24(1):642.
19. Kupferschmidt K. New drugs target growing threat of fatal fungi. Science. 2019;366:407.
20. Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Executive summary: Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63:433-42.
21. McCreary EK, Pogue JM. Coronavirus disease 2019 treatment: a review of early and emerging options. Open Forum Infect Dis. 2020;7:a105.
22. Puelles VG, Lütgehetmann M, Lindenmeyer MT, Sperhake JP, Wong MN, Allweiss L, et al. Multiorgan and renal tropism of SARS-CoV-2. N Engl J Med. 2020;383:590-2.
23. Walsh TJ, Raad I, Patterson TF, Chandrasekar P, Donowitz GR, Graybill R, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. Clin Infect Dis. 2007;44:2-12.

CHAPTER 130

Post-COVID Vaccine Complications

Sandeep Kantor, Sunil Garg, Mayank Vats

"Covid-19 vaccine is the new baptism"

—Nkwachukwu Ogbuagu

INTRODUCTION

The first coronavirus disease 2019 (COVID-19) case was reported in December 2019, and the World Health Organization (WHO) declared the outbreak a public health emergency of international concern on January 30, 2020,[1] and a pandemic on March 11, 2020.[2] In response to the COVID-19 pandemic, which has resulted in significant loss of human life globally, 102 candidate vaccines on 10 platforms are in clinical development, out of which 15 vaccines have already been licensed or approved for emergency use which includes Sinopharm, AstraZeneca/Covishield, Cansino, Sputnik V, Johnson & Johnson, Novavax, messenger ribonucleic acid (mRNA) vaccines by Moderna and Pfizer, nCov vaccine by Zydus Cadila, Covaxin, Sanofi Pasteur, and Covigen.[3] These vaccine platforms are classified either as traditional approaches that have previously resulted in licensed vaccines (e.g., inactivated, recombinant proteins, vectored vaccines) or as techniques that have never been used before for a licensed vaccine, e.g., like those used in RNA and deoxyribonucleic acid (DNA) vaccines.[4] This rapid process of research and subsequent lack of follow-up time postvaccination has led to a lot of skepticism about the safety profile of COVID-19 vaccine candidates. The US government approved the "Operation Wrap Speed"[5] programs focusing on quick production and testing of experimental coronavirus vaccines, which also fueled concerns already laid bare by vaccine skeptics to a great deal. Since then, nine announcements of safety and efficacy have been made, ranging from 50 to 95% efficacy.[6] The numerous variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strains are frequently emerging, which makes the situation more complicated. In addition to that is the concern that the epidemic rebounds even in some countries/areas where it was initially controlled, which has led to major concerns about the "vaccine-resistant" strains.

ARE COVID VACCINES SAFE?

Elaborate safety mechanisms are in place for vaccines to be approved for use anywhere globally, including a careful analysis of clinical trial data, ingredients used in the production of vaccines, their chemistry, manufacturing processes, and other factors. Vaccine ingredients vary depending on what the vaccine is for.

They may contain some of the following ingredients:

- Protein component of a virus
- Piece of genetic code (DNA or mRNA)
- Minimal dose of a weakened virus
- Substance to boost the immune response (an adjuvant)
- Small amount of preservative
- Sterile salt water (saline) for injections.

SAFETY PROFILE AND SIDE EFFECTS OF AVAILABLE VACCINES

mRNA Vaccines

The Pfizer BioNTech and Moderna COVID-19 vaccines are nucleoside-modified mRNA vaccines. mRNA vaccines utilize the pathogen's genetic code as the vaccine, which is then exploited by the host cells to translate the code and then make the target spike protein. This spike protein acts as an intracellular antigen to stimulate the immune response.[7] mRNA usually is degraded within a few days. Both the Moderna mRNA-1273 and the Pfizer BioNTech COVID-19 BNT162b2 vaccines have been entirely generated in vitro and are formulated in lipid nanoparticles which are then imbibed by the host cells.[8,9]

Pfizer BioNTech COVID-19 mRNA Vaccine BNT162b2 (Comirnaty®)

Local reactions at the injection site are usual after the Pfizer BioNTech COVID-19 mRNA vaccine, which includes primarily pain at the injection site, usually without redness and swelling. Systemic events reported were generally mild and short-lived.[10]

The most common side effects are injection site pain, fatigue, and headache. Myalgia, arthralgia, and chills with fever are less common but seen mainly after the second dose.

Polack et al. reported lymphadenopathy in the axillary, supraclavicular, or cervical nodes on the same side in <1%. Four cases of Bell's palsy were found in vaccine recipients in their study. Side effects are less common in those over 55 years than those in the 16–55 years age group. Severe systemic effects, defined as those that interfere with daily activity, included fatigue in 4% and headache in 2%.[11]

Most recently, several cases of myocarditis and pericarditis have been reported after the Pfizer BioNTech vaccine. This side effect appears to be highest in the male population, especially under 25 years of age, and is common after the second dose. Onset is within a few days of vaccination, and most cases are mild and recover without any sequelae.[12] The Medicine and Healthcare Products Regulatory Agency (MHRA) has advised that the benefits of vaccination still outweigh any risk in most individuals.

A very small number of Guillain–Barre syndrome (GBS) cases have been reported after the Pfizer–BioNTech vaccination. Still, these reports have not reached the number expected to occur by chance in the immunized population.

Moderna COVID-19 Vaccine (Spikevax®)

The most common symptom seen is localized pain at the injection site after the first and second doses of the Moderna mRNA-1273 vaccine. Some people report an increased incidence of redness and swelling after the second dose. Mild systemic effects include headaches, fatigue, myalgia, joint pains, and chills. Systemic events seen are more severe after the second dose, with fever being reported after dose 2. Both local and systemic reactions were less common in older participants.[13] Adverse events seen are less common in those with preexisting SARS-CoV-2 antibodies.

Axillary lymphadenopathy and Bell's palsy are less commonly seen. Like the Pfizer vaccine, several cases of myocarditis and pericarditis have also been reported after the Moderna vaccine, in young males < 25 years, mostly seen after the second dose. Onset is within a few days of vaccination, and most cases are mild and have recovered without any sequelae. The MHRA advisory says that the benefits of vaccination outweigh the risk.

Adenovirus Vector Vaccines

These include the AstraZeneca, Janssen, Gamaleya (Sputnik), and CanSino Biologics vaccines internationally.

AstraZeneca COVID-19 Vaccine/ Covishield Vaccine

AstraZeneca COVID-19 vaccine employs a replication-deficient chimpanzee adenovirus (ChAd) as a vector to deliver the full-length SARS-CoV-2 spike protein genetic sequence into the host cell.[14]

Chimpanzee adenovirus is a nonenveloped virus, where glycoprotein antigen is expressed once the genetic code within the vector enters the target cells. The vector genes are also modified to render the virus replication incompetent and to enhance immunogenicity. Once the vector enters the nucleus, mRNA encoding the spike protein is produced, entering the cytoplasm. It leads to the translation of the target protein, which acts as an intracellular antigen.[15]

Mild pain and tenderness at the injection site is the most common side effect of the AstraZeneca COVID-19 vaccine after each dose, irrespective of age. Short-lived systemic symptoms, including fatigue and headache, are common but decrease with age. Most of these were unusual with the second dose and were classified as mild to moderate.[16]

Voysey et al., in the phase 3 study, reported that 10% of vaccine recipients reported injection site reactions, mild fever, headache, myalgia, and arthralgia. In contrast, <1% reported lymphadenopathy or an itchy rash. Only one serious adverse event of transverse myelitis was reported as possibly linked to the vaccine, which occurred 14 days after dose 2. Still, there was no association to suggest that prior vaccination led to enhanced disease.[17]

A rare condition occurring between 5 and 16 days following the AstraZeneca vaccination involving life-threatening thromboembolic events accompanied by thrombocytopenia has been reported. This condition presents with unusual venous thrombosis, including cerebral venous sinus thrombosis, portal vein thrombosis, and sometimes arterial thrombosis with low platelet count and high D-dimer measurements. The condition has similitude to heparin-induced thrombocytopenia and thrombosis (HITT or HIT type 2), and these patients also have positive antibody to platelet factor 4.[18] The Joint Committee on Vaccination and Immunisation (JCVI), MHRA, and the WHO have stated very clearly that the benefits of vaccination outweigh this small risk for adults aged 40 years and over.

The GBS has been reported very rarely within 6 weeks of AstraZeneca vaccination. However, it is not a serious cause of concern at this stage, as the syndrome has affected about 1 in 300,000, which is less than the rate at which it normally occurs in the population.

Another infrequent adverse effect is seen in a small number of cases, which is capillary leak syndrome, and it has been reported across Europe within 4 days of AstraZeneca vaccination. Around half of those affected had a history of capillary leak syndrome.

Janssen (Johnson & Johnson) COVID-19 Vaccine

The Janssen COVID-19 vaccine uses a replication-incompetent human adenoviral type 26 vector platform[2] and is administered as a single intramuscular dose.

The most frequently reported side effects are headache, fever, chills, injection site pain, and fatigue. These side effects usually start within a day or two of getting the vaccine. Side effects might affect the ability to do daily activities, but they typically go away in a few days.

Thrombosis and thrombocytopenia syndrome (TTS) after Johnson & Johnson's Janssen (J&J/Janssen) COVID-19 is rare, and despite the acknowledgment of the possibility of thrombotic events as rare adverse events associated with such vaccines, the health regulatory agencies have emphasized the benefits outweighing the risks given the COVID-19 pandemic.[19]

Sputnik Vaccine

Sputnik V is an adenovirus vaccine; it uses an engineered adenovirus—a family of viruses that generally cause only mild illness—as a delivery mechanism for inserting the genetic code for the SARS-CoV-2 spike protein into human cells. It is like the Oxford–AstraZeneca and Johnson & Johnson vaccines, but instead of using one engineered adenovirus (as those two vaccines do), Sputnik V uses different adenoviruses, called rAd26 and rAd5, for the first and second doses, respectively. The two adenoviruses have slightly different methods of introducing their genetic material into a host cell, theoretically improving the success rate of getting the viral genetic material where it needs to go.

The vaccine appears safe in multiple published trials. The most common side effects are pain in the injection site, fatigue, body pain, headache, fever, joint pain, chilling, and drowsiness.[20,21] No hospitalizations or deaths were reported.[22]

Covaxin (BBV152) Vaccine

BBV152 (manufactured by Bharat Biotech) or Covaxin is a whole virion β-propiolactone-inactivated SARS-CoV-2 vaccine. The NIV-2020-770 strain contains the Asp614Gly mutation and is characterized by aspartic acid to glycine shift at the amino acid position 614 of the spike protein.[23]

The local and systemic adverse reactions reported after both doses of vaccine were mild and moderate in intensity. The frequent adverse events across all groups included pain 17 of 375 (5%), headache 13 of 375 (3%), fatigue 11 of 375 (3%), fever 9 of 375 (2%), and nausea and vomiting 7 of 375 (2%).[24]

After vaccination, the essential abnormal laboratory parameters included derangements in bilirubin, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and cholesterol C-reactive protein levels. These findings had no corroborating clinical manifestations.

Sinopharm COVID-19 Vaccine

Sinopharm COVID-19 vaccine is an inactivated vaccine that introduces a dead copy of SARS-CoV-2 intramuscularly into the body; after insertion, the dead antigens from the virus are engaged to make antibodies that will prepare the immune system for future attacks by the virus.[25] In this way, the inactivated viruses maintain their ability to replicate in vivo with mild or no symptoms.[26]

The side effects of this vaccine appear to be mild. The most common side effects include pain at the vaccination site, redness, induration, pruritis, fever, headache, nausea, diarrhea, myalgia, allergic reactions, etc. Women had more symptoms from both the first and the second dose than males.[27]

DURATION OF PROTECTION

Israel was the first country to demonstrate waning immunity from the Pfizer BioNTech vaccine, showing a decline in protection at around 6 months, even against severe disease.[28] In the USA, protection against hospitalization for Pfizer BioNTech and Moderna vaccines remained high (approximately 84%) between 3 and 6 months.[29]

Data from the UK till late August 2021 suggests that protection against symptomatic infection due to the Delta variant appears to decline after the second dose, although it remains above 50% overall after 5 months.[30]

REINFORCING IMMUNIZATION

To boost or not to boost? That is the question facing countries fortunate enough to have vaccinated much of their adult population. In the face of soaring infection numbers caused by the highly contagious Delta variant of SARS-CoV-2 and hints that immunity triggered by COVID-19 vaccines might fade over time, some countries are considering whether to give further doses to those who have been fully vaccinated. Studies of boosting in the various countries have shown that the third dose of AstraZeneca, Moderna, and Pfizer BioNTech vaccines successfully augmented individuals who had received two doses of Pfizer BioNTech or AstraZeneca vaccine around 3 months earlier. Levels of immunoglobulin G (IgG) and pseudoneutralizing antibody, including against Delta variant, were higher where an mRNA vaccine was used as either a heterologous or a homologous boost, or where AstraZeneca was used as a heterologous boost after a primary course of Pfizer BioNTech.[31]

All boosters resulted in short-term local and systemic reactions, like those seen after the primary course, including local pain, fatigue, headache, and muscle pain. Rates of reactions were higher with heterologous than homologous boosters and in those aged under 70 years when compared to older recipients. Rates of local and systemic symptoms were higher where a full dose of Moderna was used to boost those who had received either AstraZeneca or Pfizer BioNTech for the primary course and when AstraZeneca was used to boost those who had Pfizer as a primary course when compared for Pfizer after either primary vaccination.[32]

PRECAUTIONS

Individuals with a history of allergy/anaphylaxis: A very small number of individuals have experienced anaphylaxis when receiving a COVID-19 vaccine. Anyone with a history of allergic reaction to an excipient in the COVID-19 vaccine should receive that vaccine only with an expert's advice. Those with any other allergies (such as a food allergy)—including those with prior anaphylaxis—can have the vaccine with careful monitoring.[33]

Anaphylaxis is an infrequent, recognized side effect of most vaccines, and suspected cases should be reported to the concerned regulatory authorities.

CONCLUSION

To conclude, we would like to quote from a joint statement by the WHO for healthcare professionals, released on June 11, 2021, titled "How COVID-19 vaccines are regulated for safety and effectiveness?"[34]

The safety profiles of COVID-19 vaccines are still incomplete, even for those currently in use. Despite this enigma, healthcare professionals and public health authorities have a decisive role in discussing vaccination against COVID-19 with their patients. Emerging data on the effectiveness of vaccines indicate that licensed COVID-19 vaccines contribute to controlling the spread of the disease. Still, the safety and efficacy of COVID-19 vaccines in certain subpopulations, such as children and adolescents, pregnant woman, and people with multiple underlying conditions, have not yet been fully studied and conclusive data will be available soon.

"Unfortunately, reports of adverse events with vaccines, some of which are exaggerated, have led to a few individuals to express fears about getting vaccinated or delay in getting vaccinated, or even be strongly opposed to vaccination. Clear and consistent communication is therefore essential to support people in making a choice to be vaccinated."[34]

Moreover, health regulators meticulously assess scientific and clinical evidence provided by vaccine manufacturers. Vaccine manufactures are law-bound to follow defined standards and the data they provide. Before a vaccine is approved for use, each vaccine is thoroughly assessed for safety, efficacy, and quality. To that effect, safety evidence is an essential part of each regulatory submission for a COVID-19 vaccine. This extensive monitoring of patients continues for up to 6–12 months or more to follow up to assess the duration of protection and longer-term safety of individual vaccines.

After an emergency approval of a vaccine [emergency use authorization (EUA)], health regulators collect data about its robust effectiveness and monitoring of safety and risk-minimization activities which is called pharmacovigilance.

Therefore, it is imperative that, as healthcare professionals, we diligently report any adverse events seen in our patients and encourage people who are vaccinated to immediately report adverse events to their respective healthcare providers or the medicine regulators.

It is therefore not surprising that while body builds immunity, minor side effects after vaccination will continue to be reported, but the benefits of COVID-19 vaccines far outweigh the risks. In majority of cases, the adverse effects of COVID-19 vaccinations are mild and restricted to minor local reaction at the injection site or fever, myalgia, and asthenia which is short-lived. The health regulators and scientific community understand that the widespread use of COVID-19 vaccines, especially in the elderly patients with underlying health conditions, will mean that there will be deaths and serious illnesses that are purely coincidental and unrelated to vaccinations.

"As part of the safety monitoring and review of all suspected side effects reporting for vaccines, regulators have developed '*Adverse Events of Special Interest'* lists. These lists include some events that have been associated with other vaccines (e.g., anaphylaxis), and some others are included in these lists because they are serious events that are important to monitor like myocarditis/pericarditis and TTS leading to blood clots."[34]

At the same time, it is paramount to understand that no single vaccine is safer than others. The Centers for Disease Control and Prevention (CDC)/Food and Drug Administration (FDA), Drug Controller General of India, National Health System (NHS), and other major health regulators globally recommend that people get vaccinated to curb the spread of the virus that causes COVID-19, except in very specific circumstances: However, receiving a vaccine does not guarantee full protection against COVID-19. People must continue to follow social distancing guidelines, wear a mask in public, and wash their hands frequently, among other precautions.

REFERENCES

1. World Health Organization. (2020). Statement on the second meeting of the International Health Regulations (2005) emergency committee regarding the outbreak of novel coronavirus (2019-nCoV). [online] Available from: https://www.who.int/news/item/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov) [Last accessed March, 2022].
2. World Health Organization. (2020). WHO Director-General's opening remarks at the media briefing on COVID-19. [online] Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 [Last accessed March, 2022].
3. World Health Organization. (2022). COVID-19 vaccine tracker and landscape. [online] Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines [Last accessed March, 2022].
4. Krammer F. SARS-CoV-2 vaccines in development. Nature. 2020;586:516-27.

5. Slaoui M, Hepburn M. Developing safe and effective COVID vaccines—operation warp speed's strategy and approach. N Engl J Med. 2020;383(18):1701-3.
6. Kim J, Marks F, Clemens JD. Looking beyond COVID-19 vaccine phase 3 trials. Nat Med. 2021;27:205-11.
7. Amanat F, Krammer F. SARS-CoV-2 vaccines: status report. Immunity. 2020;52(4):583-9.
8. Vogel A, Kenevsky I, Che Y, Swanson KA, Muik A, Vormehr M, et al. (2020). A prefusion SARS-CoV-2 spike RNA vaccine is highly immunogenic and prevents lung infection in non-human primates. [online] Available from: https://www.biorxiv.org/content/10.1101/2020.09.08.280818v1 [Last accessed March, 2022].
9. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA vaccine against SARS-CoV-2 – a preliminary report. N Engl J Med. 2020;383:1920-31.
10. Walsh EE, Frenck RW Jr, Falsey AR, Kitchin M, Absalon J, Gurtman A, et al. Safety and immunogenicity of two RNA-based COVID-19 vaccine candidates. N Engl J Med. 2020;383(25):2439-50.
11. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383:2603-15.
12. Diaz GA, Parsons GT, Gering SK, Meier AR, Hutchinson IV, Robicsek A. Myocarditis and pericarditis after vaccination for COVID-19. JAMA. 2021;326(12):1210-12.
13. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384:403-16.
14. van Doremalen N, Lambe T, Spencer A, Belij-Rammerstorfer S, Purushotham JN, Port JR, et al. ChAdOx1 nCoV-19 vaccination prevents SARS-CoV-2 pneumonia in rhesus macaques. Nature. 2020;586;578-82.
15. Garafalo M, Staniszewska M, Salmaso S, Caliceti P, Panser KW, Weiczorek M, et al. Prospects of replication-deficient adenovirus based vaccine development against SARS CoV-2. Vaccines (Basel). 2020;8(2):293.
16. Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet. 2020;396:1979-93.
17. Voysey M, Clemens S, Shabir AM, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397:99-111.
18. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 vaccination. N Engl J Med. 2021;384:2092-101.
19. Malik B, Kalantary A, Rikabi K, Kunadi A. Pulmonary embolism, transient ischaemic attack, and thrombocytopenia after the Johnson & Johnson COVID-19 vaccine. BMJ Case Rep. 2021;14(7):e243975.
20. Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, et al.; Gam-COVID-Vac Vaccine Trial Group. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet. 2021;397(10275):671-81.
21. Montalti M, Soldà G, Di Valerio Z, Salussolia A, Lenzi J, Forcellini M, et al.; San Marino Republic COVID ROCCA Group. ROCCA study protocol and interim analysis on safety of Sputnik V vaccine (Gam-COVID-Vac) in the Republic of San Marino: an observational study using active surveillance. medRxiv. 2021.
22. Xia S, Duan K, Zhang Y, Zhao D, Zhang H, Xie Z, et al. Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes: Interim analysis of 2 randomized clinical trials. JAMA. 2020;324(10):951-60.
23. Sarkale P, Patil S, Yadav PD, Nyayanit DA, Sapkal G, Baradkar S, et al. First isolation of SARS-CoV-2 from clinical samples in India. Indian J Med Res. 2020;151(2 & 3):244-50.
24. Ella R, Vadrevu KM, Jogdand H, Prasad S, Reddy S, Sarangi V, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial. Lancet Infect Dis. 2021;21(5):637-46.
25. Forni G, Mantovani A; COVID-19 Commission of Accademia Nazionale dei Lincei, Rome. COVID-19 vaccines: where we stand and challenges ahead. Cell Death Differ. 2021;28(2):626-39.
26. Saeed BQ, Al-Shahrabi R, Alhaj SS, Alkokhardi ZM, Adrees AO. Side effects and perceptions following sinopharm COVID-19 vaccination. Int J Infect Dis. 2021;111:219-26.
27. Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman L, Haas EJ, et al. Waning immunity of the BNT162b2 vaccine: A nationwide study from Israel. medRxiv. 2021.
28. Tenforde MW, Self WH, Naioti EA, Ginde AA, Douin DJ, Olson SM, et al. IVY Network Investigators; IVY Network. Sustained effectiveness of Pfizer-BioNTech and Moderna vaccines against COVID-19 associated hospitalizations among adults — United States, March–July 2021. MMWR Morb Mortal Wkly Rep. 2021;70(34):1156-62.
29. Andrews N, Tessier E, Stowe J, Gower C, Kirsebom F, Simmons R, et al. (2021). Vaccine effectiveness and duration of protection of Comirnaty, Vaxzevria and Spikevax against mild and severe COVID-19 in the UK. [online] Available from: https://khub.net/documents/135939561/338928724/Vaccine+effectiveness+and+duration+of+protection+of+covid+vaccines+against+mild+and+severe+COVID-19+in+the+UK.pdf/10dcd99c-0441-0403-dfd8-11ba2c6f5801 [Last accessed March, 2022].
30. Flaxman A, Marchevsky NG, Jenkin D, Aboagye J, Aley PK, Angus B, et al.; Oxford COVID Vaccine Trial group. Reactogenicity and immunogenicity after a late second dose or a third dose of ChAdOx1 nCoV-19 in the UK: a substudy of two randomised controlled trials (COV001 and COV002). Lancet. 2021;398(10304):981-90.
31. Choi A, Koch M, Wu K, Chu L, Ma LZ, Hill A, et al. Safety and immunogenicity of SARS-CoV-2 variant mRNA vaccine boosters in healthy adults: an interim analysis. Nat Med. 2021;27(11):2025-31.
32. https://www.clinicalguidelines.scot.nhs.uk/nhsggc-paediatric-clinical-guidelines/nhsggc-guidelines/public-health/greenbook-chapter-14a-covid-19/
33. Greenhawt M, Abrams EM, Shaker M, Chu DK, Khan D, Akin C et al. The risk of allergic reaction to SARS-CoV-2 vaccines and recommended evaluation and management: a systematic review, meta-analysis, GRADE assessment, and international consensus approach. J Allergy Clin Immunol Pract. 2021; 9:3546–67.
34. World Health Organization. (2021). Statement for healthcare professionals: How COVID-19 vaccines are regulated for safety and effectiveness. [online] Available from: https://www.who.int/news/item/11-06-2021-statement-for-healthcare-professionals-how-covid-19-vaccines-are-regulated-for-safety-and-effectiveness [Last accessed March, 2022].

131

CHAPTER

Immunomodulators in Coronavirus Disease-2019

Subhankar Paul, Rajesh Kumar Pande

INTRODUCTION

There exists a knowledge gap in our understanding of the pathophysiology and key determinants of coronavirus disease-2019 (COVID-19) severity. Evolving data points toward strong involvement of inflammatory mediators as a part of cytokine storm or cytokine release syndrome (CRS).[1,2] CRS represents a state of intense generalized inflammatory response in association with a deranged immune regulation, which if continues unabated may lead to multiple organ dysfunction syndrome (MODS), and is associated with a worse prognosis in COVID-19.[2,3] The search for therapeutic options in COVID pandemic is focused on using therapies that are otherwise reserved for management of inflammatory and/or autoimmune disorders.[4] Published literature suggests that elderly patients with multiple comorbidities have increased intensive care unit (ICU) requirements and a higher hospital mortality, probably due to potential risk of immunosuppression in COVID-19.[5] This chapter focuses on the potential therapeutic use of immunomodulators in COVID-19 and interpretation of the available evidence.

PATHOGENESIS[6-9]

Pathogenesis and immune response to COVID-19 are depicted in **Flowchart 1 and Figure 1**.

IMMUNOMODULATOR THERAPY

In severe COVID-19 patients, the main issues in critical patients include an exaggerated inflammatory response along with a blunted antiviral immune response. The reported findings in these patients are leukocytosis, lymphopenia, increased acute phase reactants such as C-reactive protein (CRP), ferritin, interleukin 1 and 6 (IL-1, IL-6), and elevated levels of chemokines such as C-X-C motif chemokine ligand 10 (CXCL10) and C-C motif chemokine ligand 2 (CCL2).[8] This hyperinflammatory response provokes CRS leading to capillary leak, thromboembolism, multiorgan failure, and finally death.[1] Developing novel immune-based therapeutics that target viral infection and dysfunctional immune response can improve the clinical outcome of patients with COVID-19. **Table 1** lists the main trials involving the major immunomodulators use in COVID-19.

Corticosteroids

Corticosteroids are effective anti-inflammatory agents used in a wide variety of diseases to treat dysregulated inflammatory response. The proposed mechanism of their action in COVID-19 includes down-regulation of angiotensin converting enzyme-2 (ACE-2) receptor expression in the airway epithelium, dampening effect on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication in vitro, and the inflammatory cascade, reducing the damage, and organ dysfunction.[10] Corticosteroid use in COVID-19 has shown promising results, despite delayed viral clearance and no significant benefits in previous coronaviral diseases [SARS-CoV-1 and Middle East respiratory symptoms-coronavirus (MERS-CoV)].[10] Inhaled ciclesonide use targeting viral replication-transcription complex was associated with inhibited SARS-CoV-2 ribonucleic acid (RNA) replication in cultured cells.[11] Reduced mortality and duration of supplemental oxygen was seen with use of methylprednisolone in COVID-19-associated acute respiratory distress syndrome (ARDS).[12]

Recently published RECOVERY trial using dexamethasone showed a significant 17% reduction in 28-day mortality both in patients on oxygen therapy as well as those on invasive mechanical ventilation. However, its use did not reduce mortality in patients who were not requiring oxygen or respiratory support.[13] A major meta-analysis of seven randomized controlled trials (RCTs) concluded that corticosteroids reduced 28-day all-cause mortality in severe COVID-19 patients when compared to placebo or usual care.[5,14-19] But corticosteroid use in nonsevere COVID-19 has been found to be associated with increase in disease severity and poor clinical outcomes along with an increase in hospital length of stay.[12,20,21] However, a recent meta-analysis

Flowchart 1: Algorithm showing simplified immunopathogenesis of COVID-19.

(AMI: acute myocardial infarctions; ARDS: acute respiratory distress syndrome; COVID-19: coronavirus disease-2019; GM-CSF: granulocyte-macrophage colony-stimulating factor; IFN-γ: interferon gamma; IL: interleukin; PAMPs: pattern-associated molecular patterns; RNAs: ribonucleic acids; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; TNF: tumor necrosis factor)

involving 15,710 patients surprisingly concluded that corticosteroid use in patients with SARS-CoV-2 infection delayed viral clearance and did not convincingly improve survival.[22]

Subset analysis of COVID-19 disease in very elderly intensive care patients (COVIP) study showed a significantly higher 30-day mortality in COVID-19 patients who were >70 years of age and received corticosteroids when compared to those who did not.[23] This was in contrast to the results of RECOVERY trial, which showed no effect of corticosteroids in patients >70 years of age. The STOIC trial has shown that inhaled budesonide use is associated with reduction in hospital admission.[24]

In hospitalized, severe or critically ill COVID-19 patients, the Infectious Disease Society of America (IDSA) recommends dexamethasone or an equivalent dose of alternative glucocorticoid. Severe disease is defined as oxygen saturation is <94% on room air, or supplemental oxygen requirement, or mechanical ventilation or extracorporeal membrane oxygenation (ECMO). Critical

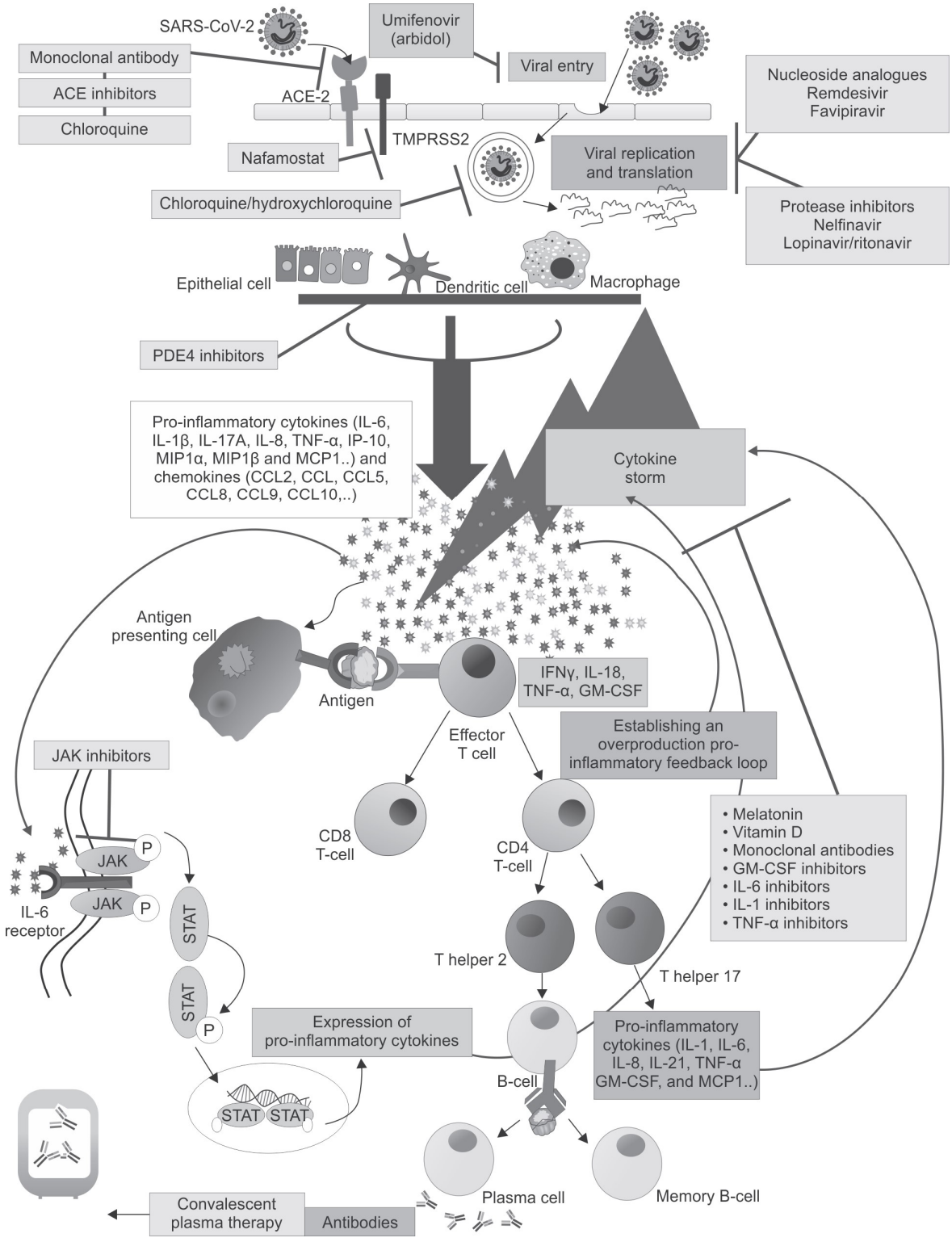


Fig. 1: Schematic diagram of complex interplay of immue mechanisms in pathogenesis of COVID-19 and potential therapeutic options targeting various systems. (ACE: angiotensin-converting enzyme; COVID-19: coronavirus disease-2019; GM-CSF: granulocyte-macrophage colony-stimulating factor; IFN-γ: interferon gamma; IL: interleukin; TNF: tumor necrosis factor)

disease is defined as organ dysfunction in association with mechanical ventilation and ECMO.[25] IDSA recommends no corticosteroids in hospitalized nonsevere COVID-19 patients.[25] In contrast, the National Institute of Health-the United States of America (NIH-USA) recommends use of dexamethasone along with remdesivir in patients who are on supplemental oxygen and hospitalized for nonsevere COVID-19 disease.[26]

The recommended corticosteroid dosing is given in ***Table 2***.[25,26]

TABLE 1: Summary of landmark trials of major immunomodulatory therapies in COVID-19.

Name of the study	*Groups*	*Conclusion*
	Corticosteroids	
RECOVERY[13]	N = 104, hospitalized, dexamethasone + usual care versus usual care	Dexamethasone lowered 28-day mortality
CoDEX[16]	N = 299, hospitalized, moderate/severe ARDS dexamethasone + standard care versus standard care	Dexamethasone + standard care resulted in a significant increase in the number of days alive and free of mechanical ventilation over 28 days
CAPE COVID[17]	N = 149 critical, acute respiratory failure Groups hydrocortisone and placebo	Low-dose hydrocortisone, compared with placebo, did not significantly reduce death or persistent respiratory support at day 21 (terminated early)
REMAP-CAP[18]	N = 403, ICU—suspected or confirmed severe COVID-19. Three groups: Fixed dose hydrocortisone, shock-dependent hydrocortisone, and no hydrocortisone	A 7-day fixed-dose hydrocortisone or shock-dependent hydrocortisone, were superior in improving organ support–free days within 21 days compared with no hydrocortisone
STOIC Trial[24]	Hospitalized, mild disease Groups: Inhaled budesonide, compared with usual care	Early administration of inhaled budesonide reduced the likelihood of needing urgent medical care and reduced time to recovery
	Interleukin inhibitors	
REMAP-CAP[30]	N = 353, Groups: Tocilizumab, sarilumab, and control	IL-6 receptor antagonists improved outcomes, including survival in critically-ill COVID-19 patients receiving organ support in ICUs
RECOVERY[31] *(tocilizumab)*	N = 4,116, hospitalized, and hypoxia with systemic inflammation Groups: Tocilizumab or usual care	Tocilizumab improved survival and other clinical outcomes in hospitalized COVID-19 patients with hypoxia and systemic inflammation
COVACTA[34]	N = 438 hospitalized, severe disease Groups: Tocilizumab versus placebo	Tocilizumab did not significantly improve clinical status or lower mortality than placebo at 28 days in hospitalized patients with severe COVID-19 pneumonia
BACC Bay tocilizumab Trial[35]	N = 243 hospitalized, hyperinflammatory states, or the need for supplemental O_2 Groups: Tocilizumab and placebo	Tocilizumab was not effective for preventing intubation or death in moderately-ill hospitalized patients with COVID-19
EMPACTA[36]	N = 377 hospitalized, not on MV Groups: Standard care plus one or two doses of either tocilizumab or placebo	Tocilizumab reduced the likelihood of progression to the composite outcome of mechanical ventilation or death, but did not improve survival
COVINTOC[37]	N = 180, hospitalized moderate to severe COVID-19 Groups: Tocilizumab plus standard care or standard care alone	Routine use of tocilizumab in patients admitted to hospital with moderate to severe COVID-19 is not supported
	JAK inhibitors	
ACTT-2[43] *(baricitinib/ remdesivir)*	N = 1,033, hospitalized, on high flow or NIV Groups: Baricitinib plus remdesivir, remdesivir plus placebo	Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and clinical improvement
COV-BARRIER[44]	N = 1,525 hospitalized severe COVID-19 Groups: Baricitinib plus standard of care or standard of care alone	Baricitinib plus standard of care had 28-day mortality benefit but no statistically significant difference in progression to high-flow oxygen or noninvasive or invasive mechanical ventilation
STOP COVID[45]	N = 289, hospitalized adults with COVID-19 pneumonia Groups: Tofacitinib versus placebo	Tofacitinib decreased the risk of 28 days mortality or respiratory failure
	Interferons	
Davoudi-Monfared et al.[48]	N = 81 hospitalized, severe disease Groups: IFN β-1a + national protocol medication versus national protocol medications alone	No significant difference in time to clinical improvement. The 28-day overall mortality was significantly lower in the IFN than the control group
WHO SOLIDARITY[49]	N = 1,1330 hospitalized patients with COVID-19 Groups: Remdesivir, HCQ, lopinavir, interferon + lopinavir, no drug	Interferon regimens had little or no effect on overall mortality, initiation of ventilation, and duration of hospital stay

Contd...

Name of the study	Groups	Conclusion
Hyperimmune globulin and convalescent plasma		
RECOVERY[54] *(convalescent plasma)*	N = 11,558 hospitalized with COVID-19 Groups: Convalescent plasma + usual care, usual care alone	High-titer convalescent plasma did not improve survival or receipt of ventilation, time to successful cessation of invasive mechanical ventilation, and use of renal dialysis or hemofiltration
Placid[55]	N = 464 hospitalized, moderate disease Groups: Convalescent plasma + best standard of care, best standard of care only	Convalescent plasma was not associated with a reduction in progression to severe COVID-19 or all-cause mortality
PlasmAr[56]	N = 333 hospitalized Groups: Convalescent plasma or placebo	Convalescent plasma use could not show any significant differences in clinical status or overall mortality over placebo
Non-SARS-CoV-2 specific intravenous immunoglobulin		
Gharebaghi et al.[61]	N = 59 hospitalized, severe disease, Groups: IVIG versus placebo	IVIG improved clinical outcome and significantly reduced mortality in patients who did not respond to initial treatment

(COVID-19: coronavirus disease-2019; HCQ: hydroxychloroquine; ICU: intensive care unit; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2)

TABLE 2: Recommended corticosteroids dosing in severe/critical COVID-19 hospitalized patients.

Corticosteroids	Dose	Route	Frequency	Duration
Dexamethasone	6 mg	IV or oral	OD	10 days or until discharge
Methylprednisolone	2 mg/kg	IV	Total daily dose	Dose tapered after 5 days/10 days
Methylprednisolone	32 mg	Oral	Total daily dose	10 days or until discharge
Prednisone	40 mg	Oral	Total daily dose	10 days or until discharge
Budesonide	800 ug	Inhaled	BD	Until duration of symptoms

(COVID-19: coronavirus disease-2019; IV: intravenous)

Interleukin Inhibitors

Interleukin inhibitors are used in hyperinflammatory and autoimmune disorders. The inhibition of many interleukins such as IL-1B, IL-6, and IL-8, which are responsible for causing cytokine storm.[8]Anakinra (ANK) is a recombinant human IL-1 receptor inhibitor approved by the Food and Drug Administration (FDA), which prevents activation of this receptor by either IL-1β or IL-1α. Significant reduction in mortality was reported in COVID-19 patients receiving either IL-1 (ANK) or IL-6 inhibitors. ANK has been reported to have a role in the treatment of respiratory dysfunction in COVID-19 patients, which needs further evaluation.[27]

Tocilizumab is an IL-6 receptor monoclonal antibody used in chimeric antigen receptor T cells (CAR-T)-associated CRS. The similarity of CRS in CAR-T and COVID-19 led to a significant interest in the use of tocilizumab in COVID-19 patients early in the pandemic.[28] Other IL-6 inhibitors such as sarilumab and siltuximab have also been investigated.

It has been shown that in patients high CRP, use of tocilizumab is effective in inhibiting IL-6.[29] In the REMAP CAP trial, improved survival was seen in critical COVID-19 patients with the use of IL-6 inhibitors.[30] Tocilizumab was found to reduce 28-day mortality and increase the probability of discharge in severe COVID-19 patients.[31]Further, a meta-analysis showed that tocilizumab use in prospective trials was associated with a lower risk of mortality.[32,33]

Other major trials reported conflicting results with no benefit with the use of IL-6 inhibitors.

Tocilizumab use was not found to improve clinical status or reduce mortality in severe COVID-19 patients in the COVACTA RCT.[34] In moderately ill COVID-19 patients, tocilizumab did not reduce intubation or mortality.[35] Although no survival benefit was seen with tocilizumab in hospitalized COVID-19 patients in the EMPACTA study, but it decreased progression to mechanical ventilation or death.[36] These studies suggested that tocilizumab may exhibit different clinical outcomes depending on the severity of COVID-19 and the need for mechanical ventilation. Indian COVID India Tocilizumab (COVINTOC) trial also did not support routine use of tocilizumab in hospitalized moderate-to-severe COVID-19 patients.[37] Further studies are needed to verify the benefit of siltuximab, sarilumab, and anakinara in COVID-19 patients.

The CAN-COVID-RCT found that use of anti-IL-1β antibody canakinumab in severe COVID-19 nonventilated patients with elevated inflammatory markers was not associated with significant difference in mechanical ventilation-free survival, when compared to placebo.[38] In patients with severe progressive or critical COVID-19 disease, IDSA gives a conditional recommendation in addition to standard care. Sarilumab can be used if tocilizumab is not available.[25] A single 8 mg/kg dose of tocilizumab (maximum

800 mg) is recommended only in combination with dexamethasone in hospitalized patients who exhibit rapid respiratory decompensation due to COVID-19.[26]

Tocilizumab should be avoided in patients with fulminant sepsis, raised transaminases-alanine transaminase (ALT) > 5 times the upper normal limit, absolute neutrophil count (ANC) <500, thrombocytopenia (platelets < 50,000), and in patients who have a high-risk of gastrointestinal perforation, or are significantly immunosuppressed or have a known hypersensitivity to the drug. Emergency use authorization (EUA) has been allowed by US FDA for tocilizumab in severe hospitalized COVID-19 patients >2 years of age, who are either on oxygen therapy or mechanical ventilation or ECMO and have been prescribed corticosteroids.[39]

Janus Kinase Inhibitors

Janus kinase (JAK) inhibitors inhibit kinases involved in various stages in the viral life cycle and may help in viral infections.[40] Oral baricitinib, a selective JAK 1 and JAK 2 inhibitor was proposed as a repurposed drug for COVID-19 based on predictions by artificial intelligence algorithms.[41] Baricitinib inhibits key regulators such as adaptor-associated protein kinase-1 (AP2) and cyclin G-associated kinase involved in endocytosis SARS-CoV-2 virus.[42]

Baricitinib and remdesivir combination was superior to remdesivir alone in providing early clinical improvement and recovery in severe COVID-19 patients who were either on noninvasive ventilation (NIV) or high flow oxygen therapy.[43] However the benefit was unclear in patients already on mechanical ventilation.[43] The large COV-BARRIER trial did not show any overall significant reduction in the rate of disease progression, when baricitinib was added to standard treatment (including dexamethasone).[44]

Another JAK inhibitor, tofacitinib (a selective inhibitor of JAK1 and JAK3 with functional selective inhibition of JAK2), also blocks intracellular signaling and reduces production of interferon (IFN) and IL-6 by helper T cells. In the Brazilian STOP-COVID trial, oral tofacitinib 5–10 mg administered twice daily for 14 days or until discharge was associated with a lower incidence of mortality or respiratory failure in COVID-19 patients not yet on mechanical ventilation.[45]

The Infectious Disease Society of America suggests baricitinib for severe COVID-19 hospitalized patients. IDSA also endorses use of baricitinib in combination with remdesivir for severe COVID not ventilated patients, who cannot be given corticosteroids. 4 mg oral daily for 2 weeks or until discharge is recommended.[25] Although there are concerns about risk of thrombosis with long-term baricitinib therapy, but it was found to be safe and tolerated well by COVID patients. The incidence of venous thromboembolism in patients on deep vein thrombosis (DVT) prophylaxis was found to be similar in the baricitinib group when compared to nonbaricitinib group.[43] Baricitinib and remdesivir combination was found to be associated with lower risk of serious adverse events and fewer secondary infections. In the STOP-COVID trial, tofacitinib was found to be quite safe except for the elevated aminotransferase levels and lymphopenia.[45]

Interferons

Interferons are released in response to viral pathogens by host cells and reduce viral replication and spread. SARS-CoV-2 virus alters the effect of IFN and escapes the effects of innate immunity.[46] In patients with moderate COVID-19, who were nebulized with IFNα-2b, there was early viral clearance and reduced inflammation.[47,48] The World Health Organization (WHO) solidarity trial, however, could not show any benefit of IFN therapy compared to standard care.[49] But more studies are required as the emerging data points toward a florid type-I IFN response in patients with severe COVID-19 as compared to suppressed IFN response initially in SARS-CoV-2 infection.[50]

Convalescent Plasma and Hyperimmune Globulin

Convalescent plasma (CP) and hyperimmune globulin provide passive immunity against a specific infectious agent and are derived from recovered individuals with high specific antibody titers. CP was found to be useful in previous coronaviral infections, e.g., SARS-CoV-1 and MERS-CoV infections, where it reduced mortality and increased the discharge rate.[51] Initial retrospective observational studies showed that CP reduced the oxygen requirements at day-14 after transfusion, and improved survivals with severe or life-threatening COVID-19 patients. Early initiation of CP therapy resulted in shorter duration of hospitalization.[52,53] However, such observations were not reflected in further trials. RECOVERY trial did not show improved survival or other prespecified clinical outcomes by using high-titer CP.[54]

A major meta-analysis reported that addition of CP to standard therapy did not provide any clinical benefit or reduction in mortality.[55-57] Early administration of CP was however, associated with improved survival in COVID-19 patients with hematological malignancies, as well as in B-cell–depleted patients with prolonged COVID-19.[58,59] Overall, the large body of robust data suggest against use of CP, and its application in COVID-19 remains very limited.

Standard intravenous immunoglobulin (IVIG) is derived from pooled donor plasma and provides passive immunity. It is used against many immunodeficiency states, autoimmune and neurological disorders, etc.[60] IVIG is believed to exert beneficial effect by modulating inflammation and decreasing plasma IL-6, and CRP levels in

COVID-19 disease. It blocks the FC gamma receptor (FCTR) activation on the innate immune effector cells, complement scavengers, and regulation of Th1, Th17, and regulator T cells.[8,60] Use of IVIG in patients who were not improving with standard therapy resulted in clinical improvement and reduced mortality.[61] Several retrospective studies have also reported the benefits of early IVIG in reducing the 28- and 60-day mortality, hospital stay, inflammatory response, and improving multiorgan physiology, and clinical outcome of severe COVID-19 patients.[62] Further large scale studies are needed to make a definitive recommendation about use of IVIG in COVID-19 patients.

Tumor Necrosis Factor-Alpha Blockers

Tumor necrosis factor-alpha (TNF-α) is an important proinflammatory cytokine, mostly expressed by immune and other cells involved in inflammation and has a role in pathogenesis of inflammatory conditions.[63] Animal studies have shown that neutralizing the activity of TNFs or blocking their receptors results in a protective effect and decreases morbidity and mortality rate of induced SARS-CoV.[64] However, the current evidence is limited to anecdotal reports and at present it cannot be recommended as a standard therapy in COVID-19.[65]

Anti-SARS-CoV-2 Monoclonal Antibodies

Monoclonal antibodies (MABs) act against specific target and have been developed for prophylaxis and treatment of serious viral infections such as Zika, MERS-CoV, Ebola, human immunodeficiency virus (HIV), respiratory syncytial virus (RSV), etc., but have only been found to be effective against RSV and Ebola.[66,67]

Monoclonal antibody targets spike protein of SARS CoV-2 virus and blocks its attachment and entry into human cells. [66] Bamlanivimab is a recombinant neutralizing MAB directed against spike protein and was originally derived from the blood of patients who had recovered from COVID-19. Etesevimab is an MAB directed against the SARS-CoV-2 surface spike protein's receptor binding domain. In BLAZE-1 trial, bamlanivimab plus etesevimab lowered the COVID-19-related hospitalization and mortality and reduced the viral load faster.[68]

Antibody cocktail of casirivimab and imdevimab binds to the spike protein-receptor binding domain on the SARS-CoV-2 virus. The virologic efficacy study (REGEN-CoV) found comparable drop in viral load at all dose levels over 7 days period in nonhospitalized asymptomatic or mild symptomatic patients.[69] Another study looked at impact of two different doses (2,400 mg and 1,200 mg) on clinical outcomes in high-risk COVID-19 patients, and observed a significant reduction in hospitalization, faster recovery or death at both the dose groups as compared to placebo. Patients with no SARS-CoV-2 antibodies and very high viral load had the strongest effect.[70] A subsequent safety analysis of these two studies found no serious safety concern and reduced severe adverse events (SAE). The RECOVERY trial from United Kingdom (UK) found a significant mortality benefit from receiving the combination of casirivimab and imdevimab as compared to standard of care, in seronegative hospitalized patients.[71]

The preventive use of REGEN-CoV as a passive vaccine in household contact of COVID patient is also being explored.[72] The US FDA gave EUA for bamlanivimab and REGEN-CoV in 2020 and the combination of bamlanivimab and etesevimab in 2021 for outpatients with mild-to-moderate COVID-19 at high risk for severe COVID-19.[73,74] Sotrovimab, a new MAB has also been given EUA approval.[70] A new US FDA advisory recommends using MABs in patients with high risk factors.

Current Recommendations for Monoclonal Antibodies

- Bamlanivimab and etesevimab combination is recommended for treatment and postexposure prophylaxis in SARS-CoV-2, mild to moderate COVID-19 adults, and children ≥12 years at high risk for progression to severe COVID-19. The recommended dose is bamlanivimab 700 mg + etesevimab 1,400 mg for these patients. For indoor mild-to-moderate COVID-19 hospitalized patients, it is recommended to be used if they are admitted for non-COVID reasons, or in context of clinical research only if hospitalized for COVID reasons.
- Casirivimab and imdevimab combination is recommended for postexposure prophylaxis and in unvaccinated outpatients with mild to moderate COVID-19 who are at high-risk for progression to severe disease. The recommended dose is 600 mg of casirivimab and 600 mg of imdevimab within 10 days of onset of symptoms.
- Postexposure prophylaxis is recommended in individuals who are not fully vaccinated or have no immune response to vaccination and either are exposed or at risk for SARS-CoV-2 exposure. The prophylactic dose is 600 mg casirivimab and 600 mg imdevimab and further 300 mg of each drug again every 4 weeks if they remain exposed to SARS-CoV-2 infection.
- Sotrovimab is also recommended for patients who have a high risk of progression to severe disease or death.

Antigranulocyte Macrophage-Colony Stimulating Factor Antibodies

Coronavirus disease-2019 patients who died were found to have a ten-fold higher level of the cytokine granulocyte macrophage-colony stimulating factor (GM-CSF), compared to mild disease. GM-CSF is believed to play a major role in development of CRS in COVID-19 patients and more

so in the elderly. The anti-GM-CSF antibodies block this hyperinflammatory response in a nonspecific manner.[75] Lenzilumab, an MAB targeting GM-CSF was found to be associated with early clinical improvement and better oxygenation in patients with ARDS.[76] Compassionate use of lenzilumab has been approved by FDA in the COVID-19 setting. Other anti-GM-CSF MABs in the pipeline are TJ003234, namilumab and regimsilumab/gimsilumab, mavrilimumab, and otilimab.[70] However, IDSA and NIH have so far not given any recommendation for anti-GM-CSF antibodies for use in COVID-19.

CONCLUSION

Immunomodulation as well as immunosuppression are exciting areas in COVID-19 therapeutics, and may eventually emerge as both treatment and prophylactic therapies for those who have moderate-to-severe disease and have high risk of developing CRS, and organ failure. Many newer agents with different immunologic targets such as TLR receptors, cytokines such as TNF-α, IL-18, complement system, etc. are also being tested.

TAKE HOME POINTS

- Immunomodulators act by inhibiting the hyperinflammatory CRS, which is associated with uncontrolled immune dysregulation leading to capillary leak, thromboembolism, multiorgan failure, and finally death in COVID-19.
- Convalescent plasma provides passive immunity against that infectious viral diseases, but the large body of robust data suggest against use of CP in COVID-19 patients.
- Corticosteroids have potent anti-inflammatory effects and cause down-regulation of ACE-2 receptor expression in the airway epithelium. They reduce SARS-CoV-2 replication and the inflammatory cascade, reducing the organ dysfunction and death.
- Tocilizumab is an IL-6 receptor MAB associated with significant reduction in mortality by inhibiting IL-6 and increase in the probability of being discharged alive in patients with progressive severe or critical COVID-19 disease.
- Monoclonal antibody combinations are recommended for treatment and postexposure prophylaxis in mild-to-moderate COVID-19 adults and children ≥12 years, who are at high risk for progression to severe disease. They are also recommended for postexposure prophylaxis.

REFERENCES

1. Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine storm in COVID-19: the current evidence and treatment strategies. Front Immunol. 2020;11:1708.
2. Fajgenbaum DC, June CH. Cytokine storm. N Engl J Med. 2020;383(23):2255-73. doi:10.1056/NEJMra202613118.
3. Bonam SR, Kaveri SV, Sakuntabhai A, Gilardin L, Bayry J. Adjunct immunotherapies for the management of severely Ill COVID-19 patients. Cell Rep Med. 2020;1(2):100016.
4. Burrage DR, Koushesh S, Sofat N. Immunomodulatory Drugs in the Management of SARS-CoV-2. Front Immunol. 2020;11:1844.
5. Belsky JA, Tullius BP, Lamb MG, Sayegh R, Stanek JR, Auletta JJ. COVID-19 in immunocompromised patients: a systematic review of cancer, hematopoietic cell and solid organ transplant patients. J Infect. 2021;82(3):329-38.
6. Stratton CW, Tang YW, Lu H. Pathogenesis-directed therapy of 2019 novel coronavirus disease. J Med Virol. 2021;93(3):1320-42.
7. Esmaeilzadeh A, Elahi R. Immunobiology and immunotherapy of COVID-19: A clinically updated overview. J Cell Physiol. 2021;236(4):2519-43.
8. Hertanto DM, Wiratama BS, Sutanto H, Wungu CDK. Immunomodulation as a Potent COVID-19 Pharmacotherapy: Past, Present and Future. J Inflamm Res. 2021;14:3419-28.
9. Ohadian Moghadam S. A Review on Currently Available Potential Therapeutic Options for COVID-19. Int J Gen Med. 2020;13:443-67.
10. Chatterjee K, Wu CP, Bhardwaj A, Siuba M. Steroids in COVID-19: an overview. Cleve Clin J Med. 2020.
11. Matsuyama S, Kawase M, Nao N, Shirato K, Ujike M, Kamitani W, et al. The inhaled steroid ciclesonide blocks SARS-CoV-2 RNA replication by targeting the viral replication-transcription complex in cultured cells. J Virol. 2020;95(1):e01648-20.
12. Fadel R, Morrison AR, Vahia A, Smith ZR, Chaudhry Z, Bhargava P, et al. Early short-course corticosteroids in hospitalized patients with COVID-19. Clinical Infectious Diseases. 2020;71(16):2114-20.
13. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384(8):693-704.
14. Villar J, Anon JM, Ferrando C, Aguilar G, Muñoz T, Ferreres J, et al. Efficacy of dexamethasone treatment for patients with the acute respiratory distress syndrome caused by COVID-19: study protocol for a randomized controlled superiority trial. Trials. 2020;21(1):717.
15. Petersen MW, Meyhoff TS, Helleberg M, Kjaer MN, Granholm A, Hjortsø CJS, et al. Low-dose hydrocortisone in patients with COVID-19 and severe hypoxia (COVID STEROID) trial-protocol and statistical analysis plan. Acta Anaesthesiol Scand. 2020;64(9):1365-75.
16. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. JAMA. 2020;324(13):1307-16.
17. Dequin PF, Heming N, Meziani F, Plantefève G, Voiriot G, Badié J, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. JAMA. 2020;324(13):1298-306.
18. Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP

COVID-19 corticosteroid domain randomized clinical trial. JAMA. 2020;324(13):1317-29.
19. Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA. 2020;324(13):1330-41.
20. Li Q, Li W, Jin Y, Xu W, Huang C, Li L, et al. Efficacy evaluation of early, low-dose, short-term corticosteroids in adults hospitalized with non-severe COVID-19 pneumonia: a Retrospective Cohort Study. Infect Dis Ther. 2020;9(4):823-36.
21. Spagnuolo V, Guffanti M, Galli L, Poli A, Querini PR, Ripa M, et al. Viral clearance after early corticosteroid treatment in patients with moderate or severe covid-19. Sci Rep. 2020;10(1):21291.
22. Wang J, Yang W, Chen P, Guo J, Liu R, Wen P, et al. The proportion and effect of corticosteroid therapy in patients with COVID-19 infection: a systematic review and meta-analysis. PLoS One. 2021;16(4):e0249481.
23. Jung C, Wernly B, Fjølner J, Bruno RR, Dudzinski D, Artigas A, et al. Steroid use in elderly critically ill COVID-19 patients. Eur Respir J. 2021;58(4):2100979.
24. Ramakrishnan S, Nicolau DV Jr, Langford B, Mahdi M, Jeffers H, Mwasuku C, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. Lancet Respir Med. 2021;9(7):763-72.
25. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America 2021; Version 5.3.1. [online] Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/ [Last accessed March, 2022].
26. NIH. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. [online] Available from: https://www.covid19treatmentguidelines.nih.gov/ [Last accessed March, 2022].
27. Franzetti M, Forastieri A, Borsa N, Pandolfo A, Molteni C, Borghesi L, et al. IL-1 Receptor Antagonist Anakinra in the Treatment of COVID-19 Acute Respiratory Distress Syndrome: A Retrospective, Observational Study. J Immunol. 2021;206(7):1569-75.
28. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-4.
29. Cavalli G, Larcher A, Tomelleri A, Campochiaro C, Della-Torre E, De Luca G, et al. Interleukin-1 and interleukin-6 inhibition compared with standard management in patients with COVID-19 and hyperinflammation: a cohort study. Lancet Rheumatol. 2021;3(4):e253-61.
30. Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med. 2021;384(16):1491-502.
31. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10285):1637-45.
32. Khan FA, Stewart I, Fabbri L, Moss S, Robinson K, Smyth AR, et al. Systematic review and meta-analysis of anakinra, sarilumab, siltuximab and tocilizumab for COVID-19. Thorax. 2021;76(9):907-19.
33. Wei Q, Lin H, Wei RG, Chen N, He F, Zou DH, et al. Tocilizumab treatment for COVID-19 patients: a systematic review and meta-analysis. Infect Dis Poverty. 2021;10(1):71.
34. Rosas IO, Brau N, Waters M, Go RC, Hunter BD, Bhagani S, et al. Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. N Engl J Med. 2021;384(16):1503-16.
35. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med. 2020;383(24):2333-44.
36. Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. N Engl J Med. 2021;384(1):20-30.
37. Soin AS, Kumar K, Choudhary NS, Sharma P, Mehta Y, Kataria S, et al. Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial. Lancet Respir Med. 2021;9(5):511-21.
38. Caricchio R, Abbate A, Gordeev I, Meng J, Hsue PY, Neogi T, et al. Effect of canakinumab vs placebo on survival without invasive mechanical ventilation in patients hospitalized with severe COVID-19: a randomized clinical trial. JAMA. 2021;326(3):230-9.
39. US Food and Drug Administration. Commissioner of the. Coronavirus (COVID-19) update: FDA authorizes drug for treatment of covid-19 [Internet]. US Food and Drug Administration. FDA. [online] Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-drug-treatment-covid-19 [Last accessed March, 2022].
40. Weisberg E, Parent A, Yang PL, Sattler M, Liu Q, Liu Q, et al. Repurposing of kinase inhibitors for treatment of COVID-19. Pharm Res. 2020;37(9):167.
41. Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet. 2020;395(10223):e30-1.
42. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. Clin Immunol. 2020; 214:108393.
43. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. N Engl J Med. 2021;384(9):795-807.
44. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med. 2021;9(12):1407-18.
45. Guimarães PO, Quirk D, Furtado RH, Maia LN, Saraiva JF, Antunes MO, et al. Tofacitinib in patients hospitalized with covid-19 pneumonia. N Engl J Med. 2021;385(5):406-15.
46. Calabrese LH, Lenfant T, Calabrese C. Interferon therapy for COVID-19 and emerging infections: prospects and concerns. Cleve Clin J Med. 2020.

47. Zhou Q, Chen V, Shannon CP, Wei XS, Xiang X, Wang X, et al. Interferon-alpha2b treatment for COVID-19. Front Immunol. 2020;11:1061.
48. Davoudi-Monfared E, Rahmani H, Khalili H, Hajiabdolbaghi M, Salehi M, Abbasian L, et al. A randomized clinical trial of the efficacy and safety of interferon beta-1a in treatment of severe COVID-19. Antimicrob Agents Chemother. 2020;64(9):e01061-20.
49. Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, et al. Repurposed antiviral drugs for Covid-19 - interim WHO solidarity trial results. N Engl J Med. 2021;384(6):497-511.
50. Lee JS, Shin EC. The type I interferon response in COVID-19: implications for treatment. Nat Rev Immunol. 2020;20(10): 585-6.
51. Cagdas D. Convalescent plasma and hyperimmune globulin therapy in COVID-19. Expert Rev Clin Immunol. 2021;17(4):309-16.
52. Liu STH, Lin HM, Baine I, Wajnberg A, Gumprecht JP, Rahman F, et al. Convalescent plasma treatment of severe COVID-19: a propensity score-matched control study. Nat Med. 2020;26(11):1708-13.
53. Jeyaraman P, Agrawal N, Bhargava R, Bansal D, Ahmed R, Bhurani D, et al. Convalescent plasma therapy for severe Covid-19 in patients with hematological malignancies. Transfus Apher Sci. 2021;60(3):103075.
54. RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. Lancet. 2021;397(10289):2049-59.
55. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P. Convalescent plasma in the management of moderate covid-19 in adults in India: open label Phase II multicentre randomised controlled trial (PLACID trial). BMJ. 2020;371:m3939.
56. Simonovich VA, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, Vázquez C, et al. A randomized trial of convalescent plasma in Covid-19 severe pneumonia. N Engl J Med. 2021;384(7):619-29.
57. Janiaud P, Axfors C, Schmitt AM, Gloy V, Ebrahimi F, Hepprich M, et al. Association of convalescent plasma treatment with clinical outcomes in patients with COVID-19: a systematic review and meta-analysis. JAMA. 2021;325(12):1185-95.
58. Biernat MM, Kolasinska A, Kwiatkowski J, Urbaniak-Kujda D, Biernat P, Janocha-Litwin J, et al. Early administration of convalescent plasma improves survival in patients with hematological malignancies and COVID-19. Viruses. 2021;13(3):436.
59. Hueso T, Pouderoux C, Pere H, Beaumont AL, Raillon LA, Ader F, et al. Convalescent plasma therapy for B-cell-depleted patients with protracted COVID-19. Blood. 2020; 136(20):2290-5.
60. Nguyen AA, Habiballah SB, Platt CD, Geha RS, Chou JS, McDonald DR. Immunoglobulins in the treatment of COVID-19 infection: proceed with caution! Clin Immunol. 2020;216:108459.
61. Gharebaghi N, Nejadrahim R, Mousavi SJ, Sadat-Ebrahimi S-R, Hajizadeh R. The use of intravenous immunoglobulin gamma for the treatment of severe coronavirus disease 2019: a randomized placebo-controlled double-blind clinical trial. BMC Infect Dis. 2020;20(1):786.
62. Cao W, Liu X, Hong K, Ma Z, Zhang Y, Lin L, et al. High-dose intravenous immunoglobulin in severe coronavirus disease 2019: a Multicenter Retrospective Study in China. Front Immunol. 2021;12:627844.
63. Shehu S, Kurya AU, Farouq KM, Toro AU. Molecular Pathogenesis, Clinical Efficacy and Safety of Therapeutics used in the Treatment of Osteoarthritis. AJI. 2020;4:1-10.
64. Channappanavar R, Fehr AR, Vijay R, Mack M, Zhao J, Meyerholz DK. Dysregulated Type I Interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-cov-Infected Mice. Cell Host Microbe. 2016;19(2):181-93.
65. Duret PM, Sebbag E, Mallick A, Gravier S, Spielmann L, Messer L. Recovery from COVID-19 in a patient with spondyloarthritis treated with TNF-alpha inhibitor etanercept Ann Rheum Dis. 2020;79(9):1251-2.
66. Marovich M, Mascola JR, Cohen MS. Monoclonal Antibodies for Prevention and Treatment of COVID-19. JAMA. 2020; 324(2):131-2.
67. Marston HD, Paules CI, Fauci AS. Monoclonal antibodies for emerging infectious diseases—borrowing from history. N Engl J Med. 2018;378(16):1469-72.
68. Dougan M, Nirula A, Azizad M, Mocherla B, Gottlieb RL, Chen P, et al. Bamlanivimab plus Etesevimab in mild or moderate covid-19. N Engl J Med. 2021;385(15):1382-92.
69. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. Regn-COV2, a neutralizing antibody cocktail, in outpatients with covid-19. N Engl J Med. 2021;384(3): 238-51.
70. IDSA. (1970). Immunomodulators [Internet]. IDSA Home. [online] Available from https://www.idsociety.org/covid-19-real-time-learning-network/therapeutics-and-interventions/immunomodulators [Last accessed, March, 2022].
71. RECOVERY Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021.
72. Taylor PC, Adams AC, Hufford MM, de la Torre I, Winthrop K, Gottlieb RL. Neutralizing monoclonal antibodies for treatment of COVID-19. Nat Rev Immunol. 2021;21(6):382-93.
73. US Food and Drug Administration. Fact sheet for health care providers Emergency Use Authorization (EUA) of REGEN-COV2TM (casirivimab with imdevimab). [online] Available from: https://www.fda.gov/media/145611/download [Last accessed March, 2022].
74. Food and Drug Administration. Fact sheet for health care providers emergency use authorization (EUA) of bamlanivimab and etesevimab. Indianapolis: Eli Lilly. [online] Available from: https://www.fda.gov/media/145802/download. opens in new tab [Last accessed March, 2022].
75. Thwaites RS, Sevilla Uruchurtu AS, Siggins M, Liew F, Russell CD, Moore SC, et al. Elevated antiviral, myeloid and endothelial inflammatory markers in severe COVID-19. 2020. [online] Available from: https://doi.org/10.1101/2020.10.08.20209411 [Last accessed March, 2022].
76. Temesgen Z, Assi M, Shweta FNU, Vergidis P, Rizza SA, Bauer PR, et al. GM-CSF neutralization with Lenzilumab in severe covid-19 pneumonia: a case-cohort study. Mayo Clin Proc. 2020;95(11):2382-94.

CHAPTER 132

Decrease in COVID-19-associated Mortality Rates

Mradul Daga, Raghu RV, Siddharth Chand

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused a pandemic which has been razing on for almost 2 years now. As of 21st September 2021, >230 million patients have been affected and >4.7 million deaths have occurred.[1] The clinical spectrum of COVID-19 may vary from asymptomatic disease, who acts as carriers to severe respiratory disease with acute respiratory distress syndrome (ARDS) and death.[2]

Almost one in six patients ends up suffering from severe disease with nearly 5% becoming critically ill.[3] Whilst it was initially presumed to be a disease of the pulmonary system, gradually it was recognized that it can affect other systems as well and lead a number of symptoms.[3,4] The involvement of the extrapulmonary sites often lead to increased complications and morbidity. The overall mortality is around 2–3% with mortality in hospitalized patients ranging from 6.3 to 26.85% in different parts of the world.[5]

PATHOPHYSIOLOGY

SARS-CoV-2 affects the cells which express angiotensin-converting enzyme 2 (ACE2) receptors which is responsible for penetration of the virus into host cell, with a mechanism similar to the pathogenesis to SARS. The spike glycoprotein receptor binding domain of SARS-CoV-2 has a unique structural feature which confers higher binding affinity for ACE2 on host cells as compared with SARS-CoV.[6] The ACE2 receptor is expressed in various tissues such as lungs, intestinal tracts, kidneys, and endothelium. All of these organs and systems which have high expression of ACE2 receptors are speculated to be targets for SARS-CoV-2 infection.[7] Binding of spike protein to the ACE2 receptor results in fusion of viral envelop protein with host cell membrane which is followed by the release of viral RNA into the host cytoplasm that undergoes further replication inside the host cell.[8] All this leads to a dysimmune response by the body leading to a hyperinflammatory state which fails to the clear the virus but leads to damage of the host tissue.

As the pandemic progressed, it became clear much of the mortality is due to the hyperinflammatory state and not only the viral infection of the cell. Also sequelae of the disease leading to conditions such as secondary bacterial infections, post-COVID fibrosis leads to significant number of deaths.

MORTALITY IN COVID-19

Mortality in COVID-19 appears to be lower than what was observed in SARS-CoV-1 and Middle East respiratory syndrome (MERS). The deaths in COVID-19 are predominantly due to severe ARDS which ranges widely from 12 to 78% with an average of 25–50%. However, death can occur from several other conditions including sepsis with multiorgan failure, cardiac arrhythmia, cardiac arrest, and pulmonary embolism.

Risk Factors for Mortality

- Occurrence of ARDS
- Requirement for mechanical ventilation
- Obesity, hypertension, diabetes, chronic cardiac and pulmonary conditions, chronic kidney disease on renal replacement therapy, and cancer are associated with high mortality
- Presence of immune dysregulation as manifested by fever, elevated D-dimer levels, fibrin degradation products, prolonged activated partial thromboplastin, and prothrombin times
- Persistent lymphopenia, neutrophilia, and increased troponin level are few parameters associated with increased mortality
- Male sex
- Severity of organ dysfunction on admission
- In resource-limited settings, risk factors for death were similar but also included human immunodeficiency virus (HIV) infection and delay in admission due to resource limitation.[9]

Decrease in COVID-19-associated Mortality Rates (Fig. 1)

The mortality among COVID-19 patients is appearing to decrease with time. Many factors are postulated for this decrease. We discuss in this chapter some of the important reasons for this decrease in death rates. In an analysis of patients during a resurgence of COVID-19 in Houston, Texas, in-hospital mortality was lower during the second surge compared with the first surge (5 vs. 12%) but the difference in ICU mortality was not significant (23 vs. 28%).[10] In another French cohort of over 4,000 critically-ill patients, mortality decreased from 42 to 25% over a 4-month period during the pandemic.[11] In a United States analysis of 468 patients with COVID-19-related critical illness from March 1, 2020 to May 11, 2020, the mortality decreased from 44 to 19%.[12]

Many reasons have been tried to explain the gradual decrease in mortality associated with COVID 19.

- *Understanding the pathophysiology of the disease:* As the pandemic has progressed, we have developed better understanding of the pathophysiology of the disease.[13] It is now known that dysimmune response by the body leading to hyperimmune state along with prothrombotic milieu is associated with significant higher mortality.
- *Pharmacological treatment:* With better understanding of the pathophysiology, various drugs underwent clinical trial. The initial findings of the RECOVERY(15) trial in UK published in the month of July, 2020 reported that the use of corticosteroid (6 mg dexamethasone) leads to lower 28-day mortality among those who required respiratory support at randomization.

Subsequent to publication of this finding, steroids were recommended for all patients needing respiratory support. Also anticoagulants (either parenteral or oral) were also added in guidelines for patients suffering from moderate or severe category illness.

In the following months, other trial results were also published regarding efficacy of adjunctive tocilizumab or baricitinib in reducing mortality. The RECOVERY trial in UK assessed the efficacy of tocilizumab with/without steroids. They noted that patients allocated to tocilizumab were more likely to be discharged from hospital within 28 days (57% vs. 50%; rate ratio 1.22; 1.12–1.33; $p < 0.0001$). Patients who were not receiving invasive mechanical ventilation at baseline and were randomized to tocilizumab were less likely to reach the composite endpoint of invasive mechanical ventilation or death (35% vs. 42%; risk ratio 0.84; 95% CI 0.77–0.92; $p < 0.0001$).[14] The COV-BARRIER trial assessing the efficacy of baricitinib as compared to placebo found that once-daily baricitinib (4 mg) reported 38.2% relative reduction in mortality with one mortality prevented per 20 baricitinib-treated participants.[15]

The data regarding the benefit of remdesivir is conflicting. Meta-analysis by Bansal et al. of three clinical trials in 2020 reported that use of remdesivir significantly reduces the mortality compared to the placebo (OR 0.70, 95% CI 0.58–0.84, $p \leq 0.001$; I2 = 16.6).[16] The interim findings of the SOLIDARITY trial by WHO did not report any reduction in mortality with use of remdesivir.[17] However, it has been widely used in patients who required respiratory support.

Based on the pathogenesis of COVID-19, approaches that target the virus itself (e.g., antivirals, passive immunity, and interferons) are more likely to work early in the course of infection, whereas approaches that modulate the immune response may have more impact later in the disease course.[18]

Appropriate usage of drugs targeting specific pathway depending upon the day of illness contributed to better outcomes among hospitalized patients in later part of the pandemic.

- *The establishment of the national lockdown and government policies:* The role of demographic characteristics of the population as well as government stringency and increased and targeted testing as important factors in reducing the incidence of COVID-19.[19] Most administrations around the world made mask wearing compulsory in public places, enforced curfews, or partial confinements for movement. These actions during the early part of the pandemic may have helped to mitigate the spread of the virus. The best course of action for the countries with high COVID-19 cases will be to continue implementing periodic lockdowns, while increasing the number of COVID-19 testing.

  Studies have shown that the mortality was higher in areas with more uninsured individuals and fewer primary care physicians per capita. The mortality was higher in places in which more deaths occurred at home.[20]

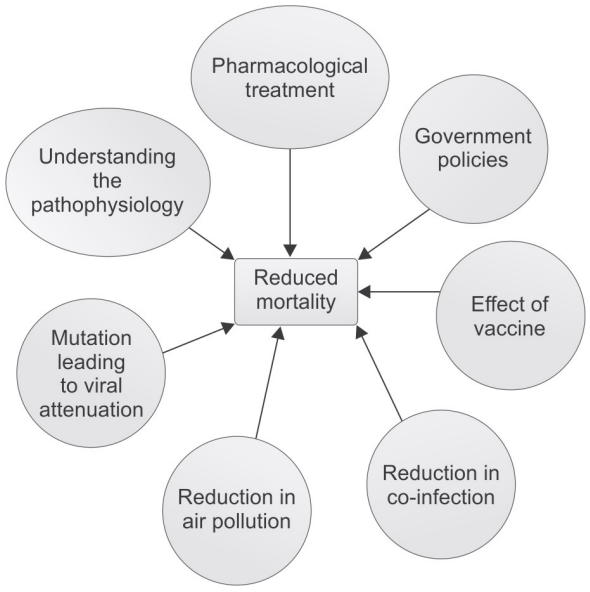


Fig. 1: Factors responsible for decrease in COVID-19 mortality.

- *Coinfection of respiratory pathogens (i.e., seasonal influenza viruses) might have decreased, and this factor could have had an impact on disease severity*. Influenza virus is not structurally related to COVID-19, but has similar transmission method, disease symptoms, risk factors, at-risk population, and mortality trends. It is suggested that influenza vaccination coverage in the elderly population is negatively associated with mortality from COVID-19.[21] It is hypothesized that coinfection with influenza virus might have decreased with the course of this pandemic and this has also contributed to decreased mortality.
- *Effect of vaccination*: Vaccination has been largely successful in reducing asymptomatic infection and transmission of SARS-CoV-2.[22] One study showed that cases of COVID-19 were less common among household members of vaccinated healthcare workers during the period beginning 14 days after the first dose than during the unvaccinated period before the first dose (event rate per 100 person-years, 9.40 before the first dose and 5.93 beginning 14 days after the first dose). After the healthcare worker's second dose, the rate in household members was lower still (2.98 cases per 100 person-years).[23]

Most real world experiences with vaccines have reported decrease in mortality in patients who suffered breakthrough infection. In an analysis of almost 1 million vaccinated people in Bahrain, it was shown that all fours vaccines used in the country namely Pfizer/BioNtech, Sinopharm, Sputnik V, and Astra-Zeneca (AZ/Covishield) were effective in reducing infections, symptomatic diseases in breakthrough infections, and rate of hospitalization and death. However, subgroup analysis reported higher incidence of infections and death in recipients of Sinopharm vaccine. Similar experiences have been reported in other countries as well. An epidemiological study from Canada reported decrease in mortality from COVID-19 in the community as the vaccination coverage increased.[24,25]

COVID-19 and Air Pollution

Apart from the respiratory complications in COVID-19, cardiovascular complications of such as myocardial infarction, heart failure, and venous thromboembolisms also cause mortality. These complications are also present in with increased levels of air pollutants. In a study of 5,700 COVID-19 patients hospitalized in the New York City area, the most common comorbidities were hypertension (57%), obesity (42%), and diabetes (34%). These cardiovascular risk factors are also observed in relation to elevated PM2.5 concentrations,[26] highlighting additive or synergistic effects on the cardiovascular system.

Some of the recent analyses have suggested the possible correlation between the regional pollutant emissions and climate with incidences of COVID-19 outbreaks.[27]

Decrease in air pollution could be associated with decrease of the cardiovascular risk factors and morbidity associated with COVID-19.

- *Finally, the tracking of virus population diversity in time through SARS-CoV-2[28] mutations* could potentially establish a correlation of viral fitness and eventually viral attenuation with observed clinical outcomes. Study conducted in National Institute of Biomedical Genomics, Kalyani, West Bengal, India showed that Clade-G genomes were found to be evolving more rapidly and were also found in higher proportions in three states with highest mortality rates namely, Gujarat, Madhya Pradesh and West Bengal. Thus, the findings of this study and results from in vitro studies highlighting the role of these variants in increasing transmissibility and altering response to antivirals reflect the role of viral factors in disease prognosis.[29]

Another study showed in the UK as the epidemic curve grew gradually from September to December 2020, peaked in early January 2021 with the daily number of COVID-19 cases over 60,000, and declined thereafter. The number of COVID-19 deaths time series presents a similar trend as the cases curve with a lag accounting for the progression of COVID-19. The 501Y variants emerged around September, and maintained at a relatively low prevalence below 5% until November 2020. Then, the 501Y variants rapidly increased and dominated with prevalence at 50% by the end of December 2020, and trended to reach fixation after January 20.[30]

CONCLUSION

COVID-19 leads to varied range of disease severity; may have asymptomatic disease or may result in ARDS and death. The mortality amongst COVID-19 patients is appearing to decrease with time. Many factors are postulated for this decrease. Improved understanding of the disease pathogenesis with improved management protocol targeting the dysimmune response and hypercoagulable state has led to reduction of mortality as the pandemic has evolved. Other measures as implementation of lockdowns, face mask mandates, and improved vaccination coverage have also contributed to the decrease in the mortality trends.

REFERENCES

1. COVID Live. Coronavirus statistics. Worldometer(Internet) (accessed on 2021 sep 21). [online] Available from: http://www.worldometer.info/coronavirus/about
2. Bal A, Agrawal R, Vaideeswar P, Arava S, Jain A. COVID-19: an up-to-date review–from morphology to pathogenesis. Indian J Pathol Microbiol. 2020;63(3):358-66.
3. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-42.

4. Behzad S, Aghaghazvini L, Radmard AR, Gholamrezanezhad A. Extrapulmonary manifestations of COVID-19: radiologic and clinical overview. Clin Imaging 2020;66:35-41.
5. Zheng KI, Feng G, Liu WY, Targher G, Byrne CD, Zheng MH. Extrapulmonary complications of COVID-19: a multisystem disease? J Med Virol. 2020;10:1002/jmv.26294.
6. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798): 270-3.
7. Ding Y, Wang H, Shen H, Li Z, Geng J, Han H, et al. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. J Pathol. 2003;200(3):282-9.
8. Coutard B, Valle C, de Lamballerie X, Canard B, Seidah NG, Decroly E. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antivir Res. 2020;176:104742.
9. Noor FM, Islam MM. Prevalence and associated risk factors of mortality among COVID-19 patients: a meta-analysis. J Community Health. 2020;45(6):1270-82.
10. African COVID-19 Critical Care Outcomes Study (ACCCOS) Investigators. Patient care and clinical outcomes for patients with COVID-19 infection admitted to African high-care or intensive care units (ACCCOS): a multicentre, prospective, observational cohort study. Lancet. 2021;397(10288):1885-94.
11. Vahidy FS, Drews AL, Masud FN, Schwartz RL, Askary BL, Boom ML, et al. Characteristics and Outcomes of COVID-19 Patients During Initial Peak and Resurgence in the Houston Metropolitan Area. JAMA. 2020;324(10):998-1000.
12. COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med. 2021;47(1): 60-73.
13. Anesi GL, Jablonski J, Harhay MO, Atkins JH, Bajaj J, Baston C, et al. Characteristics, Outcomes, and Trends of Patients With COVID-19-Related Critical Illness at a Learning Health System in the United States. Ann Intern Med. 2021;174(5):613-21.
14. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021;384(8):693-704.
15. Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, COV-BARRIER Study Group, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med. 2021;9(12):1407-18.
16. Bansal V, Mahapure KS, Bhurwal A, Gupta I, Hassanain S, Makadia J, et al. Mortality Benefit of Remdesivir in COVID-19: A Systematic Review and Meta-Analysis. Front Med (Lausanne). 2021;7:606429.
17. WHO Solidarity Trial Consortium, Pan H, Peto R, Henao-Restrepo AM, Sathiyamoorthy V, Karim QA, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med. 2021;384(6):497-511.
18. Cantini F, Goletti D, Petrone L, Fard SN, Niccoli L, Foti R. Immune Therapy, or Antiviral Therapy, or Both for COVID-19: A Systematic Review. Drugs. 2020;80:1929-46.
19. Ciceri F, Beretta L, Scandroglio AM, Colombo S, Landoni G, Ruggeri A, et al. Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis. Crit Care Resusc. 2020;22(2):95-7.
20. Chaudhry R, Dranitsaris G, Mubashir T, Bartoszko J, Riazi S. A country level analysis measuring the impact of government actions, country preparedness and socioeconomic factors on COVID-19 mortality and related health outcomes, E Clinical Medicine. 2020;25:100464.
21. Stokes AC, Lundberg DJ, Bor J, Elo IT, Hempstead K, Preston SH. Association of Health Care Factors With Excess Deaths Not Assigned to COVID-19 in the US. JAMA Netw Open. 2021; 4(9):e2125287.
22. Zanettini C, Omar M, Dinalankara W, Imada EL, Colantuoni E, Parmigiani G, et al. Influenza Vaccination and COVID-19 Mortality in the USA. Preprint medRxiv. 2020;2020.06.24. 20129817.
23. Voysey M, Costa Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet. 2021;397: 881-91.
24. Leung G, Verma A. Epidemiological Study of COVID-19 Fatalities and Vaccine Uptake: Insight From a Public Health Database in Ontario, Canada. Cureus. 2021;13(7):e16160.
25. Qahtani MA, Bhattacharyya S, Alawadi A, Mahmeed HA, Sayed JA, Justman J, et al. (2021). Morbidity and mortality from COVID-19 post-vaccination breakthrough infections in association with vaccines and the emergence of variants in Bahrain. [online] Available from https://icap.columbia.edu/tools_resources/morbidity-and-mortality-from-covid-19-post-vaccination-breakthrough-infections-in-association-with-vaccines-and-the-emergence-of-variants-in-bahrain/ [Last accessed March, 2021].
26. Münzel T, Sorensen M, Gori T, Schmidt FP, Rao X, Brook J, et al. Environmental stressors and cardio-metabolic disease: part I—epidemiologic evidence supporting a role for noise and air pollution and effects of mitigation strategies. Eur Heart J. 2017;38:550-6.
27. Frontera A, Martin C, Vlachos K, Sgubine G. Regional air pollution persistence links to COVID-19 infection zoning. J Infect. 2020;30173-0(20):S0163-4453.
28. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395(10224):565-74.
29. Pandit B, Bhattacharjee S, Bhattacharjee B, Association of clade-G SARS-CoV-2 viruses and age with increased mortality rates across 57 countries and India. Infect Genet Evol. 2021;90:,104734.
30. Zhao S, Lou J, Chong MKC, Cao L, Zheng H, Chen Z, et al. Inferring the Association between the Risk of COVID-19 Case Fatality and N501Y Substitution in SARS-CoV-2. Viruses. 2021;13:638.

CHAPTER 133

Post-COVID Pulmonary Syndrome

Jasbir Singh Chhabra, Vijay Narain Tyagi, Lalit Mishra

INTRODUCTION

Since the start of the coronavirus diseases (COVID) pandemic in December 2019, more than 183 million people have been infected worldwide with over 3.97 million fatalities and the number continues to increase.[1] Recent evidence suggests that a range of symptoms can remain after the clearance of acute infection in patients with COVID-19. The prevalence of "long COVID" gained worldwide attention following an account published by an infectious disease professor who shared his roller-coaster experience 7 weeks into contracting COVID-19 on May 5, 2020, in the journal "BMJOpinion."[2] This *patient made* the term "long COVID" popular on Twitter—#LongCovid.

The National Institute of Health and Care Excellence (NICE) defines *long COVID* as the symptoms that continue or develop after an acute COVID-19 infection and that cannot be explained by an alternative diagnosis. This includes "ongoing symptomatic COVID--19" from 4 to 12 weeks post infection and "post-COVID-19 syndrome" beyond 12 weeks post infection.[3] In contrast, the National Institutes of Health (NIH) uses the US Center for Disease Control and Prevention (CDC) definition of "long COVID," which describes the condition as a sequel that extended beyond 4 weeks after the initial infection.[4]

There is a huge variation in the reported incidence of long COVID symptoms. About 60–80% of patients infected with COVID developed one or more long-term symptoms. The most commonly reported symptoms include fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%).[5] These figures are worrying not only for patients but also for healthcare providers as well as governments as patients with long COVID will require long-term support and treatment. Systematic review and meta-analysis reveal that 80% of individuals with a confirmed diagnosis of COVID-19 continue to have at least one complication beyond 2 weeks following an acute infection with COVID-19.[5]

What is not clear is how does gender, ethnicity, age, viral dose, or severity of COVID-19 disease affect the risk of developing long-term effects of COVID-19.[6] Any patient with COVID-19 can develop long COVID regardless of the severity of his/her infection or the treatment he/she has received. Thus, whether a person is treated in the respiratory ward or in the intensive care unit, there is little difference in the incidence of long COVID. Whether a patient has received oxygen alone, with continuous positive airway pressure or mechanical ventilation, the incidence of long COVID is similar. In fact, there is minimal difference between the prevalence of long COVID symptoms no matter the patient was admitted to the hospital or received home treatment.

PATHOPHYSIOLOGY AND CLINICAL FEATURES

Long COVID is multisystemic disease. The virus responsible for COVID-19, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), enters the cells via the angiotensin-converting enzyme 2 (ACE2) receptor.[7] The virus is then internalized and uses the cellular mechanisms to undergo replication and maturation provoking an inflammatory response that involves various cytokines. The ACE2 receptor is present in various cells of the body including oral and nasal mucosa, heart, lungs, gastrointestinal tract, liver, kidneys, spleen, brain, and arterial and venous endothelial cells, thus highlighting how it can cause damage to multiple organs leading to multiorgan failure.

Fatigue is the most common symptom of long COVID-19.[8] It is present even after 4 months of the first symptom of COVID-19. In addition to other respiratory complications such as acute respiratory distress syndrome (ARDS) due to COVID, fatigue has been reported in up to 70% of patients after a year of contracting COVID-19. Fatigue describes the fact that the patient is much more than just being tired very easily; it is a persistent state of lack of energy, motivation, and concentration. The symptoms are very similar to what has been defined as the chronic fatigue syndrome (CFS).[9] This includes the presence of severe debilitating fatigue, sleep deprivation, neurocognitive disability, autonomic dysfunction, and worsening of global fatigue following small increase in physical activity. Several other viruses have

been related to the diagnosis of CFS including cytomegalovirus, Epstein–Barr virus, enterovirus, and herpesvirus. CFS is also called myalgic encephalomyelitis (ME) in some countries. The pathophysiology of fatigue is not completely understood. A cross-sectional study found that there was no association between the levels of proinflammatory markers and the long-term fatigue in COVID-19 patients. In one of the reviews, it is explained that congestion of the lymphatic system and the subsequent build-up of toxins in the central nervous system due to increased resistance to cerebral spinal fluid drainage through the cribriform plate as a result of olfactory neuron damage may contribute to the symptom of fatigue. Hypometabolism in the frontal lobe and cerebellum caused by systemic inflammation and cell-mediated immune mechanisms has been implicated as one of the mechanisms of fatigue. Peripheral factors such as damage to the skeletal muscle durable systemic inflammation and cell-mediated immune damage to the neuromuscular junctions may also contribute toward fatigue. Peripheral factors such as direct virus-induced damage to the skeletal muscle cells and cell-mediated immune damage to the neuromuscular junctions may also contribute toward fatigue.

About 25% of patients complain of dyspnea, chest pain, and cough. Persistent abnormalities in CT scan of thorax are present in 35% of patients even after 60–100 days from the initial presentation. In a follow-up study conducted in China among patients who did not require admission to intensive care but required hospitalization, X-ray changes persisted in up to 75% of patients 90 days after discharge from hospital.[10] It is important to note that this is very similar to patients who recovered from other viral pneumonia. Long-term abnormalities in pulmonary function, such as reduced diffusion capacity, are noted in 10% of patients following COVID-19 infection. There is some evidence that older people, people who developed ARDS, and those with preexisting lung abnormalities are more likely to develop fibrotic light changes to the lung tissue. These fibrotic changes may be provoked by cytokines such as interleukin-6 which is raised in COVID-19. Endothelial damage triggers the activation of fibroblasts which deposit collagen and fibronectin resulting in fibrotic changes. Other common symptoms include sudden loss of body weight, palpitations, cold nose, burning feeling in trachea, pain or burning feeling in the lungs, pain between shoulder blades, and body aches. All these are fairly similar to those seen following SARS and Middle East respiratory syndrome (MERS). For example, 28% of survivors with SARS and 33% of patients with MERS had decreased lung function and pulmonary fibrosis at 1 year's follow-up.[11]

In the cardiac system, the patient experiences chest pain, palpitations, myocardial inflammation (myocarditis), and increased serum troponins.[12] In some instances, myocarditis and arrhythmias have attributed to sudden death in these patients. Even young, competitive athletes who were considered to be at low risk of severe COVID-19 have been found to have residual myocarditis long after the recovery. Dysfunction of the afferent autonomic nervous system can cause complications such as postural orthostatic tachycardia syndrome (POTS). Prolonged inflammation and cellular damage prompt fibroblasts to secrete extracellular matrix molecules and collagen resulting in fibrosis, which leads to displacement of desmosomal proteins predisposing to arrhythmias. As mentioned before, ACE2 receptors are highly prevalent in the heart, thus providing a direct entry into the myocardial cells. Pathologically sarcomere fragmentation, enucleation, intense local immune response, endothelial damage, and micro-thrombosis have been found.

There are several neuropsychiatric conditions that have been reported as a side effect of COVID-19.[13] They present as various signs and symptoms such as cognitive impairment, anosmia, headache, attention disorders, brain fog, seizures, hypoxic brain injuries, insomnia, cortical spinal tract signs, dysexecutive syndrome, and dementia. The pathophysiology of neuropsychiatric symptoms is complex and multifactorial and could be related to cerebral vascular disease including hypercoagulation, direct effect of the infection, hypoxia, side effects of medications, and the psychosocial effects of having a potentially fatal illness. Blood–brain barrier damage and dysregulation lead to increased permeability allowing blood-derived substances and white blood cells to infiltrate the brain parenchyma. Chronic inflammation in the brain stem can cause autonomic dysfunction. Abnormalities of olfactory and gustatory function persist following the recovery from COVID-19. The incidence in literature varies anything from 11 to 45%. It has been estimated that adults have twice the risk of a new diagnosis of psychiatric disorder after a COVID-19 diagnosis. Hence, it is important to follow these patients in a follow-up clinic, specifically looking for these neuropsychiatric conditions, and provide them with prompt rehabilitation. It is estimated that because patients with COVID require prolonged ventilation, the incidence of critical illness myoneuropathy, delirium, and long-term cognitive impairment will rise. COVID-19 has also been associated with increased risks of developing Guillain–Barre syndrome and other neurodegenerative conditions such as Alzheimer's disease.

Hair loss is a common problem after COVID-19 infection and can last for approximately 3 months. This condition is similar to "telogen effluvium" where patients experience diffuse hair loss after a systemic disturbance or infection.[3] Fortunately this is a self-limiting condition; however, it does contribute to considerable emotional distress and loss in confidence.

Other systemic manifestations include pancreatitis, acute kidney injury, acute liver injury, and diarrhea. The vascular system specifically manifests as vasculitis, coagulopathy, and microangiopathy.

What is concerning is the increasing number of COVID variants. The first virus was called the alpha virus or the B.1.1.7. Following this, we have the beta, gamma, zeta, theta, and kappa variants. Of greatest concern is the "Kent" variant which shows 50% increased transmissibility and likely increase in severity of disease. This will have implications in the incidence of long COVID for years to come. It is quite possible that one variant causes more damaging long-term effects than others which would mean that patients infected with these variants go on to develop long COVID more frequently than others and hence will require additional support as well as intensive treatment strategies in order to overcome their long-term disabilities.

DETERMINING THE BURDEN

Determining the true incidence of long COVID is difficult. This is because there was no standard definition of "long COVID-19," with some authors using alternative terms such as persistent COVID-19 symptoms, chronic COVID-19, post-COVID-19 manifestations, long-term COVID-19 effects, long haulers, etc., in their studies. The reported incidence and mortality rates vary considerably between different countries making it difficult to accurately report long COVID. Other reasons include variation in their population, accuracy of diagnosis, reporting systems, variability in the length of follow-up period, accuracy of self-reporting, and the symptoms examined in various studies.

However, on the positive side now that we have got the above standard definitions of long COVID, it will become easier to understand and collect this data with increasing accuracy.

MANAGING LONG COVID

Various guidelines are now available through institutions such as National Institute for Health and Care Excellence (NICE), World Health Organization (WHO), CDC, and NIH.[3,14-16]

Most of these focus on certain common elements. First, it is important to establish a diagnosis of long COVID and then the focus is on symptomatic management. NICE recommends that breathlessness should be investigated using exercise tolerance test, chest X-ray, and echocardiography. The Mayo Clinic suggests that shortness of breath should be self-managed by limiting factors that exacerbate recklessness such as stopping smoking and widening extremes in temperature and pollutants and gradually improving exercise capacity. Nonpharmacological strategies include breathing exercises, pulmonary rehabilitation, and yoga whereas opioids may be used as a pharmacological strategy to manage breathlessness. Patients with pulmonary fibrosis should be managed in accordance with NICE guidelines (National Institute of Clinical Excellence, UK) on idiopathic pulmonary fibrosis. Exacerbation of bronchiectasis should be management of antimicrobials and airway clearance strategies. Other strategies include stretching, body rotations, acupressure, and massage.

History of cardiac chest pain should warrant urgent referral to rule out myocarditis. Beta-blockers are recommended in patients with angina, cardiac arrhythmias, and acute coronary syndromes. Myocarditis usually resolves naturally with time, but it may require supportive and/or immune-modulating therapy. Anticoagulation may be used to reduce the risks of hypercoagulability. Self-management and support are important in managing fatigue. Some guidance may be taken from recommendations for managing CFS. These include cognitive behavioral therapy (CBT) and graded exercise therapy (GET). Fatigue can also be managed by a strategy called "pacing," whereby patients gradually increase their ability to manage tasks and activities with the aim of avoiding overexertion and worsening fatigue. Group therapy wire videoconferencing in patients with early psychosis shows promising results. A more holistic approach is more likely to be successful including professionals such as occupational therapists, speech and language therapists, and physiotherapists. Conditions such as brain fog can be managed by repeating exercises, understanding precipitating cause, stress relief, and coping strategies. Several medications have been recommended, for example, methylphenidate, donepezil, modafinil, memantine, and luteolin, but clinical trials are required.

There is a lot that is enigmatic, and it is unclear what impact the new variants of COVID-19 will have on the incidence and severity of long COVID. Further research is required to understand the pathogenesis and risk factors which predispose to development of long COVID, how long it persists for, and which treatment strategies are successful in which subgroup of patients.

REFERENCES

1. World Health Organization. (2021). Weekly operational update on COVID-19 - 5 July 2021 [online] Available from https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19—5-july-2021 [Last accessed March, 2022].
2. Garner P. BMJ Opinion. (2020). For 7 weeks I have been through a roller coaster of ill health, extreme emotions, and utter exhaustion. [online] Available from https://blogs.bmj.com/bmj/2020/05/05/paul-garner-people-who-have-amore-protracted-illness-need-help-to-understand-and-cope-with-the-constantly-shifting-bizarre-symptoms/
3. National Institute for Health and Care Excellence (NICE). (2020). COVID-19 rapid guideline: managing the long-term effects of COVID-19 NICE guideline. [online] Available from https://www.nice.org.uk/guidance/ng188 [Last accessed March, 2022].
4. Datta SD, Talwar A, Lee JT. A proposed framework and timeline of the spectrum of disease due to SARS-CoV-2

infection: Illness beyond acute infection and public health implications. JAMA. 2020;324:2251-2.
5. Lopez-Leon S, Wegman-Ostrosky T, Perelman P, Sepulveda R, Rebolledo PA, Cuapio A, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. Sci Rep. 2021;1116144.
6. Gemelli Against COVID-19 Post-Acute Care Study Group. Post-COVID-19 global health strategies: The need for an interdisciplinary approach. Aging Clin Exp Res. 2020;32: 161320.
7. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181:271-80.e8.
8. Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. PLoS One. 2020;15:e0240784.
9. Wostyn P. COVID-19 and chronic fatigue syndrome: Is the worst yet to come? Med Hypotheses. 2021;146:110469.
10. Zhao YM, Shang YM, Song WB, Li QQ, Xie H, Xu QF, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine. 2020;25:100463.
11. Ngai JC, Ko FW, Ng SS, To KW, Tong M, Hui DS. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. Respirology. 2010;15:543-50.
12. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffman J, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5:1265-73.
13. Maury A, Lyoubi A, Peiffer-Smadja N, de Broucker T, Meppiel E. Neurological manifestations associated with SARS-CoV-2 and other coronaviruses: A narrative review for clinicians. Rev Neurol (Paris). 2020;177(1–2):51-64.
14. World Health Organization. (2021). COVID-19 clinical management: living guidance. [online] Available from https://www.who.int/publications/i/item/WHO- 2019-nCoV-clinical-2021-1 [Last accessed March, 2022].
15. National Institute of Health. (2021). Coronavirus disease 2019 (COVID-19) treatment guidelines. [online] Available from https://www.covid19treatmentguidelines.nih.gov/.
16. USnews.com. (2021). CDC expected to release guidance on identifying, managing long COVID. [online] Available from: https://www.usnews.com/news/health-news/articles/2021-05-07/cdc-to-release-clinical-guidance-on-identifying-managing-long-covid

CHAPTER 134

Right Ventricle Failure in COVID-19

Sharmili Sinha, Ravi Jain, Raj Raval

INTRODUCTION

The global pandemic caused by SARS COVID-19 (severe acute respiratory syndrome coronavirus disease 2019) virus has inflicted significant morbidity and mortality across nations. It primarily affects the respiratory system though it is well known to involve extrapulmonary systems mainly cardiovascular, gastrointestinal, and nervous systems, as well. The cardiovascular system gets affected by direct and indirect mechanisms. Directly, it is known to involve the myocardium and can cause conduction blocks and thrombotic events. In the most severe form of respiratory involvement, it manifests as acute respiratory distress syndrome (ARDS), which is usually associated with various degrees of pulmonary arterial hypertension (PAH). This in-turn strains the right ventricle (RV). Right ventricular dysfunction is reported in up to 40% cases of COVID-19 infection. RV dysfunction associated with respiratory failure has a worse prognosis.

PHYSIOLOGY OF RIGHT HEART

The close interactions between the RV and pulmonary artery (PA) are known as RV–PA coupling.

Right Ventricle–Pulmonary Artery Coupling

Coupling of RV and PA is essential for optimal output and maintenance of RV and pulmonary vascular pressures **(Fig. 1)**.

Ventricular contractility is implied by end-systolic elastance (Ees). Effective arterial elastance (Ea) refers to net stiffness of the PA and thus indicates afterload. An Ees/Ea ratio of 1.0–2.0 is ideal and indicates healthy RV–RV unit. The PA hydraulic load has two main components, i.e., pulmonary vascular resistance (PVR) and pulmonary vascular capacitance or PA compliance (PAC). PAC is defined as the ratio of the stroke volume (SV) to PA pulse pressure. There is an inverse relation between PVR and PAC and their product is a constant.

It is interesting to note that RV has a lower systolic elastance and greater diastolic compliance. Therefore, it more often adapts to changes in preload and not afterload. In chronic pathologies of slow rise in PA pressure, RV–PA coupling is maintained by progressive RV hypertrophy. However, if there is any acute rise in RV afterload, it can only be adapted transiently to a limit and beyond that it gets dilated to cope with raised afterload. Hence, RV systolic function declines with simultaneous increase in RV filling pressure with raised wall stress and reduced cardiac output (CO). CO further decreases due to shifting of interventricular septum and reduction of left ventricular (LV) filling. This

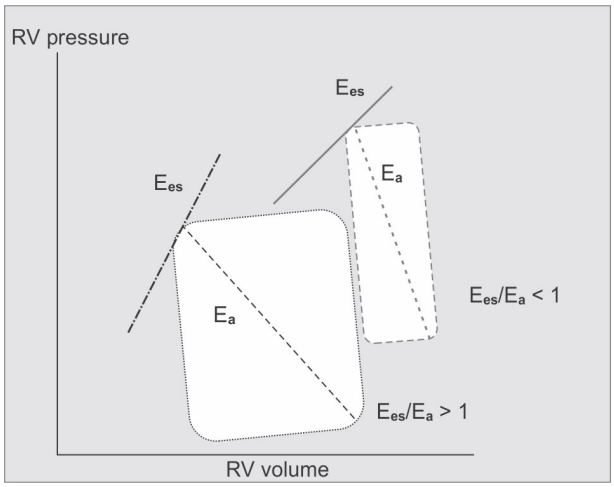


Fig. 1: RV–PA coupling. The pressure–volume curve of the RV allows characterization of the end-systolic PV relationship, whose slope corresponds to the RV systolic elastance (Ees), a load-independent measure of RV contractility. The line joining the RV end-systolic volume with its end-diastolic volume is termed as the pulmonary arterial elastance (Ea), which is a measure of the afterload as it is seen by the RV. The ratio between the Ees and Ea defines the RV–PA coupling, which should always be kept >1 for optimal RV efficiency (black lines). Increased Ea or/and reduced Ees precipitates RV uncoupling (Ees/Ea <1). The RV must dilate (Frank–Starling mechanism) to maintain its output, at the expense of a marked increase in wall stress, hence myocardial oxygen demand (gray lines). (PA: pulmonary artery; RV: right ventricle)
Source: Bonnemain J, Ltaief Z, Liaudet L. The right ventricle in COVID-19. J Clin Med. 2021;10(12):2535.[1]

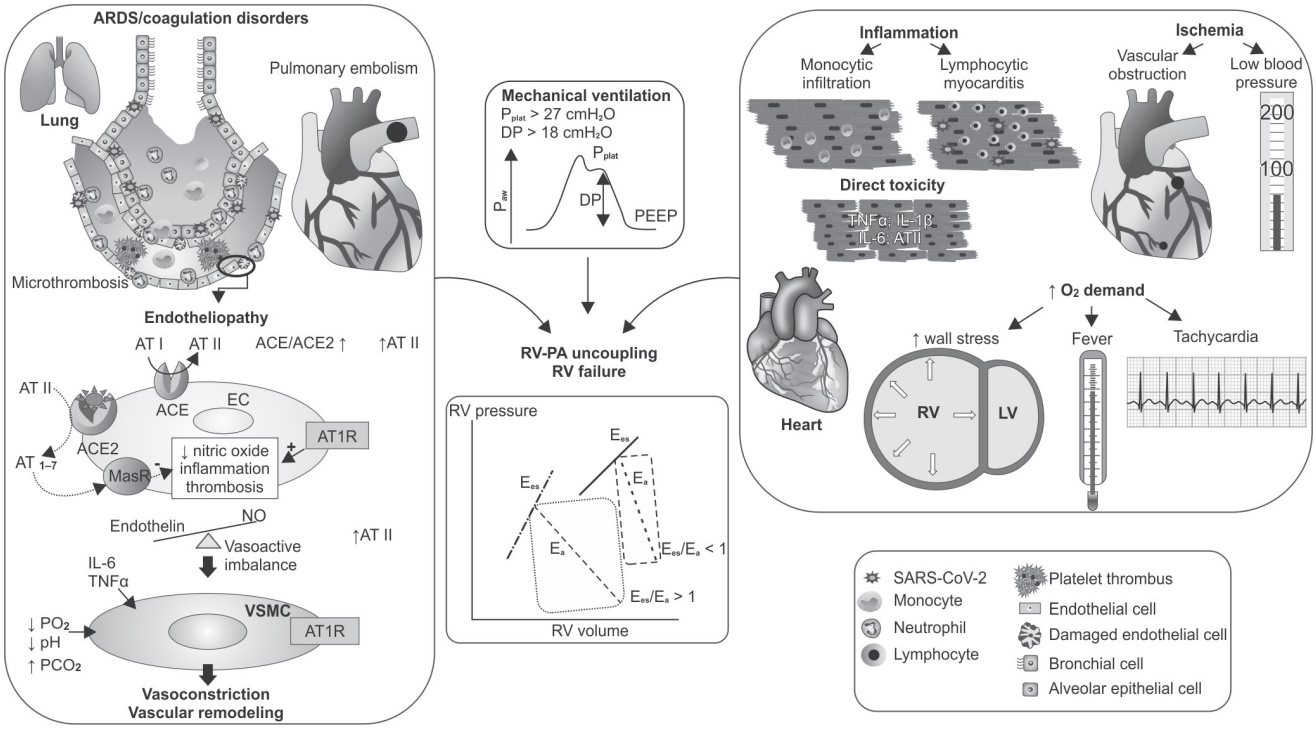


Fig. 2: Pathophysiology of right ventricle (RV) dysfunction in COVID-19. (AT1R: angiotensin II type 1 receptor; ARDS: acute respiratory distress syndrome; ACE2: angiotensin-converting enzyme 2; EC: endothelial cell; IL-6: interleukin-6; PA: pulmonary artery; TNFα: tumor necrosis factor α; VSMC: vascular smooth muscle cell)

Source: Bonnemain J, Ltaief Z, Liaudet L. The right ventricle in COVID-19. J Clin Med. 2021;10(12):2535.

becomes responsible for hypotension and therefore gives rise to RV dysfunction due to compromise in coronary perfusion pressure.

Pathophysiology of Right Ventricle Dysfunction in COVID-19 (Fig. 2)

- *Pulmonary hydraulic load*:
  - *Obstruction in pulmonary vasculature*: It happens due to micro- and macrovascular thrombotic complications due to immune-mediated coagulopathy, widely reported in ARDS associated with COVID-19.
  - *Disturbances in pulmonary vasomotor tone*:
    - Hypoxic pulmonary vasoconstriction
    - Hypercarbia
    - Imbalance in vasoactive substances
  - *Angiotensin II-mediated vasoconstriction*: Due to destruction of angiotensin-converting enzyme 2 (ACE2) receptors, there is an increased level and hence unopposed action of angiotensin II.
  - *Mechanical ventilation*: High plateau pressures cause excess distension of alveoli and thus compress the alveolar vessels and increase PVR.
- *Reduction of RV contractility*: Myocardial injury in COVID-19 mainly due to inflammation, ischemic injury and dysregulated reticular activating system (RAS), and cytokines.

LITERATURE EVIDENCE FOR RIGHT VENTRICLE DYSFUNCTION

A review by Dandel et al. has sighted RV dysfunction and failure as a significant finding in cases of COVID-19-related ARDS. Alterations in RV function are more commonly found than LV,[2] and there is association with higher levels of biomarkers of myocardial injury and inflammation along with thrombotic processes. A study has revealed that for every 1 mm decrease of tricuspid annular plane systolic excursion (TAPSE), there is a 20% rise in mortality in COVID-19 patients.[3] The higher the pulmonary arterial pressures, the worse is the disease severity.[4]

Right ventricle dysfunction reported in SARS-CoV-2 infection has a unique pattern as reported by Bleakley et al.[5] They described a distinct phenotype with right ventricular radial dysfunction in >70% cases among 90 mechanically ventilated COVID-19 ARDS patients. The unique characteristics are substantial reduction of RV velocity time integral (RV VTI) and of RV fractional area change (FAC). On the contrary, the estimated indices of longitudinal dysfunction as RV strain (RVS), RV free wall strain, and TAPSE were beyond normal ranges only in 24%, 35%, and 12% respectively. Thus, if the traditional longitudinal parameters are considered only, the RV dysfunction associated with COVID-19 illness will be underestimated.

CLINICAL FEATURES

Most of the patients with RV dysfunction/failure are affected with moderate-to-severe COVID-19 disease and have varying grades of respiratory failure requiring ventilation. Systemic backpressure changes might lead to congestion of liver, kidneys, and other internal organs, also peripheral edema.

Historically, raised jugular venous pressure (JVP) with prominent V wave, right-sided third heart sound, and holosystolic murmur of tricuspid regurgitation have been described as clinical signs of right-sided heart failure. But in the subset of patients with RV failure associated with COVID-19, the classic clinical features are difficult to elicit. RV failure is a grave prognostic indicator in COVID-19-related acute respiratory distress syndrome (CARDS) patients with severe hypoxia and elevated pulmonary and airway pressures. Multiorgan dysfunction very often sets in during the course of illness.

DIAGNOSIS

Once the patient develops sudden severe hypoxemia and/or hypotension with COVID-19, the evaluation protocol remains the same as if in non-COVID-19 patient. After initial thorough physical examination, electrocardiographic (ECG), arterial blood gas (ABG) analysis, biomarkers of inflammation [C-reactive protein (CRP), D-dimer] and cardiac injury [Troponin T/I, N-terminal pro-brain natriuretic peptide (NT-ProBNP)], chest roentgenogram and point-of-care echocardiographic (2D Echo) evaluation should be done to examine the worsening patient carefully.

Acute right heart failure (ARHF) can have sinus tachycardia, qR pattern in lead V1, a distinct SI, QIII, and inverted T wave in lead III points at acute RVS. Other atrial arrhythmias such as atrial flutter can also be seen.

Among laboratory parameters, transaminase levels along with specific cardiac injury biomarkers such as NT-ProBNP, Trop I, and Trop T levels could be high in right heart failure (RHF).[6,7] However, these remain indiscriminative for RV versus LV failure.

The echocardiography remains the mainstay for rapid diagnosis and categorization of heart failure.

The criteria delineated by the American Society of Echocardiography for RV dysfunction include RA FAC (right ventricle fractional area change) <35%, pulsed Doppler systolic myocardial velocity < 9.5 cm/s, RV ejection fraction of <45%, and TAPSE < 17 mm. RV dilatation (basal diameter > 41 mm and intermediate horizontal diameter > 35 mm) in early pressure overloaded situations.[8,9] Numerous literature has reported varying degrees of RV dysfunction.

Echocardiography use can be very subjective based on the experience of the operator. Cardiac magnetic resonance imaging (MRI) and multidetector computed tomography also have been described for accurate assessment of three-dimensional cardiac structural and functional evaluation but generally not applicable to COVID-19 patients in RV failure.

TREATMENT

Management of RV dysfunction/failure includes:

- Optimization of volume load
- Augmentation of RV contractility
- Reduction of pulmonary arterial pressure

Optimization of volume load: The normal RV filling pressure is around ~8–12 mm Hg. RV pressure monitoring is necessary to guide appropriate fluid replacement in case of hypotension caused by hypovolemia. Central venous pressure and mixed venous oxygen saturation can guide RV filling and oxygen supply. RV dilatation with restriction of LV filling implies excess preload.

Volume repletion: When volume repletion is indicated, this is generally performed by carefully monitored intravenous fluid challenges (e.g., aliquots of 200–300 mL of crystalloids over 5 minutes). Patients with ARHF with hypotension or other signs of low CO (hypoperfusion) are generally treated with volume repletion which is followed by vasopressor therapy if hypoperfusion persists.

Diuretics

Furosemide or loop diuretics can be given if evidence of volume overload exists. The RV sterling curve is flat, and optimization in RV function can be achieved with a large negative fluid balance.

Other Drugs

Inhaled nitric oxide can cause selective dilatation of pulmonary vessels, improve ventilation–perfusion (V/Q) mismatch, significantly decrease PVR, and enhance CO.

In patients with pulmonary embolism and ARDS, prostacyclin can help achieve similar goals to nitric oxide.

Intravenous epoprostenol may have a role in improving symptoms, hemodynamics, and RV systolic function.

Bosentan is a specific endothelin receptor antagonist, which decreases mean pulmonary arterial pressure and increases the cardiac index.

Arrhythmia Management

Complications in patients with RHF may include conduction system disease and arrhythmias. Management of these conditions and the risk of sudden death are based upon general treatment principles along with specific approaches.

Adjusting Ventilation

Protective lung ventilation strategy with low tidal volume and limiting plateau pressure < 32 cmH_2O is the best proposed way for invasive ventilation in ARDS patients. Avoiding hypoxia, hypercarbia, and acidosis beyond permissible limits helps to minimize pulmonary vasoconstriction. Thus, effects on right heart can also be avoided.

In CARDS, the distribution of pathology is heterogenous. Only part of the diseased lungs is recruitable which is known as "baby lungs." Ultrasonography can be used to adjust ventilator settings so as to maintain a balance between lungs recruitment and unintended hyperventilation.

Excess positive end-expiratory pressure (PEEP) can cause compression of extra-alveolar capillaries due to dilatation of alveoli. This gives rise to constriction of pulmonary vessels and thus raises PVR. As a consequence, there is increased RV afterload, which in turn affects LV filling. Optimum PEEP is thus important for hemodynamics as well.

Weaning from mechanical ventilation in CARDS has unique challenges. Higher incidences of ventilator–patient dyssynchrony due to prolonged ventilator dependence and critical illness polyneuromyopathy also amplify RV afterload and pulmonary hypertension.

Worsening of RV function is an important cause of weaning failure in COVID-19 patients on mechanical ventilation.

Devices

Devices-like intra-aortic balloon pump (IABP) have been used occasionally in patients with RV dysfunction with severe LV dysfunction with limited benefits. But these in general have not been tried in COVID-19 patients due to limitations. In patients with fluid overload which is resistant to drugs, continuous renal replacement therapy (CRRT) can be used to remove fluids.

SPECIFIC TREATMENT FOR RIGHT VENTRICLE FAILURE IN COVID-19

Anticoagulation

Standard thromboprophylaxis with low-molecular-weight heparin (LMWH) or standard heparin is advocated for all hospitalized patients with moderate-to-severe COVID-19 disease.[10] For patients with severe inflammation and very high D-dimers, there are varying recommendations and practices to start intermediate or therapeutic dose anticoagulation.[11,12]

Anti-inflammatory Therapies

In COVID-19, severe inflammatory response is the principal pathophysiology responsible for ARDS and RV dysfunction. In the RECOVERY trial, the 28-day mortality was found to be significantly reduced with use of dexamethasone up to 10 days (6 mg/day) in patients who required mechanical ventilation or oxygen supplementation.[13] There is additional evidence from REMAP-CAP[14] that with early use of interleukin-6 (IL-6) receptor monoclonal antibody tocilizumab (single IV dose 8 mg/kg), there is some survival benefit in critically ill patients on high oxygen therapy and mechanical ventilation.

Maintenance of Perfusion Pressure

Normally RV is perfused during both systole and diastole. Systolic perfusion is compromised during increased RV afterload and pulmonary vascular pressure. Diastolic perfusion gets affected due to increased end-diastolic pressures, which reduces the perfusion gradient. It is necessary to maintain adequate blood pressure to ensure perfusion of RV, which is strained and overloaded. Hence, optimum systemic pressures should be targeted using vasopressors as necessary. Noradrenaline is the vasopressor of choice followed by vasopressin. Though the vasopressors are known to raise the PVR, it is less with use of vasopressin than noradrenaline. Vasopressin also does not have chronotropic action.[15,16]

Afterload Reduction

This is best achieved by avoiding hypoxia and hypercarbia in case of respiratory failure by institution of mechanical ventilation. Protective lung ventilation strategy is best recommended with the aim to keep plateau pressure <32 cmH_2O. Early prone positioning in cases of refractory hypoxia has shown to be effective in better oxygenation and reduce mortality.

Inotropes

Increase RV contractility mainly reduces RV volume and pressure overload. Dobutamine, milrinone, and levosimendan are the major ones used for this purpose **(Table 1)**. Levosimendan sensitizes the calcium channels of myocardial cells and thus increases myocardial contractility. It has neither any effect on diastolic function nor on myocardial oxygen consumption. It is not arrhythmogenic as well. Morelli et al. showed that levosimendan could be an effective treatment for ARDS with acute right heart dilatation.[16] It was believed to dilate the pulmonary vasculature and enhance RV contractility.

Extracorporeal Membrane Oxygen Therapy

Venovenous extracorporeal membrane oxygen (ECMO) has been proven to be an effective therapy in the management of refractory hypoxia in severe ARDS.

In a study by Leberton et al. in 302 COVID-19-ARDS patients in Paris, the 90-day survival was 46%. It was observed that a prolonged gap between intubation and initiation of ECMO, elderly age, and renal dysfunction are independent indicators of increased 90-day mortality.[17,18]

CONCLUSION

Right ventricle dysfunction is a poor prognostic indicator among the spectrum of cardiopulmonary diseases associated with COVID-19. It is necessary to assess the RV function in patients with CARDS and its complications such as pulmonary thromboembolism and pulmonary arterial hypertension. The pathophysiology of RV involvement in SARS-CoV-2 is predominantly immunologic and inflammatory.

TABLE 1: Various inotropes used in right heart failure.

Inotrope agent	*Mechanism of action*	*RV contractility*	*Side effects*
Dobutamine	Beta-adrenergic agonist	Yes	Tachyarrhy-thmias
Milrinone	Phosphodiesterase inhibitor	Yes and vasodilator	Can cause augment hypotension
Levosimendan	Ca sensitizer and activator of K^+ ATP channels	Improves RA/RV coupling	May induce hypotension

(ATP: adenosine triphosphate; Ca: calcium; RA: right atrial; RV: right ventricle)

It is imperative to assess RV function early for COVID-19 patients with suspected cardiac involvement with raised cardiac biomarkers and worsening respiratory symptoms. Early recognition of RV dysfunction facilitates institution of optimum treatment. Echocardiography is an important tool for risk assessment and prognostication.

In future, therapeutic research should be focused on strategies to prevent and improve RV dysfunction in patients with SARS-CoV-2 infection. Formulating an appropriate strategy of the RV will be helpful to improve prognosis and reduce mortality among patients with severe cardiorespiratory illness due to COVID-19.

KEY POINTS

- There is high association (up to 40%) of RV dysfunction/failure in patients infected with SARS-CoV-2 virus with moderate-to-severe category with respiratory failure.
- Severe inflammatory reaction with altered immune response with dysregulated pulmonary circulation are the major pathophysiological features responsible for uncoupling of right atrium (RA)–RV. This results in RV failure in COVID-19.
- Specific ECHO findings of radial indices are unique to identify RV dysfunction featured in COVID-19 patients in contrast to the classical longitudinal indices measured in non-COVID-19 cases.
- Reduction of RV volume and pressure overload are the key steps in management in COVID-19 patients.
- In CARDS, protective lung ventilation with optimal PEEP is crucial to achieve target oxygen and ventilation goals.
- Steroids and anticoagulation are specific therapies for management of RV failure related to COVID-19 infection.
- Right ventricle failure associated with COVID-19 has an overall worse prognosis.

REFERENCES

1. Bonnemain J, Ltaief Z, Liaudet L. The right ventricle in COVID-19. J Clin Med. 2021;10(12):2535.
2. Dandel M. Heart-lung interactions in COVID-19: Prognostic impact and usefulness of bedside echocardiography for monitoring of the right ventricle involvement. Heart Fail Rev. 2021;1-15.
3. Hassani NS, Shojaee A, Khodaprast Z, Sepahvandi R, Shahrestanaki E, Rastad H. Echocardiographic features of cardiac injury related to COVID-19 and their prognostic value: A systematic review. J Intensive Care Med. 2021;36(4):500-8.
4. Martha JW, Pranata R, Wibowo A, Lim MA. Tricuspid annular plane systolic excursion (TAPSE) measured by echocardiography and mortality in COVID-19: a systematic review and meta-analysis. Int J Infect Dis. 2021;105:351-6.
5. Bleakley C, Singh S, Garfield B, Morosin M, Surkova E, Mandaha MS, et al. Right ventricular dysfunction in critically ill COVID-19 ARDS. Int J Cardiol. 2021;327:251-8.
6. Szekely Y, Lichter Y, Taieb P, Banai A, Hochstadt A, Merdler I, et al. Spectrum of cardiac manifestations in COVID-19: a systematic echocardiographic study. Circulation. 2020;142(4):342-53.
7. Argulian E, Sud K, Vogel B, Bohra C, Garg VP, Talebi S, et al. Right ventricular dilation in hospitalized patients with COVID-19 infection. JACC Cardiovasc Imaging. 2020;13(11):2459-61.
8. Konstam MA, Kiernan MS, Bernstein D, Bozkurt B, Jacob M, Kapur NK, et al.; American Heart Association Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Surgery and Anesthesia. Evaluation and management of right-sided heart failure: a scientific statement from the American Heart Association. Circulation. 2018;137(20):e578-e622.
9. Zochios V, Parhar K, Tunnicliffe W, Roscoe A, Gao F. The right ventricle in ARDS. Chest. 2017;152(1):181-93.
10. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020;18(5):1023-6.
11. Casini A, Alberio L, Angelillo-Scherrer A, Fontana P, Gerber B, Graf L, et al. Thromboprophylaxis and laboratory monitoring for in-hospital patients with COVID-19: a Swiss consensus statement by the Working Party Hemostasis. Swiss Med Wkly. 2020;150:w20247.
12. Thachil J. The versatile heparin in COVID-19. J Thromb Haemost. 2020;18:1020-2.
13. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med. 2021;384:693-704.
14. Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM; REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. N Engl J Med. 2021;384(16):1491-502.
15. Grignola JC, Domingo E. Acute right ventricular dysfunction in intensive care unit. Biomed Res Int. 2017;2017:8217105.
16. Morelli A, Teboul JL, Maggiore SM, Vieillard-Baron A, Rocco M, Conti G, et al. Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: a pilot study. Crit Care Med. 2006;34(9):2287-93.
17. Lebreton G, Schmidt M, Ponnaiah M, Folliguet T, Para M, Guihaire J, et al.; Paris ECMO-COVID-19 investigators. Extracorporeal membrane oxygenation network organisation and clinical outcomes during the COVID-19 pandemic in Greater Paris, France: a multicentre cohort study. Lancet Respir Med. 2021;9(8):851-62.
18. Shaefi S, Brenner SK, Gupta S, O'Gara BP, Krajewski ML, Charytan DM, et al.; STOP-COVID Investigators. Extracorporeal membrane oxygenation in patients with severe respiratory failure from COVID-19. Intensive Care Med. 2021;47(2):208-21.

CHAPTER 135

Dilemma of D-Dimer in COVID-19

Apurba Kumar Borah, Banambar Ray, Pragyan Routray

INTRODUCTION

The coagulation cascade continues to bewilder the clinicians with its interpretation and application. The D-dimer, an end product of this cascade, is conventionally utilized to diagnose or eliminate conditions such as thrombosis, to establish severity of sepsis, disseminated intravascular coagulation (DIC) and coagulation failure of snake bite. It is also raised nonspecifically in conditions such as heart failure, malignancy, pregnancy, and in postsurgical state.

Since the COVID-19 pandemic in December 2019, D-dimer has gained new significance in predicting severity of disease. Few studies in COVID-19 patients have correlated D-dimer with morbidity, mortality, cytokine storm, hospital stay, and thrombosis.[1-3] However, there are many conditions such as sepsis, DIC, and postsurgical state which can be present along with COVID-19 and can make D-dimer interpretation confusing. Even dosing of anticoagulants could be difficult to decide on the basis of D-dimer levels as there could be many caveats. Some of those issues are addressed in this text.

GENESIS OF D-DIMER

The human hemostatic system is maintained by a fine balance between procoagulant and anticoagulant factors. It is a delicate balance between platelet aggregation with fibrin clot formation and coagulation inhibitors with fibrinolysis. The coagulation cascade has two pathways which lead to fibrin formation **(Fig. 1)**.

These are two pathways—(1) intrinsic pathway (also known as contact activation pathway) and (2) extrinsic pathway (also known as the tissue factor pathway); both leading to the same fundamental reactions that produce fibrin.

Fibrinolysis is a process that prevents blood clots from growing. In fibrinolysis, a fibrin clot, the end product of coagulation, is broken down by plasmin which is a derived from plasminogen. Plasminogen has a strong affinity for fibrin, and is incorporated into the clot during the latter's formation. The tissue plasminogen activator (which is released from damaged endothelium) and urokinase are the agents that convert plasminogen to the active plasmin, thus allowing fibrinolysis to occur. This occurs because

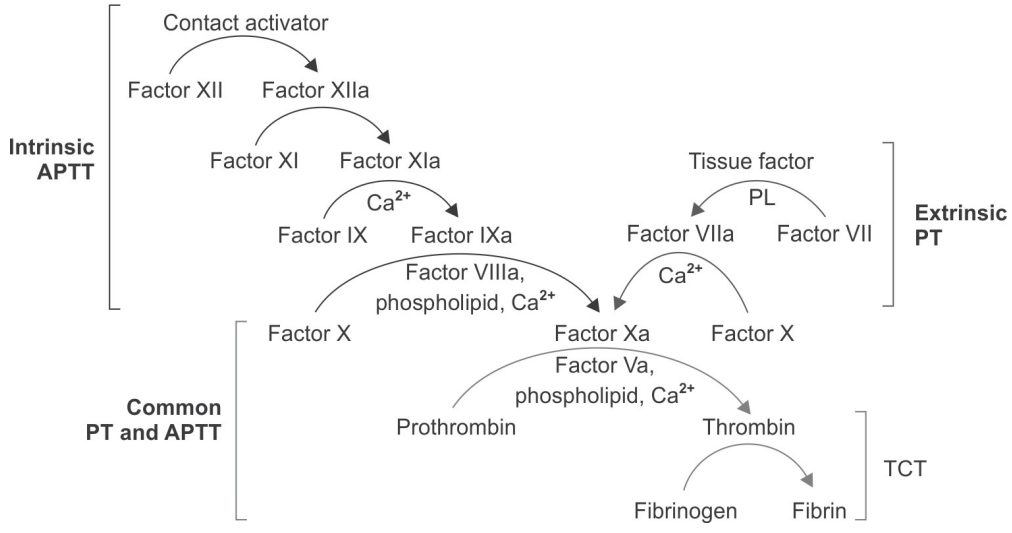


Fig. 1: Coagulation cascade.

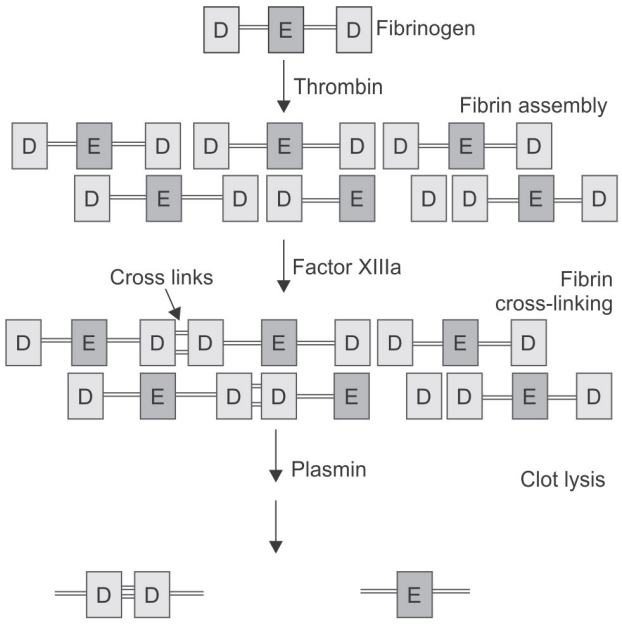


Fig. 2: Process of fibrin formation to clot lysis.

plasminogen became entrapped within the clot during the latter's formation; as it is slowly activated, it breaks down the fibrin mesh into soluble parts called fibrin degradation products (FDPs).

Plasmin cleaves (splits) fibrin at covalently cross-linked site of the molecule leading to formation of D-dimer. The structure of fibrinogen is trinodular with two D domain and one E domain. Thrombin and factor XIII cross links these D domains on adjacent location. When plasmin causes lysis at specific sites of fibrin, maintaining the cross linked D domains, it results in formation of D-dimer **(Fig. 2)**.

These fragments may be derived from soluble fibrin even before it has been incorporated into a fibrin gel, or alternatively may be derived from high-molecular-weight complexes released from an insoluble clot. Hence, D-dimer is a sensitive marker for fibrinolysis, depicting either fibrin degradation or blood clot formation.

In COVID-19, rise in D-dimer is secondary to endothelial dysfunction and microthrombi formation and may not always point toward a thromboembolic disorder or an overt DIC. It might be a benign rise which goes parallel with inflammatory mediators and settles on its own. This is fundamental to understanding of D-dimer dilemmas.

D-DIMER AND KINETICS OF THROMBOSIS IN COVID-19

Patients with COVID-19 usually present with few common laboratory abnormalities.[4] The most common deranged laboratory anomalies include prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) followed by increased fibrinogen, platelet count, D-dimer levels, and elevated C-reactive proteins. All these tests have got significant drawbacks in assessing clinical severity of COVID-19, if taken individually. So therefore, these tests need to be assessed carefully and in relation to other parameters.

Table 1[5] describes indications and limitations of these tests.

In COVID-19, D-dimer is raised in moderate and severe infections. Possible reasons for increased D-dimer values in COVID-19 patients are:

- The COVID-19 infection can cause the release of proinflammatory cytokines, such as interleukin-2 (IL-2), IL-7, granulocyte colony-stimulating factor (G-CSF), and tumor necrosis factor-alpha (TNF-α) in plasma causing a storm and T cells, macrophages, and natural killer cells rapidly proliferate and are activated accompanied by overproduction of immune or nonimmune defense cells, causing release of even more inflammatory cytokines. This phenomenon induces endothelial cell dysfunction causing damage to the microvascular system. Further there occurs activation of the coagulation system, pathological manifestations of systemic small vessel vasculitis. All these end up in extensive microthrombosis.[6]
- Different degrees of hypoxia and inflammation can lead to increased oxygen consumption. Increase oxygen demand causes abnormal hemodynamics, which triggers molecular and cellular pathways leading to thrombosis.[7]
- Severe infection or acute inflammation caused by sepsis (that often occurs in COVID-19 disease), can also affect blood coagulation, by increasing levels of plasminogen activator inhibitor 1 (PAI-1), which will eventually activate the coagulation cascade and inhibit fibrinolysis and eventually promoting thrombosis.[8]

Therefore, the rise of D-dimer in COVID-19 always may not be inferred as a new onset big thrombosis. It may just be a corollary of inflammatory process and microthrombi. Although D-dimer is one of the most frequently done tests for assessing severity of COVID-19 and morbidity, mortality, anticoagulation requirement, and post-COVID recovery associated with it, its interpretation and practical application remains debatable.

The following paragraphs help in demystifying D-dimer dilemma:

Dilemma 1: Laboratory Dilemmas in Interpreting D-dimer

D-dimers are detected by immunoassays using monoclonal antibodies specific for the cross-linked D-dimer domain in fibrinogen.

There are three commercially available assays.

1. The latex agglutination
2. Immunoturbidimetry, and
3. Enzyme-linked immunosorbent assay (ELISA)

TABLE 1: Limitations and utility of coagulation parameters in COVID-19.

Parameters	*Main limitations*	*Evaluation of the thrombotic risk*	*Screening of thromboembolic events*	*Disease severity*	*Diagnosis of DIC*	*Detection of heparin-induced thrombocytopenia*	*Monitoring of unfractionated heparin*
Platelet count	Multiple etiologies of thrombocytopenia not specific to COVID-19.	×	×	✓	✓	✓	×
aPTT (activated partial thrombo-plastin time)	Influence of pre-analytical step—differences of aPTT reagents in their sensitivity to unfractionated heparin, lupus anticoagulant and inflammatory syndrome	×	×	×	×	✓	✓
Prothrombin time (PT)	Influence of the pre-analytical step—fibrinogen level	×	×	×	✓	×	×
Fibrinogen	Lack of sensitivity for the diagnosis of DIC (infectious vs inflammatory) possibility of interference of direct thrombin inhibitors with some reagents	✓	×	✓	✓	×	×
D-dimer	Decreased analytical performances in high D-dimer values production dependent on the fibrinolytic activity	✓	✓	✓	✓	×	×

Efforts made to standardize D-dimer results have not been successful thus far, because the D-dimer analyte is not uniform across the different assays.

The ELISA needs skilled operator and it is more time-consuming (60–90 minutes) than other two tests. The immunoturbidimetric monoclonal antibody method has high enough sensitivity and negative predictive value. It also provides quantitative and operator-independent results in individual samples in a very short time of 10–15 minutes, which is particularly useful in emergency situations. In last decade, previous dilemma regarding the type of tests was sorted out with most of the labs adapting to immunoturbidimetric method.

There is a difference in the reported units [either D-dimer units (DDU)] or fibrin equivalent units (FEU), the assay cut-off values, and the absolute measuring units (mg/L, μg/mL, ng/mL), which need to be understood before the use of a clear cut-off point for decision making.

Dilemma 2: Coexisting Diseases

Several diseases/conditions such as inflammation, malignancy, pregnancy, trauma, liver disease (decreased clearance), postsurgical, and heart disease show increase D-dimer levels.[9]

Falsely raised D-dimer is also seen in high triglyceride levels, high RA factor levels, and in hemolysis. D-Dimer cut off levels also increase with age.

All common as well as uncommon causes of raised D-dimer are mentioned in **Table 2**.

All these conditions mentioned above can very well coexist with COVID-19 infection and will confound the interpretation required for decision making.

A good history taking and old reports might help us to rule out other coexisting conditions and decide on the interpretation of D-dimer values.

Dilemma 3: D-dimer in Predicting Severity of COVID-19

Several studies have hypothesized that a raised D-dimer on admission is an independent predictor of mortality. Xiaokang Ho et al. in their study involving 1,114 patients from Wuhan proved that D-dimer cutoff value of 2.205 can optimally predict death in COVID-19 patients.[10] Chen et al. studied 799 COVID-19 patients and found higher D-dimer levels in the deceased group than in survivors during hospitalization (4.6 $\mu g \cdot mL^{-1}$ versus 0.6 $\mu g \cdot mL^{-1}$); in addition, 35% of deceased patients versus 2% of survivors had D-dimer levels > 21 $\mu g \cdot mL^{-1}$.[11] Guan et al. evaluated 1,099 COVID-19

TABLE 2: Pathological causes for elevated D-dimer levels.

Conditions	*Diseases*
Thrombosis	• Venous thrombosis—deep vein thrombosis, pulmonary embolism, vein thrombosis in atypical sites like upper arms, mesenteric, cerebral) • Arterial thrombosis—acute coronary syndrome, stroke, peripheral artery disease, arterial thromboembolism, intestinal ischemia • Microvascular thrombosis—DIC • Intravascular thrombosis—catheters, pacemakers, artificial valves
Cardiovascular disease	Atrial fibrillation, LV aneurysm, congestive heart failure, heart thrombus, acute aortic dissection
Renal disease	Acute renal failure
Liver disease	Chronic liver diseases
Malignancy and its treatment	Pneumonia
Chronic inflammatory diseases	SLE
Pregnancy	Pre-eclampsia, HELLP syndrome
Others	Alzheimer's disease, sickle cell disease

(DIC: disseminated intravascular coagulation; LV: left ventricular; HELLP: hemolysis, elevated liver enzymes, low platelets)

patients and D-dimer levels were ≥0.5 μg·mL^{-1} in 65 out of 109 (59.6%) severe cases; versus 43.2% in nonsevere ones.[12] Another study by Han et al. compared 94 COVID-19 patients with 40 healthy controls during hospitalization; mean D-dimer levels were higher in infected group compared to the control group (10.36 ± 25.31 μg·mL^{-1} vs. 0.26 ± 0.18 μg·mL^{-1}).[13]

In a study involving 41 patients out of whom 13 were admitted in ICU care, Huang et al. found significantly higher D-dimer levels in ICU compared to non-ICU patients [2.4 μg·mL^{-1}, (range 0.6–14.4 μg·mL^{-1}) vs. 0.5 μg·mL^{-1} (range 0.3–0.8 μg·mL^{-1}; p = 0.0042)].[14] Zhou and colleagues showed that elevated D-dimer levels (>1 mg·L^{-1}) were strongly associated with in-hospital death (OR 18.4 95% CI 2.6–128.6, p = 0.003).[1]

So various studies have taken several cut-off values such as 1, 2.205, 2.4, 4.6, and 10.36 μg mL^{-1} to indicate severity of illness. We are yet to have a consensus on value of D-dimer which can be correlated with mortality. So therefore unless we have larger studies and guidelines, there will always be dilemma regarding cut-off value suggesting severity.

Dilemma 4: D-Dimer Guiding Anticoagulation

Early anticoagulation decreases mortality in severe COVID-19 patients. It has also been corroborated that the benefit of anticoagulation is more with patients with high D-dimer levels. In a study by Tang N et al., a comparison was done between heparin users and nonusers; 28 day-mortality was lower among nonusers in patients with sepsis-induced coagulopathy (SIC) score ≥ 4 or D-dimer > 3.0 μg/mL.[15] In this study, heparin was used as a standard prophylactic dose.

BOX 1: Protocol followed by Apostolos KT et al. study.

- On protocol—anticoagulation administration was based on D-dimer level, in the following sliding scale:
  - *D-dimer < 1,000 ng/mL*: Enoxaparin 40 mg daily
  - *D-dimer ≥ 1,000 ng/mL but < 3,000 ng/mL*: Enoxaparin 40 mg twice a day
  - *D-dimer ≥ 3,000 ng/mL*: Enoxaparin 1 mg/kg twice a day, or therapeutic anticoagulation with IV heparin (target aPTT 60–90), based on physician preference
- Escalation of anticoagulation occurred within 24 hours of a change in the D-dimer level.
  - Off protocol—physician's discretion

Yin et al. in their study took 449 severe COVID-19 and 104 severe non-COVID-19 pneumonia patients and found overall no difference in the 28-day mortality between COVID-19 heparin users and nonusers; but in a subset of patients where D-dimer was >3.0 μg·mL^{-1}, mortality was significantly lower in COVID-19 heparin users compared to COVID-19 heparin nonusers (32.8% versus 52.4%; p = 0.017), while no mortality difference was detected between non-COVID-19 heparin users and nonusers.[16]

There are several studies based on protocol-based increase in anticoagulation on the basis of D-dimer levels resulted in mortality benefit. One such study done by Apostolos KT et al. showed a protocol driven anticoagulation led to better results than "off protocol" driven physician's discretion.[17] Overall cumulative mortality (with a minimum of 4 months of follow up for all the patients) for ICU patients with severe COVID-19 was 44% (86/195). It also demonstrated that "off protocol" group patients had significantly lower mortality rates compared to the "on-protocol" group (27.47 vs. 58.6%, p < 0.001) **(Box 1)**.

Even many guidelines such as Massachusetts General Hospital Version (9.0 12.12.20) strongly discourage escalating from prophylactic dose of anticoagulation basing on D-dimer values. Most often the risk of bleeding outweighs the benefit in this scenario.

Thus there will always be a dilemma to escalate or deescalate anticoagulation basing on the D-dimer values. As per the evidence available thus far one would stick to prophylactic dose of anticoagulation.

Dilemma 5: D-dimer in Predicting Occurrence of Deep Vein Thrombosis) and Pulmonary Embolism

D-dimer has been of significant clinical value in predicting deep vein thrombosis (DVT) and pulmonary embolism (PE). Several studies have shown that the D-dimer test is highly

sensitive (>95%) in acute deep venous thrombosis or PE, usually with a cut-off value of 500 μg FEU/L.

In patients with low clinical probability (WELLS Score or Revised Geneva Score), higher value mandates aggressive investigation to rule out thromboembolic disorders. In a meta-analysis involving 31 studies by Stein et al., it was concluded that in patients with suspected venous thromboembolism (VTE), prevalence ranged from 20 to 78% (average 36%). In this study, patients with low clinical probability score had a false-positive D-dimer levels ranging from 40 to 60%. This study further demonstrated that D-dimer was 100% sensitive and had 100% negative predictive values in ruling out VTE in patients of low clinical probability.[18]

Patients with high clinical probability score should not undergo D-dimer testing because it is rare to get a level <500 μg and D-dimer > 500 μg FEU/L has a poor positive predictive value for VTE. It has a very low specificity in ruling out DVT/PE.A study by Bosson et al. suggested that a D-dimer level above 2000 μg FEU/L can predict the presence of PE, with an odds ratio of 6.9, irrespective of clinical probability.[19]

There was a positive correlation between the prevalence of PE and the D-dimer levels in a study done by Hochuli M et al. in patients of high clinical probability (7% at D-dimer levels of 500–1,000 μg FEU/L and 90% at 9,000 μg FEU/L).[20]

So therefore predicting PE in a high clinical probability case like COVID-19 patient is difficult. A decision to start, stop, or escalate treatment for thromboembolic disorder in a severe COVID-19 patient may not be correct. Postmortem studies have proven that severe COVID-19 patients are associated with immune thrombosis leading to microthrombotic complications. Most of the patients of severe COVID-19 infection have raised D-dimer due to this. This increase level of D-dimer may hinder assessment of patients with DVT or PE. One cannot conclusively decide regarding increasing the dose of anticoagulant based on raised D-dimer as it could be secondary to cytokine storm which is not so uncommon during second week of the disease. There will always be dilemma of diagnosing as well as ruling out DVT and PE in COVID-19 patients based on D-dimer values.

Till we have more answers, a bed side venous Doppler and CT pulmonary angiogram (CTPA) should always be done to aid diagnosis.

Dilemma 6: D-Dimer in Patients with COVID-19 and Secondary Sepsis with DIC

A large subset of patients of severe COVID-19 goes into secondary sepsis. If not treated appropriately, it may lead to severe sepsis with shock and subsequently DIC. These patients with sepsis and DIC will be having very high D-dimer levels. This high D-dimer value secondary to sepsis will confound clinician's decision as to whether there is new DVT or PE.

Clinical assessment along with markers of infection would help make a differentiation in such dilemmas.

Dilemma 7: D-Dimer in Bleeding Disorder

It is not very uncommon to see several occult bleeding complications in patients on anticoagulation. There are small case series and multiple case reports describing gastrointestinal bleeding, retroperitoneal bleeding, chest wall, and muscle bleed. In these situations, D-dimer remains high. So there will always be dilemma in interpreting D-dimer in presence of occult bleeding. One needs to quickly rule out these occult causes before starting anticoagulation.

CONCLUSION

The role of D-dimer in guiding treatment in COVID-19 could be misleading. Clinicians should be aware of the details of their local D-dimer test method and cut-offs values which of course are not determined as yet in COVID-19. There are several pitfalls in assessing and interpreting the results of D-dimer in clinical scenario of moderate to severe COVID-19. One should use clinical judgment and take into account other markers to avoid/minimize any dilemma in interpreting D-dimer. The present almost universal practice of linking dose and duration of anticoagulation and severity of disease with D-dimer levels in COVID-19 is risky and could be fraught with danger.

REFERENCES

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.
2. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thrombosis Haemost. 2020:18; 844-7.
3. Hadid T, Kafri Z, Al-Katib A. Coagulation and anticoagulation in COVID-19. Blood Reviews. 2021;47;100761.
4. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. Nat Med. 2020;26(7):1017-32.
5. Hardy M, Lecompte T, Douxfils J, Lessire S, Dogné JM, Chatelain B, et al. Management of the thrombotic risk associated with COVID-19: guidance for the hemostasis laboratory. Thrombo J. 2020;18:17
6. Tian, S, Hu W, Niu N, Liu H, Xu H, Xiao SY. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. J Thoracic Oncol. 2020;15:700-4.
7. Pugh CW, Ratcliffe PJ. New horizons in hypoxia signaling pathways. Exp Cell Res. 2017;356:116-21.
8. Iba T, Levy JH, Warkentin TE, Thachil J, van der Poll T, Levi M, et al. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. J Thromb Haemost. 2019;17:1989-94.

9. Cervellin G; Bonfanti L; Picanza A; Lippi G. Relation of D-dimer and troponin I in patients with new-onset atrial fibrillation. Am J Cardiol. 2014;114(7):1129-30.
10. Schutgens, Roger E. D-dimer in COVID-19: A guide with pitfalls. Hema Sphere. 2020;4(4):e422.
11. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:m1091.
12. Guan WJ, Ni ZY, Hu Y. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-20.
13. Han H, Yang L, Liu R, Liu F, Wu KL, Li J, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med. 2020;25:1116-20.
14. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.
15. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18:1094-9.
16. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. J Thromb Thrombolysis. 2020;51(4):1107-10.
17. Tassiopoulos AK, Mofakham S, Rubano JA, Labropoulos N, Bannazadeh M, Drakos P, et al. D-Dimer-Driven Anticoagulation Reduces Mortality in Intubated COVID-19 Patients: A Cohort Study With a Propensity-Matched Analysis. Front Med. 2021;8:631335.
18. Stein PD, Hull RD, Patel KC, Olson RE, Ghali WA, Brant R, et al. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: A systematic review. *Ann Intern Med*. 2004;140:589-602.
19. Bosson JL, Barro C, Satger B, Carpentier PH, Polack B, Pernod G, et al. Quantitative high D-dimer value is predictive of pulmonary embolism occurrence independently of clinical score in a well-defined low risk factor population. J Thromb Haemost. 2005;3(1):93-9.
20. Hochuli M, Duewell S, Frauchiger B. Quantitative d-dimer levels and the extent of venous thromboembolism in CT angiography and lower limb ultrasonography. VASA. 2007;36(4):267-74.

CHAPTER 136

Steroid in Acute and Post-COVID-19 Pulmonary Syndrome

Prachee Sathe, Tanima Baronia

INTRODUCTION

During the pandemic of severe acute respiratory syndrome coronavirus-2019 (SARS-CoV-19) virus which started in 2019 at Wuhan in China and spread like wild fire all over the world, out of coronavirus disease (COVID) affected 239,113,440 patients world over, 3% were hospitalized, of which 3% were in intensive care unit (ICU), and total 4,874,764 died till date, majority died due to lung failure and/or cytokine storm causing superinflammation.

Well known is a fact that the port of entry being upper respiratory tract the maximally affected organ system was respiratory. Pathophysiology of severe COVID-19, gradually revealed that dysregulated host immune response and cytokine storm producing severe inflammation are the key factors leading to widespread damage to pulmonary as well as systemic tissues. COVID-19 pneumonia is associated with both hyperinflammation and immunoparalysis in variable proportion. Pan endothelial vascular inflammation, disseminated coagulation, and acute respiratory distress syndrome (ARDS) are frequently triggered with or without shock. As much as the dysregulated immune response is responsible for acute pulmonary syndromes, it is also responsible for the extensive pulmonary damage and delayed pulmonary dysfunction. Various modalities and drug therapies came in and got discarded during the course of the pandemic, anti-inflammatory and immunomodulatory being of immense interest till date. Steroids remained an intriguing group of drugs because of its well-known anti-inflammatory and immune modulatory effects.

STEROIDS: MECHANISM OF ACTION (ANTI-INFLAMMATORY AND IMMUNOSUPPRESSIVE EFFECTS)

Corticosteroids can help as a life-saving therapy when acute anti-inflammatory and immunosuppressive effects are needed, working at many steps in the inflammatory pathways. The steroid molecule going across the cell membrane binds to glucocorticoid receptor, causing a conformational change in the receptor. Then this complex moves into the cell nucleus, binds to glucocorticoid response elements affecting the genes that either suppress or stimulate transcription in various pathways resulting in ribonucleic acid and protein synthesis. This affects the synthesis of proinflammatory mediators, from cells including macrophages, eosinophils, lymphocytes, mast cells, dendritic cells, and causes inhibition of phospholipase A2 to attenuate inflammatory response, suppressing mediator release. This response helps to attenuate the hyperimmune response.[1] The flip side of the coin is of course the immunodepression allowing side effects like secondary infections.

While understanding the behavior of a totally new virus causing devastating lung and systemic involvement, inflammatory processes and dysregulated immune response were revealed to be the pathophysiologic mechanisms, various molecules of synthetic steroids were tried in various doses at various stages of the disease with various amount of success or failure. All the steroid molecules are not the same. We will review the current evidence and guidelines.

Current Knowledge about Steroid Use in Critically Ill

Comparison of Various Steroids Available for the Clinical Use

Although synthetic steroids as a group, share a marked anti-inflammatory action and poor mineralocorticoid effects they have different bioequivalence and pharmacokinetics **(Table 1)**.

Multiple studies also have shown varied "stressed" situations to have relative deficiency of these stress hormones. Available evidence shows that hydrocortisone is indicated in septic shock at a daily dose of 200–400 mg, divided every 8 hours due to its short half-life to avoid critical illness-related corticosteroid insufficiency (CIRCI); here not for anti-inflammatory action.[2] Methylprednisolone with its prolonged half-life once a day dose, can be indicated in severe ARDS at a dose of 0.5–2 mg/kg/day, due to its

TABLE 1: Corticosteroid comparison chart.

	Equivalent glucocorticoid dose (mg)	Potency relative to hydrocortisone		Half-life	
		Anti-inflammatory	Mineral-corticoid	Plasma (minutes)	Duration of action (hours)
Short acting					
Hydrocortisone	20	1	1	90	8–12
Cortisone acetate	25	0.8	0.8	30	8–12
Intermediate acting					
Prednisone	5	4	0.8	60	12–36
Prednisolone	5	4	0.8	200	12–36
Triamcinolone	4	5	0	300	12–36
Methylprednisolone	4	5	0.5	180	12–36
Long acting					
Dexamethasone	0.75	30	0	200	36–54
Betamethasone	0.6	30	0	300	36–54
Mineralocorticoid					
Fludrocortisone	0	15	150	240	24–36
Aldosterone	0	0	400+	20	_

Note: Commonly prescribed replacement steroids equivalents
Prednisone (5 mg) = Cortisone (25 mg) = Dexamethasone (0.75 mg) = Hydrocortisone (20 mg)
Source: Adrenal Cortical Steroids in drug facts and comparison, 5th edition. St. Louis: Facts and Comparisons, Inc.; 1997. pp. 122-8.

good penetration into lung tissue. Dexamethasone is the most powerful synthetic steroid, with marked antiedema properties, a large randomized controlled trial (RCT) suggested its efficacy in moderate to severe ARDS patients.[2,3]

It is extremely important to note that these "life-saving" drugs can have short-term or long-term side effects/complications, hence they have to be used very wisely, with continuous monitoring. Steroid-induced suppression of hypothalamic–pituitary–adrenal (HPA) axis and adrenal insufficiency can cause a significant reduction in the natural killer cell function. Natural killer cells are needed for the recognition and elimination of virally infected cells. This can act as a boomerang.

Based on the current body of evidence, steroids were tried with a great hope at various stages of COVID and its severity. While many teams were confused, RECOVERY trial did come up with a definitive observation. In RECOVERY collaborative group trial,[4] which was a controlled, open-label trial in hospitalized COVID-19 patients, comparing a range of possible treatments, patients were randomly assigned to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days or to receive usual care alone. The primary outcome studied was 28-day mortality. Comparative mortality was (22.9%) out of 482 patients in the dexamethasone group and (25.7%) out of 1,110 patients in the usual care group which the group reports as a significant reduction ($p < 0.001$) in subgroup of patients who were on oxygen support or needing ventilator. It did not show any advantage in hospitalized patient not needing O_2 support. There was a better chance of weaning the patients off ventilator in dexamethasone group. If we read carefully, it would be noticed that still there was variability such that, in the dexamethasone group, 95% of the patients received at least one dose of a glucocorticoid. The median duration of treatment was 7 days (interquartile range, 3–10). In the usual care group, 8% of the patients received a glucocorticoid as part of their clinical care.[4]

Another interesting observation in the results of RECOVERY trial is that, in this trial of dexamethasone in hospitalized COVID acute lung injury (ALI) patients, the incidence of continuous renal replacement therapy (CRRT) was also less in the dexamethasone receiving group.[4]

Serious adverse events as steroid side effects also were noticed and described in RECOVERY trial.

Meta-analysis of Steroid Trials in COVID Pulmonary Syndromes

The largest meta-analysis[5] included forty-four studies, covering 20,197 patients. Obviously encountered was the heterogenicity of the studies. In twenty-two studies which included observational/RCT studies, with endpoint as mortality, tried to quantify the effect of corticosteroid. The overall pooled estimate (observational studies and RCTs) showed a significantly reduced mortality in the corticosteroid group (OR 0.72 (95% CI 0.57–0.87).

Point of concern was delayed viral clearance time, which ranged from 10 to 29 days in the corticosteroid group and from 8 to 24 days in the standard of care group.

Fourteen studies looked at the need for mechanical ventilation and its duration as an endpoint. These studies reported a positive effect of corticosteroids on both.

A trend toward more infections and antibiotic use was present, more so if used with other immunomodulators like tocilizumab.

The authors concluded based on the findings from both observational studies and RCTs, a beneficial effect of corticosteroids on short-term mortality and a reduction in need for mechanical ventilation, but with a rising trend of delayed viral clearance and an increase in secondary infections.

Alternative Routes: Inhaled Corticosteroids

Budesonide was considered as a molecule of interest because it was observed that patients with airway diseases who were already on inhaled steroids were doing better than those who were not on it. Budesonide is a synthetic, inhaled potent glucocorticosteroid with broad anti-inflammatory properties. It is regularly used in chronic bronchitis and asthma by such route. Certain inhaled corticosteroids have been shown to impair viral replication of SARS-CoV2 and reduce cell entry, creating the interest in potential of inhaled corticosteroids as therapeutic agents for COVID-19. However, observational studies of individuals who were chronic inhaled corticosteroid users have found that its use either had no effect on COVID-19 outcomes or increased risk of hospitalization.[6] Hence, there is insufficient evidence for or against the use of inhaled budesonide for the treatment of COVID-19.

Special Subgroups Needing Mention: Considerations in Pregnancy

It is well-known fact that a short course of betamethasone and dexamethasone which cross the placenta, is routinely used to decrease neonatal complications of prematurity in women with threatened preterm delivery. As steroids can help potentially to reduce mortality in a COVID positive pregnant women, with low-risk of fetal adverse effects for a short course of dexamethasone therapy, it is recommended to use dexamethasone in hospitalized pregnant patients with COVID-19 who are mechanically ventilated or who require supplemental oxygen.

Complications

While known complications include acute psychosis, glucose intolerance, gastrointestinal (GI) hemorrhage, and secondary infections, the delayed ones can be more dangerous such as avascular necrosis, diabetes mellitus, HPA axis suppression, etc.

In addition to known side effects and complications of systemic corticosteroids, there was a humongous rise in rhinocerebellar mucormycosis, 80% cases coming from India. In a study reporting 101 cases of mucormycosis in people with COVID-19, 82 cases were from India and 19 from the rest of the world. Mucormycosis was predominantly seen in males (78.9%), in patients having active COVID disease or post-COVID. Risk factors identified were pre-existing diabetes mellitus in 80% of cases and associated diabetic ketoacidosis (DKA) in 14.9%. Notably, corticosteroid intake for the treatment of COVID-19 was recorded in 76.3% of cases. Mucormycosis involving nose and sinuses (88.9%) was most common followed by rhino-orbital (56.7%) with mortality of 30.7% of the cases.[7]

A cumulative prednisone dose of >600 mg or a total methylprednisone dose of 2–7 g given during the month before predisposes immunocompromised people to mucormycosis. Nonetheless, there are a few case reports of mucormycosis resulting from even a short course (5–14 days) of steroid therapy, especially in diabetics.[7] COVID-19 disease and rampant use of corticosteroids in unregulated dose/duration raises a red flag for treating physicians.

Current World Health Organization and Centers for Disease Control and Prevention Guidelines and Recommendations

(*Reference* quoted verbatim guidelines for the benefit of readers)

Recommendation 1: We recommend systemic corticosteroids rather than no systemic corticosteroids for the treatment of patients with severe and critical COVID-19 (strong recommendation, based on moderate certainty evidence).[8]

Recommendation 2: We suggest not to use corticosteroids in the treatment of patients with nonsevere COVID-19 (conditional recommendation, based on low certainty evidence) **(Table 2)**.[8]

POST-COVID-19 SYNDROME

Post-COVID-19 syndrome is a condition seen in patients with history of SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that cannot be explained by an alternative diagnosis, lasting for at least 2 months. Symptoms commonly seen are easy fatiguability, cough, shortness of breath, chest pain, intermittent fever, cognitive dysfunction, anxiety disorders, depression, memory issues, neuralgias, muscle pain or spasms, postexertion malaise, and sleep disorders among others. Most of these symptoms have a significant impact on day-to-day functioning, but the most incapacitating are the respiratory symptoms, so much so that the term "pulmonary long COVID (LC)" was coined.[9]

TABLE 2: Management of COVID-19 patients based on disease severity.

Disease severity	*Treatment options*
Patient hospitalized but no supplemental oxygen needed	No role of steroids (AIII)
Requiring supplemental oxygen	• Remdesivir if minimal supplemental oxygen needed (BIIa) • Dexamethasone + remdesivir where supplemental oxygen requirement steadily increases (BIII) • Dexamethasone alone if remdesivir not available or contraindicated
Requiring HFNC or NIV	• Dexamethasone (AI) • Dexamethasone + remdesivir (BIII) • If rapidly increasing oxygen requirement and systemic inflammation • Consider baricitinib (BIIa) or IV tocilizumab (BIIa)
Requiring IMV or ECMO	• Dexamethasone (AI) • If within 24 hours of admission to ICU • Dexamethasone + IV tocilizumab (BIIa)

Rating of recommendation: A = strong, B = moderate, and C = optional
Rating of evidence: I = 1 or more randomized controlled trials (RCTs), IIa = Other RCTs or subgroup analyses of randomized trials, IIb = non-randomized trials or observational cohort studies, and III = expert opinion.
(COVID-19: coronavirus disease-2019; ECMO: extracorporeal membrane oxygenation; HFNC: high flow nasal cannula; IMV: intermittent mandatory ventilation; NIV: noninvasive ventilation)

Source: https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/hospitalized-adults--therapeutic-management/

Need and Timing for Pulmonary Follow-up

It is being strongly recommended that all symptomatic COVID-19 affected individuals including those with mild disease must undergo a pulmonary follow-up within 3 months after the infection. Follow up may include plethysmography, exercise testing with 6-minute walk test or its equivalent, blood gas analysis, pulmonary function tests (PFTs), diffusion capacity measurements (TLCO), and chest computed tomography (CT) scans depending upon the severity of persisting symptoms.[9] High-resolution CT (HRCT) findings may range from interstitial opacities, consolidations, pneumatoceles, persistent ground-glass opacities to traction bronchiectasis, and fibrotic changes **(Figs. 1 to 3)**. Reduced diffusion capacity may be the result of alveolar surface loss, interstitial fibrosis or vascular impairment. Though the 6-minute walk test is not validated in post-COVID 19-associated pulmonary impairment, it may help the diagnosis of exercise-related hypoxia and decreased exercise capacity.[9] These pulmonary follow ups have brought to light with increasing frequency the occurrence of lung fibrosis in those who suffered from moderate-to-severe COVID-19.[10,11] It has

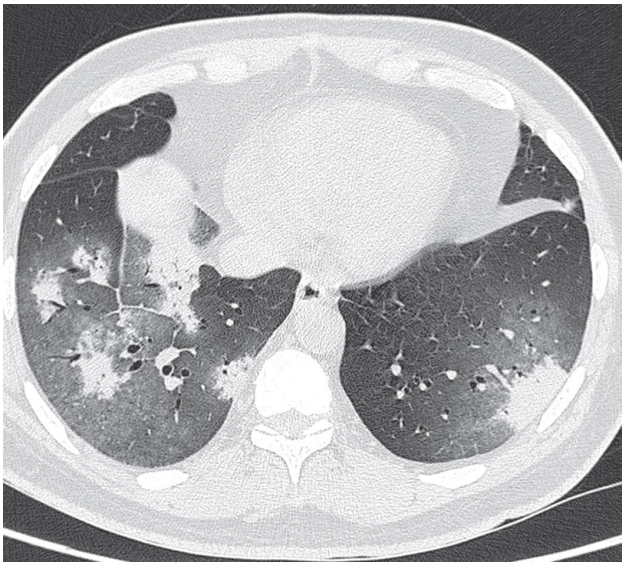


Fig. 1: CT scan of chest showing post-COVID fibrosis.
(COVID: coronavirus disease; CT: computed tomography)

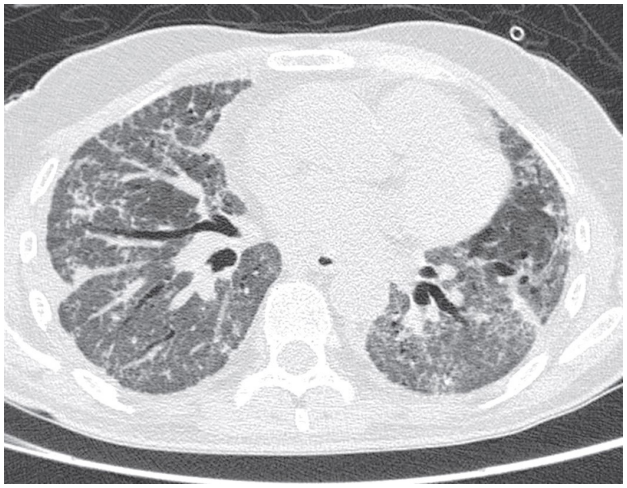


Fig. 2: CT scan of chest showing organizing pneumonia in post-COVID patient.
(COVID: coronavirus disease; CT: computed tomography)

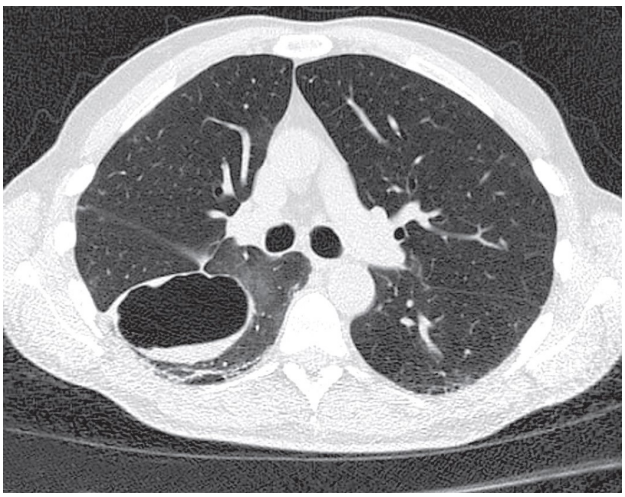


Fig. 3: CT scan of chest showing post-COVID pneumatocele.
(COVID: coronavirus disease; CT: computed tomography)

been described in literature by various terms such as organizing pneumonia, pulmonary fibrosis, fibrotic lung disease, or interstitial lung disease (ILD). The sustained inflammation with release of inflammatory mediators causes progressive destruction of lung parenchyma and persistence of fibroblasts, leading to deposition of collagen and extracellular matrix components, ultimately resulting in fibrous remodeling.[12]

The role of reactive oxygen species, barotrauma, and microthrombi has also been suggested.[10]

Use of Steroids and Antifibrotics: What is the Current Evidence?

Many pharmaceutical measures have been tried in the prevention and/or treatment of this condition, including steroids and antifibrotic agents such as, nintedanib, pirfenidone, treamid to name a few, with varying results and no conclusive evidence of benefit.[13] The role of dexamethasone in acute COVID-19 for up to 10 days is now considered based on the RECOVERY trial.[14] But its use beyond this short time frame for prevention of fibrosis remains a matter of uncertainty. Steroids are considered first-line treatment in conditions like organizing pneumonia, which is part of the spectrum of post-COVID lung sequelae. There is paucity of long-term studies and evidence in the treatment of this disabling and increasingly common condition. There is some evidence that steroids can slow down the progression of pulmonary fibrosis in rat idiopathic pulmonary fibrosis (IPF) models, and its mechanism may be related to the reduction of tumor necrosis factor-alpha (TNF-α), transforming growth factor beta-1 (TGF-β1) and PDGF levels, and the elevation of caveolin-1 levels.[13]

Inhaled corticosteroids may improve COVID-19-related bronchial syndromes as is seen with other viral exacerbations in asthma or COPD.[14] In post-COVID-19 patients with persistent cough, inhaled corticosteroids may suppress mucosal inflammation in airways with a clinically relevant reduction in bronchial hyperreactivity, though its role in other causes of cough remains controversial.[14] There have been reports of reduced lung remodeling in these patients with the use of methylprednisolone. Some have reported improved functional states after 1 month of treatment with steroids.[15] Oral prednisone 0.5 mg/kg with a dose reduction scheme over 6 weeks was shown to be associated with significant symptomatic, spirometric, and radiological improvement in patients with post-COVID-19 persistent inflammatory ILD seen 6 weeks after discharge.[16] An ongoing trial with comparison of two corticosteroid regimen for post-COVID-19 diffuse lung disease (COLDSTER), compares an oral prednisolone regimen with 40 mg/day given for 1 week, 30 mg/day for 1 week, 20 mg/day for 2 weeks, and 10 mg/day for 2 weeks (medium dose) with 10 mg/day for 6 weeks (low dose). The investigators hypothesize that in post-COVID diffuse lung disease, the medium dose of glucocorticoid will be more effective than the low dose in causing a radiological resolution, however the actual results are awaited on completion of the study in December 2021.[17] Despite numerous case reports and emerging studies optimal dose and duration of systemic steroids is as yet, uncertain. A variety of regimens have been tried with varying degrees of benefit. There is also the concern that the steroids may worsen the hypercoagulability[18] seen in these patients. Additionally, they may contribute further to increased incidence of intercurrent infections and psychological problems, fatigue,[19] etc. that is seen in long COVID. There is concern that these drugs may in fact increase the mortality.

Uncertain Points Needing Future Research

Long-term effect of systemic corticosteroids on mortality, development of long-term diabetes mellitus, and functional outcomes in COVID-19 survivors are still unknown. As novel immune modulator therapies may emerge, their interaction will have to be studied with systemic corticosteroids. Comparison will have to be ongoing for new investigational therapies for severe and critical COVID-19 in combination with systemic corticosteroids or systemic corticosteroids alone. Incidence of mucormycosis, especially after the second wave of COVID-19 in India, has highlighted the impact of systemic corticosteroids on immunity with the risk of a subsequent infection and the risk of death after 28 days.

Hence, further trials need to be planned to study steroid preparation, dosing, and optimal timing of drug initiation. Different study populations that were under-represented in the trials (e.g., children, immunocompromised patients, and patients with tuberculosis) need to be studied. Effect of steroids on viral replication needs to be studied as well. Vaccination on one side and the COVID-19 variants of concern on the other side will keep making the changes in clinical scenarios in coming times.

CONCLUSION

Corticosteroids are double-edged sword because "appropriate" immunity is needed to recover from a disease. The use of such potent immune modulators with potential life-threatening side effects has to be made judiciously, keeping in mind drug/dose/duration/de-escalation and taking into account newly emerging evidence. In the face of a tidal wave of patients with crippling pulmonary compromise, despite the various concerns and awaiting further robust evidence from randomized trials, steroids, systemic or inhaled, along with pulmonary rehabilitation, remain a viable and economical treatment option for post-COVID fibrosis.

REFERENCES

1. Shang L, Zhao J, HU Y, Du R, Cao B, et al. On the use of corticosteroids for 2019-nCoV pneumonia. Lancet. 2020;395(10225):683-4.
2. Berton AM, Prencipe N, Giordano R, Ghigo E, Grottoli S. Systemic steroids in patients with COVID19: pros and contras, an endocrinological point of view. J Endocrinol Invest. 2020;44(4):873-5.
3. Villar J, Ferrando C, Martinez D, Ambrós A, Muñoz T, Soler JA, et al. Dexamethsone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med. 2020;8(3):267-76.
4. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID19-preliminary report. N Engl J Med. 2021;384:693-704.
5. van Paassen J, Vos JS, Hoekstra EM, Neumann KMI, Boot PC, Arbous SM. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. Crit Care. 2020;24(1):696.
6. Yu LM, Bafadhel M, Dorward J, Hayward G, Saville BR, Gbinigie O, et al. Inhaled Budesonide for COVID19 in people at high risk of complicaions in the community in UK (PRINCIPLE): a randomised , controlled, open-label, adaptive platform trial. Lancet. 2021;398(10303):843-55.
7. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes Metab Syndr. 2021;15(4):102146.
8. WHO. (2020). Corticosteroids for COVID-19. [online] Available from WHO/2019-nCoV/Corticosteroids/2020 [Last accessed March, 2022].
9. Funke-Chambour M, Bridevaux PO, Clarenbach CF, Soccal PM, Nicod LP, von Garnier C. Swiss Recommendations for the follow-up and Treatment of Pulmonary Long COVID. Respiration. 2021;100(8):826-41.
10. Scelfo C, Fontana M, Casalini E, Menzella F, Piro R, Zerbini A, et al. A Dangerous consequence of the recent pandemic: early lung fibrosis following COVID-19 pneumonia. Ther Clin Risk Manag. 2020;16:1039-46.
11. Tale S, Ghosh S, Meitei SP, Kolli M, Garbhapu AK, Pudi S. Post-COVID-19 pneumonia pulmonary fibrosis. QJM. 2020;113(11):837-8.
12. Sime PJ, O'Reilly KM. Fibrosis of the lung and other tissues: new concepts in pathogenesis and treatment. Clin Immunol. 2001;99(3):308-19.
13. Bazdyrev E, Rusina P, Panova M, Novikov F, Grishagin I, Nebolsin V. Lung Fibrosis after COVID-19: Treatment Prospects. Pharmaceuticals. 2021;14(8):807.
14. Lipworth B, Chan R, Kuo CR. Use of inhaled corticosteroids in asthma and coronavirus disease 2019: Keep calm and carry on. Ann Allergy Asthma Immunol. 2020;125(5):503-4.
15. Cano EJ, Fonseca Fuentes X, Corsini Campioli C, O'Horo JC, Abu Saleh O, Odeyemi Y, et al. Impact of corticosteroids in COVID-19 outcomes: systematic review and meta-analysis. Chest 2021;159(3):1019-40.
16. Myall KJ, Mukherjee B, Castanheira AM, Lam JL, Benedetti G, Mak SM, et al. Persistent post COVID19 Interstitial lung disease.An observational study of corticosteroid treatment. Ann Am Thorac Soc. 2021;18(5):799-806.
17. NIH. Comparision of Two Corticosteroid Regimens for Post COVID-19 Diffuse Lung Disease (COLDSTER). [online] Available from ClinicalTrials.gov Identifier: NCT04657484 [Last accessed March, 2022].
18. Brotman DJ, Girod JP, Posch A, Jani JT, Patel JV, Gupta M, et al. Effects of short-term glucocorticoids on hemostatic factors in healthy volunteers. Thromb Res. 2006;118(2):247-52.
19. Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. Mayo Clin Proc. 2006;81(10):1361-7.

CHAPTER 137

Fluid Management in COVID-19: Principles and Practice

Roop Kishen, Saurabh Taneja

Primum non nocere (First, do no harm)

INTRODUCTION

Fluids are drugs and like drugs, they have their beneficial and adverse effects. Fluid administration is fundamental to the clinical care of the hospitalized patients, especially critically ill, making fluids the most common drugs prescribed in these patients. Although about 80% of patients infected with severe acute respiratory syndrome coronavirus 2019 disease (SARS COVID-19, henceforth referred to as COVID-19) are asymptomatic or exhibit only mild symptoms, about 20% require hospitalization, some becoming seriously ill.[1] Most centers report that about 25% of hospitalized patient require intensive care unit (ICU) admission.[1] Besides lungs, COVID-19 infections involve many other systems such as cardiovascular, renal, and coagulation systems. Although the pandemic has been present for just 2 years, much has been learned about the pathophysiology of the disease; however, much more still needs to be learned. Accepted basic principles of ICU care are advocated for clinical management of critically ill patients with COVID-19 infection. Specifically, there is lack of substantial data on optimal fluid management in these patients, making this aspect of their care difficult. However, principles of resuscitation and fluid therapy in non-COVID-19 infected have been applied to these patients; but some differences exist, partly because of the pandemic proportion of the infection as well as some therapeutic maneuvers that might be required (e.g., lung recruitment maneuvers and prone position ventilation). This chapter addresses the principles of fluid management in the critically ill adult COVID-19 patients but not in the pediatric patients.

WHY ARE FLUIDS NEEDED?

Water is the essence of life and about 60% of our bodies (80% in infants and 60% in adults) is composed of water. Water is present in all cells of the body and is the medium in which all the reactions of the living cells, essential for life, take place. In health, we fulfil the need for water and electrolytes by voluntary intake of fluids and food. An average adult, under nonextreme weather conditions, ingests ≈2,200 mL of fluids a day (as water, beverages, and food), whereas a small amount, ≈300 mL, is generated by aerobic metabolism, a total normal intake of 2,500 mL/day.[2] An equal amount of fluid is lost from the body in a day (≈1,500 mL as urine; ≈900 mL in exhaled air and sweat, and ≈100 mL in feces).[2] Body homeostasis is maintained by precise regulation mechanisms which keep the quantity of fluids and electrolytes constant. In disease, intake of fluids may be compromised due to the very nature of illness (e.g., loss of appetite and altered level of consciousness). There may also be excessive losses due to vomiting, diarrhea, and excessive sweating in febrile illness.

Fluids are needed for cardiovascular resuscitation in trauma, sepsis, and septic (distributive) shock. Once the resuscitation phase is over, fluids are required for maintenance of vascular volume where oral intake is not possible or compromised, for drug carriage and as enteral or parenteral nutrition. It is important to take into account all these fluids or accumulation can easily occur.

FLUID REQUIREMENT IN COVID-19 PATIENTS

Patients infected with COVID-19 present with a variety of clinical syndromes. Majority of the infected people (≈80%) are either asymptomatic or exhibit mild symptoms such as fever, dry cough, fatigue, and myalgia[1,3]; these patients are cared for at home with self-isolation and supportive care. About 14–15% of the total infected population develop severe symptoms and require hospitalization.[3] A small proportion of patients (≈5%) become critically ill and require ICU admission and care, depending on local medical services and available infrastructure[3,4]—a substantial burden on critical care services, given the sheer volume of the pandemic.[3] Severe form of disease usually presents with acute respiratory failure with respiratory rates of ≥30 breaths/minute, oxygen saturation ≤93%, and lung infiltrates of >50%.[1,3,4] Many of the COVID-19 patients may develop septic shock requiring fluids for hemodynamic resuscitation. Some patients may present with gastrointestinal symptoms (vomiting and diarrhea), causing further fluid loss. Some may present late to the hospital and in hot and humid weather, the fluid loss may be

enhanced. As exhaled air contains sizeable quantities of water vapor, tachypneic respiratory failure will exacerbate fluid loss further, sometimes amounting to 2–4 L/day. Moreover, these patients usually do not receive much fluid in prehospital setting during retrieval and transport to hospital.

COVID-19 AND FLUIDS MANAGEMENT: WHAT SHOULD WE BE SPECIFICALLY AWARE OF?

Fluid requirements in COVID-19 patients are dynamic, complex, and can be difficult to optimize. There are no "COVID-19 specific" guidelines for fluid management simply because data from randomized controlled trials are lacking. Published "guidelines" for COVID-19 patients from learned professional organizations are extrapolated from those for managing sepsis and septic shock in non-COVID-19 patients; all these guidelines draw upon Surviving Sepsis Campaign Guidelines – Updated for COVID-19 (SSCG-Cov-19).[5]

Majority of the hospitalized COVID-19 patients present with respiratory failure due to pulmonary infiltrates causing lung inflammation, often with additional secondary bacterial pneumonia. This complex clinical syndrome can lead to acute respiratory distress syndrome (ARDS) in a significant subset of patients.[3] Many patients may also suffer from sepsis and septic shock.[3,4] Moreover, angiotensin-converting enzyme II (ACE-II), which is the primary receptor of COVID-19 virus in the host cells and is widely distributed in the body, allows this virus to affect a variety of cells and cause multiple organ dysfunction syndrome besides pulmonary dysfunction, with evidence of cardiac, hepatic, and renal dysfunction, altered consciousness, and clotting disturbances.[6] Fever, possible starvation in prehospital phase, tachypnea (causing increased water loss from lungs), vomiting, diarrhea, and hot and humid weather in many parts of the world can cause significant fluid losses, serious hypovolemia, and hypoperfusion; which, if not addressed promptly and effectively, can cause nonpulmonary organ damage [viz., acute kidney injury (AKI)], which considerably increases mortality and morbidity.

Conversely, patients may have been transferred to a secondary or tertiary hospital from a primary healthcare facility, where they may have received fluids as part of their clinical management. This may not be apparent initially and must be carefully enquired into, as excess fluid has adverse consequences for the patient.[7] Development of ARDS complicates fluid management in these severely ill patients, who may still be hypovolemic. Although distributive shock is the most common form of shock in these patients, myocardial injury (≈23%) as well as cardiac morbidity (≈40%) in the critically ill have also been reported.[8] Autopsy examinations in these patients have shown cardiomegaly and left ventricular dilatation which may have been part of the clinical syndrome or caused by excessive fluid administration.[8] Thus, most of these critically ill patients will require fluid infusion as part of their initial resuscitation and ongoing care, some may have had adequate or excess fluid and this must be looked for, documented, and taken into account when planning fluid management. Besides, in a sizeable majority, because of ARDS and/or concomitant myocardial problems, caution is advised to avoid fluid overload.[8] Thus, the clinicians need to be aware that fluid requirements in patients with this novel disease can change several times in the course of disease. Careful consideration needs to be given to this dynamic fluid requirement in order to avoid untoward clinical consequences.[9]

ASSESSMENT OF FLUID REQUIREMENT

As the fluid requirements change overtime and both too little or too much fluid is undesirable in any, especially critically ill COVID-19 patients, judicious fluid infusions, where fluids are cautiously administered after assessment of preload responsiveness is the way forward.[10] This assessment is dependent upon available resources, medical infrastructure, cost, and experience of the medical staff.

Fluid responsiveness in a patient can be assessed by static and dynamic parameters. Static markers such as central venous pressure (CVP) are still commonly used as a measure of fluid responsiveness,[11] despite poor relationship between CVP and blood volume or its predictability of hemodynamic response to fluid infusion.[12] Clinical parameters such as capillary refill time (CRT), skin temperature, measured hourly urine output as well as the laboratory parameters such as base deficit and serum lactate are used to guide fluid resuscitation. Although a recent study did not find any difference in mortality between CRT targeted resuscitation strategy versus reduction in serum lactate amongst septic shock patients, the former group had less incidence of organ failures.[13] It has been suggested that dynamic measures such as pulse pressure variation (PPV) and stroke volume variation (SVV) are better as against static measures in assessing volume requirements. But these too are considered unreliable in many common conditions in critically ill patients, namely spontaneously breathing patients, ARDS patients with low tidal volume ventilation, and patients having cardiac arrhythmias or intra-abdominal hypertension.[14]

A method to assess fluid responsiveness without any external fluid infusion is passive leg raising (PLR) test. This equates to giving a reversible fluid challenge (FC) of about 300 mL fluid. PLR has the advantage that it can be repeated without causing excessive fluid accumulation. The effect of this and/or FC test on preload can be assessed by various noninvasive and invasive techniques. Echocardiography can be used to detect changes in cardiac output within 1–2 minutes of PLR.[15] In a single center study, Trendelenburg maneuver has been found useful to assess fluid responsiveness in mechanically ventilated ARDS patients in prone position.[16] In patients on controlled mechanical

ventilation, intrathoracic pressure swings lead to changes in inferior vena cava (IVC) diameter. This variation in IVC diameter (maximum–minimum/average) can be used to assess responsiveness to fluids.[17]

The methods of assessing fluid responsiveness are continuously evolving with improving area under the receiver operator characteristic curve as we move from static pressure and volume parameters [receiver operating characteristic (ROC) ~0.5–0.6] to dynamic techniques based on heart–lung interactions during mechanical ventilation (ROC ~0.7–0.8) to techniques based on real or virtual fluid challenge (ROC ~0.9) like PLR.[18]

WHAT GUIDELINES ARE AVAILABLE TO US?

Surviving Sepsis Campaign provided their guidelines (SSCG-Cov-19) in 2020.[5] Other professional bodies followed and also produced guidelines mainly based on SSCG-Cov-19.[5] Guidelines published by National Institute of Health (NIH)[19] and World Health Organization (WHO)[20] endorsed SSCG-Cov-19 recommendations. Anaesthesia and Intensive Care Medicine in the UK also published guidelines, which were recently updated.[21] Besides these guidelines, some "thoughts" and recommendations were also made by the International Fluid Academy (IFA).[10] All these guidelines are based on sound intensive care principles and their recommendations are for conservative fluid management in these patients. National Institute of Care and Excellence (NICE) in the UK published guidelines on management of AKI in COVID-19 patients recommending conservative fluid management as well.[22]

SSCG-Cov-19[5] and NIH guidelines[19] recommend assessing fluid responsiveness with the aid of dynamic parameters and using conservative fluid administration strategy. WHO guidelines[20] also recommend conservative fluid management in patents without evidence of hypoperfusion. For resuscitation in septic shock, they advocate a fluid bolus of 250–500 mL over 15–30 minutes (much like SSCG-Cov-19) and suggest using dynamic parameters to assess fluid responsiveness. UK's Joint Anaesthesia and Intensive Care Medicine guidelines[21] also advocate conservative fluid management in ARDS patients but also caution about "running patients too dry" in order to avoid AKI. IFA's recommendations[10] for fluid management in COVID-19 patients are similar to others; however, IFA suggests smaller quantities of fluids (4 mL/kg) as initial bolus and de-escalating fluids sooner than later.[10] They also advocate using 20% albumin to bring up the serum albumin level and strongly advocate "Fluid Stewardship" in our ICUs. NICE guidelines follow the same pattern and advocate conservative fluid management in COVID-19 patients.[22] Thus, clinicians should always strive for conservative fluid management *but maintaining euvolemia; however, this is easier said than done!*

WHAT KIND OF FLUIDS ARE APPROPRIATE IN THESE PATIENTS?

All guidelines agree on using crystalloids as resuscitation as well as maintenance fluids in these patients. Balanced salt solutions are recommended against 0.9% saline. Colloids are not recommended at all and there is strict caution about using starches in these patients. Rather than continue with fluid infusion, all guidelines recommend early use of vasoactive drugs to maintain mean arterial pressure ≥65 mm Hg to maintain organ perfusion. Albumin as a resuscitation fluid is not recommended, at least in initial phases of resuscitation. It may have a place in later stages if large fluid infusions are required.

HOW AND WHEN TO STOP FLUID RESUSCITATION? A NOTE ON DE-ESCALATE?

Fluid resuscitation can be divided into four stages, namely, rescue, optimization, stabilization, and de-escalation.[23] Rescue phase or the initial phase comprises of active fluid resuscitation of a patient in shock. This is followed by optimization phase where fluids are given in titrated manner where the patient is in a stage of compensated shock. Stabilization phase follows this where fluids are given for maintenance and there is no imminent threat or presence of shock. De-escalation phase is the last stage of resuscitation, the aim at this stage is to remove any accumulated fluids, this phase is achieved over days to weeks. Most patients with good renal function undergo spontaneous diuresis in this recovery phase. However, some may require a diuretic or ultrafiltration to remove excess fluids.[24]

PRACTICE POINTS

- Ideal fluid strategy in COVID-19 patients is not known. Guidelines and recommendations that are currently available, are extrapolated from non-COVID-19 patients and are based on poor quality of evidence.
- Fluids are drugs and must be prescribed with all due caution and care used for drug prescribing. Like drugs, fluids have beneficial as well as harmful effects depending both on their quantity as well as the quality (contents).
- Know when to prescribe fluids. Fluid requirements are never static but change overtime, sometimes from hour to hour. Individual requirements also vary depending on patients' clinical presentation, nature, and severity of presenting condition, concomitant illnesses, etc.
- Assess fluid requirements and fluid responsiveness. It is not always easy to determine fluid requirements in an individual patient from routine clinical examination. Parameters such as CRT, skin temperature, and PLR tests are noninvasive and cheap. Invasive as well as ultrasound-guided (USG) parameters are gaining popularity and acceptability, are cost-effective, and easy to carry out even in low- to middle-income countries.

- All dynamic fluid responsive tests have their limitations; they are complementary to simultaneous clinical assessment and should help in deciding how much, when, and when not to give fluids to a patient.
- Decide how much fluid to give and for how long. Too little or too much fluid is harmful. Thus, there must be at least a daily calculation of fluid intake/output. Weighing patients is a very good way of keeping track of this "fluid creep" but not always easy in the critically ill.
- Know when to stop fluid resuscitation, give fluids for maintenance only, and/or de-escalate fluids.
- There is an urgent need for "fluid stewardship" much like the antibiotic stewardship.
- Fluid management must be individualized as "*one size does not fit all!*"
- Clinicians must always treat the patient and NOT the number.
- And finally, always remember—*Primum non nocere*.

CONCLUSION

Fluid management in critically ill patients is challenging. A balance has to be maintained between aggressive resuscitation strategy and keeping patients "too dry." Fluid management in the critically ill is aided by bedside clinical parameters, point-of-care laboratory parameters, and invasive and noninvasive techniques. This fluid stewardship is made more difficult in COVID-19 patients presenting with sepsis, ARDS, and respiratory failure. Due to lack of data on fluid management strategies in COVID-19 patients, available guidelines and strategies need to be followed along with meticulous monitoring.

REFERENCES

1. Guan W-J, Ni Z-Y, Hu Y, Liang WH, Ou CQ, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Eng J Med. 2020;382:1708-20.
2. Lobo DN, Lewington AJP, Alliosn SP. 2013. Basic concepts of fluid and electrolyte therapy. [online] Available from: https://www.researchgate.net/publication/249625074_Basic_Concepts_of_Fluid_and_Electrolyte_Balance. [Last accessed March 2022].
3. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Centre for Disease Control and Prevention. JAMA. 2020;323(13):1239-42.
4. Hajjar LA, da Silva Costa IBS, Rizk SI, Biselli B, Gomes BR, Bittar CS, et al. Intensive care management of patients with COVID-19: a practical approach. Ann Intensive Care. 2021;11(1):36.
5. Alhazzani W, Møller HM, Arabis YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med. 2020;46(5):854-87.
6. Kazory A, Ronco C, McCullough PA. SARS-Cov-2 (COVID-19) and intravascular volume management strategies in the critically ill. Proc Baylor Univ Med Cent. 2020;33(3):370-75.
7. Jaffee W, Hodgins S, McGee WT. Tissue oedema, fluid balance, and patient outcomes in severe sepsis: an organ systems review. J Intensive Care Med. 2018;33(9):502-9.
8. Koratal A, Ronco C, Kazory A. Need for objective assessment of volume status in critically ill with COVID-19: The Tri-POCUS approach. Cardiorenal Med. 2020;10:209-16.
9. Hasanni A, Mostafa M. Evaluation of fluid responsiveness during COVID-19 pandemic: What are the remaining choices? J Anaesth. 2020;34(5):758-64.
10. Malbrain MLNG, Ho S, Wong A. Thoughts on COVID-19 from the International Fluid Academy. ICU Management Pract. 2020;20(1):80-5.
11. Cecconi M, Hofer C, Teboul JL, Pettila V, Wilkman E, Molnar Z, et al. Fluid challenges in intensive care: the FENICE study: A global inception cohort study. Intensive Care Med. 2015;41(9):1529-37.
12. Marik PE, Cavallazzi R. Does central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. Crit Care Med. 2013;41(7):1774-81.
13. Hernández G, Ospina-Tascón GA, Damiani LP, Estenssoro E, Dubin A, Hurtado J, et al. Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: The ANDROMEDA-SHOCK Randomised Clinical Trial. JAMA. 2019;321(7):654-64.
14. Monnet X, Marik PE, Teboul JL. Prediction of fluid responsiveness: an update. Ann. Intensive Care. 2016;6(1):111.
15. Maizel J, Airapetian N, Lorne E, Tribouilloy C, Massy Z, Slama M. Diagnosis of central hypovolemia by using passive leg raising. Intensive Care Med. 2007;33(7):1133-8.
16. Yonis H, Bitker L, Aublanc M, Perinel Ragey S, Riad Z, Lissonde F, et al. Change in cardiac output during Trendelenburg manoeuvre is a reliable predictor of fluid responsiveness in patients with acute respiratory distress syndrome in the prone position under protective ventilation. Crit Care. 2017;21(1):295.
17. Feissel M, Michard F, Faller JP, Teboul JL. The respiratory variation in inferior vena cava diameter as a guide to fluid therapy. Intensive Care Med. 2004;30(9):1834-7.
18. Marik PE, Lemson J. Fluid responsiveness: an evolution of our understanding. Br J Anaesth. 2014;112(4):617-20.
19. National Institute of Health. (2021). Hemodynamics. [online] Available from: https://www.covid19treatmentguidelines.nih.gov/management/critical-care/hemodynamics/.[Last accessed March 2022].
20. World Health Organisation. COVID-19 Clinical Management: Living Guidance 2021. [online] Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1. [Last accessed March 2022].
21. Joint AAGBI, ROC, ICS and FICM guidelines on COVID-19 patients. [online] Available from: https://icmanaesthesiacovid-19.org/clinical-guide-for-the-management-of-critical-care-for-adults-with-covid-19-during-the-coronavirus-pandemic. [Last accessed March 2022].
22. Selby NM, Forni LG, Laing CM, Horne KL, Evans RD, Lucas BJ, et al. COVID-19 and acute kidney injury in hospital: Summary of NICE guidelines. BMJ. 2020;369:m1963.
23. Hoste EA, Maitland K, Brudney CS, Mehta R, Vincent JL, Yates D, et al. Four phases of intravenous fluid therapy: a conceptual model. Br J Anaesth. 2014;113(5):740-7.
24. Finfer S, Myburgh J. Bellomo R. Intravenous fluid therapy in critically ill adults. Nat Rev Nephrol. 2018;14(9):541-57.

CHAPTER 138

Cytokine Removal in COVID-19-related Sepsis/Cytokine Storm

Vivek Nangia, Amina Mobashir, Sidhaant Nangia

INTRODUCTION

While the concept of cytokine storm syndrome (CSS) was first proposed over a century ago, by Sir William Osler, the father of Modern Medicine in his descriptive work, "The Evolution of Modern Medicine", however, most understanding about this complex syndrome has evolved over the last three decades.

It is now well-known that sepsis is an umbrella term that includes various aspects of CSS which in turn is nothing but an uncontrolled hyperimmune response caused by an excess of proinflammatory cytokines and may lead to multiorgan failure and even death. It includes formerly used terms such as hemophagocytic lymphohistiocytosis (HLH), malignancy-associated hemophagocytic syndrome (MAHS), macrophage activation syndrome (MAS), cytokine storm (CS), infection-associated hemophagocytic syndrome (IAHS), and can occur in various conditions including infections, malignancies, and rheumatological conditions.

A large number of viruses, bacteria, protozoa, and fungi have been found to cause CSS. Many viruses such as Corona SARS-CoV-1, which resulted in severe acute respiratory syndrome (SARS) outbreak in 2002, influenza H5N1 in 2006, influenza H7N9 in 2013, Corona Middle Eastern respiratory syndrome (MERS), Ebola, and now SARS-CoV-2, which has resulted in the current pandemic are known to cause CSS.[1]

Cytokine storm syndrome occurs following a complex interplay of various cells, signaling pathways, and cytokines following the entry of the pathogenic microbe. The key cytokines that play a pivotal role in the immunopathogenesis are interferon-γ (IFN- γ), interleukin-1 (IL-1), IL-6, tumor necrosis factor (TNF), and IL-18.[2]

Various therapeutic options have been trialed, but none has proven to be the gold standard yet.

IMMUNOPATHOGENESIS OF CYTOKINE STORM SYNDROME

Over 200 cytokines have been discovered and based on their structure and function, they can be classified into six major classes, namely ILs, colony-stimulating factors (CSFs), IFNs, TNF, growth factors (GF), and chemokines (CHs). Cytokines are small proteins which may exhibit their effect through different mechanisms. They act on neighboring cells via paracrine signaling or on the cytokine-secreting cells through autocrine signaling. Some cytokines act by intracrine signaling after binding to intracellular receptors, while membrane bound cytokines interact with neighboring cells via juxtacrine signaling. Usually cytokines are only locally acting, near the site of its secretion, but in certain pathological conditions, they may act on distant sites, in an endocrine manner, resulting in systemic effects.[1]

The entry of an invasive pathogenic organism is neutralized first by an innate immune response and later by an adaptive immune response. The immune response should ideally be appropriate to the pathogenic microbe, with a balance between the proinflammatory and the anti-inflammatory mediators and then return to homeostasis. While IL-1β, IL-2, IL-6, IL-7, IL-12, IL-18, TNF-α, IFN-γ, and granulocyte colony-stimulating factor (GCSF) serve as proinflammatory mediators, regulatory T cells, cytokines such as IL-10, transforming growth factor (TGF)-β, and IL-1ra serve as anti-inflammatory mediators.

However, in some patients, an exaggerated response results in an overabundance of proinflammatory mediators leading to significant collateral damage.[3] Cytokines are crucial in controlling this interplay by coordinating antimicrobial effector cells and providing regulatory signals that direct, amplify, and resolve the immune response.[4]

THERAPEUTIC STRATEGIES

The main goal of treating the CSS is to control the overexaggerated immune response and limit the collateral damage. While there is no standard treatment currently, but the general strategies include elimination of the trigger, targeted immunomodulation, or nonspecific immunosuppression and supportive care to the organs affected.[4]

The specific pharmacological options during the COVID-19 pandemic, which have been evaluated so far, include inhibitors of IL-1a receptor (anakinra and canakinumab), inhibitors of IL-6 receptors (tocilizumab, sarilumab, and siltuximab), TNF-α blocker (etanercept), IFN-γ blocker (emapalumab), and cytokine signal transducers such as Janus Kinases (JAKs) inhibitors (baricitinib). The nonspecific pharmacological options include glucocorticoids, intravenous immunoglobulin (IVIg), and convalescent plasma.[5]

BLOOD PURIFICATION TECHNIQUES

A potential nonpharmacological therapeutic option for CSS is blood purification techniques. The biggest advantage of these techniques is that they are able to target and clear a much wider panel of inflammatory mediators as compared to all the specific pharmacological options.

Continuous Renal Replacement Therapy

The experience of continuous renal replacement therapy (CRRT) in patients with severe MERS has shown that besides removing fluid from the body, it also has the potential to remove inflammatory mediators.[6]

As per a study conducted, use of high cut-off (HCO) membrane during CRRT was able to remove macromolecules such as IL-6 but its ability to clear TNF-α was limited,[7] and its usage in patients with septic shock did not result in any significant survival benefit.[8]

However, in a study involving 38 patients of septic shock and acute renal injury, using continuous venovenous hemodialysis (CVVHD) with HCO for 72 hours, resulted in significant reduction in cytokine levels. In this study, 30 patients survived while 8 died.[9]

Cytokine Adsorption Column or Immunoadsorption

Immunoadsorption involves removal of cytokines, CHs, and antibodies using extracorporeal devices and thus purifying the blood.[10] The commonly used devices for the purpose are mentioned below.

CytoSorb® (Cytosorbents, Monmouth, NJ, USA)

CytoSorb® is one such hemoadsorption device which has been used to capture and reduce inflammatory mediators. It can be applied during standard hemodialysis, hemofiltration, and extracorporeal membrane oxygenation (ECMO). It has the ability to filter out molecules 5–60 kDa in size, has CE mark, and has been granted Emergency Use Authorization by the US Food and Drug Administration (FDA) for use in COVID-19 patients.

Several retrospective studies and case reports of patients with severe sepsis and septic shock, acute respiratory distress syndrome (ARDS) have proven its role in effectively reducing the blood levels of inflammatory factors thereby significantly improving the outcomes.

In a case series of three severely ill adult patients with COVID-19 disease, published from India, single use of CytoSorb was associated with significant improvement in biochemical parameters and clinical outcomes. All three patients survived. C-reactive protein (CRP) levels decreased by 91.5, 97.4, and 55.75%, and mean arterial pressure improved by 18, 23, and 17% in patient 1, 2, and 3, respectively, on day 7 post-therapy.[11]

In a larger retrospective study from Iran, of 26 patients of COVID-19 illness with ARDS, treated with CytoSorb filter in addition to the routine therapy, 21 patients survived and a significant reduction in vasopressor requirements and plasma levels of inflammatory markers along with improvement in PaO_2/FiO_2 ratios and in Sequential Organ Failure Assessment (SOFA) score has been reported.[12]

In another similar case series of 15 patients of COVID-19 with ARDS requiring intubation and mechanical ventilation and renal replacement therapy, from Britain, 10 received CytoSorb and 5 HA 330 cartridge. Out of these, 11 patients were on ECMO, 8 expired and 7 survived. However, a significant reduction in various parameters such as ferritin (3,622 ng/mL vs. 1,682 ng/mL p = 0.022), CRP [222 mg/mL vs. 103 mg/mL, p = 0.008, 95% confidence interval (CI) 22.4–126.5], lactate (2 mmol/L vs. 1.3 mmol/L, p = 0.017), and procalcitonin (15.3 ng/mL vs. 4.2 ng/mL, p = 0.023) have been reported, while there was no difference reported in IL-6, IL-1, IL-10, and TNF-α levels.[13]

Other similar studies have also reported a significant reduction in the levels of inflammatory markers, vasopressors, and improved oxygenation. Currently two trials employing hemoadsorption therapy for infection-related CS (NCT04195126, NCT03685383) and one employing Continuous venovenous hemofiltration and adsorption for severe septic shock (NCT03974386) are ongoing.[14]

AN69 Membrane (Oxiris)

This is a high throughput membrane with highly hydrophilic hydrogel structure which is able to remove medium and high molecular weight mediators using ionic charge interactions. With slight modification of the surface with a multilayer linear structure of polyethylenimine cationic polymer, it can also remove negatively charged endotoxins.[15]

Experience in the past from Hong Kong[16] and France[17] in patients with severe sepsis showed significant improvement in SOFA score and reduction in in-hospital mortality by about 30% respectively.

A major advantage of oxiris is that it has a heparin coating and hence in patients with increased risk of bleeding, it can be used without anticoagulation.[18]

In a case reported from India, its use in a COVID-19 patient with multiorgan involvement, during CRRT, led to reduction in IL-6 levels, improvement in respiratory status and survival.[19]

In a small case series of five patients of severe COVID-19 with ARDS and septic shock, from China, use of oxiris was associated with a significant reduction in the inflammatory mediators such as IL-6, IL-8, and IL-10 ($p < 0.05$), improvement in organ dysfunction, hemodynamics and oxygenation, and no adverse event to report.[20]

In a pilot study from Italy, 37 patients of COVID-19 with multiorgan involvement, were subjected to oxiris as an extracorporeal blood purification therapy. During the first 72 hours of instituting the therapy, median IL-6 levels (baseline level—1,230 pg/mL) decreased with the most significant reduction happening in the first 24 hours ($p = 0.001$) and so did the SOFA score from a median baseline score of 13 with the most significant reduction happening in the first 48 hours ($p = 0.001$). 8.3% reduction in mortality was observed in the oxiris group as compared to the expected mortality rates. The best results were observed in patients in whom it was administered early in the course of their intensive care unit (ICU) stay. The only technical complication experienced was premature clotting in about 18.9% patients, that too was similar to CRRT performed in other critically ill patients.[21]

In a larger prospective cohort study from Macedonia, of 44 COVID-19 patients, use of oxiris was associated with a reduction in the levels of acute phase proteins such as ferritin, CRP, fibrinogen, several inflammatory markers such as IL-6, and a resolution of numerous cytopenias such as lymphocytes, basophils, eosinophils, and platelets.[22]

Other Filters

Some other filters which have been used for the purpose include polymethyl methacrylate membrane, Biosky offering different filter sizes from 150 to 350 mL, Jaffron HA 330, a synthetic resin hemofilter, and AN69ST, an acrylonitrile/methallyl sulfonate copolymer membrane. Overall, there is very limited experience of their usage and none in COVID-19 available.

Some of the technical features of these devices have been compared in **Table 1**.

Timing of the Therapy

Although no study has addressed this issue specifically, but considering that the inflammatory mediators have a very short half-life, it may be worthwhile to administer these therapies early on in the course of the CSS. Once the cascade has started, then the benefit from the removal of cytokines may be very limited.[23]

Disadvantages

No study has reported any significant adverse event or technical difficulty and hence labeled it as a safe, feasible, and simple modality. Apart from the usual catheter-related complications such as infection, dislodgement, bleeding, and pneumothorax, the major disadvantage of all these therapies is that its nonselective and adsorbs a wide range of cytokines including the anti-inflammatory ones and can even result in loss of nutrients, electrolytes, and drugs including antibiotics, thus requiring monitoring of drug levels. Another disadvantage is that patients can vary in their levels of cytokines in the blood, hence these therapies may not be beneficial to all. And above all, there are no large scale randomized controlled trials to support their use.[24]

Coupled Plasma Filtration Adsorption

This is another extracorporeal technique in which plasma is extracted from the blood, passed through a nonspecific sorbent, which removes the inflammatory mediators and then returned back into the blood. There is very limited data available to support its use.[25]

TABLE 1: Commonly used devices for the cytokine adsorption column.

Device	*Surface area*	*Blood flow rate*	*Integration*	*Material*	*Shelf life*
CytoSorb	45,000 m^2 (more than 4 European football fields)	100–700 mL/min	HP/HD/CRRT/ECMO/CPB	Crosslinked Divinylbenzene	3 years
Biosky	Biosky Brochure: "… 5 European football fields to bind uremic toxins" (more than 50,000 m^2)	100 mL/min at start, 180–400 mL/min once stabilized	HP/HD/CRRT/CPB	Medical neutral macropore synthetic resin	2 years
HA-380	100,000 m^2	100–700 mL/min	HP/HD/CRRT/CPB	Neutral macroporous resin	2 years
Oxiris	1.5 m^2	100–450 mL/min	SCUF/CVVH/CVVHD/CVVHDF	AN69 HF hollow fiber	2 years

(CPB: cardiopulmonary bypass; CRRT: continuous renal replacement therapy; CVVG: continuous venovenous hemofiltration; CVVHD: continuous venovenous hemodialysis; CVVHDF: continuous venovenous hemodiafiltration; ECMO: extracorporeal membrane oxygenation; HP: hemoperfusion; HD: hemodialysis; SCUF: slow continuous ultrafiltration)

Therapeutic Plasma Exchange

This technique is superior to CRRT for the removal of molecules from the plasma. It has often been used successfully for the treatment of antibody-mediated severe diseases such as thrombotic microangiopathies, glomerulonephritis forms, Guillain-Barré syndrome, and primary and secondary HLH.[26]

Some small studies support its use in sepsis also. In a systemic review published, therapeutic plasma exchange (TPE) was shown to reduce the mortality in adult patients with sepsis.[27]

Use of TPE has successfully led to rapid reduction in the dosage of vasopressors in patients with septic shock,[27] reduced proinflammatory cytokines (IL-6, IL-1ß, and angiopoietin-2),[28] and partially reversed coagulation disorders.[29]

Use of TPE in COVID-19 patients with CSS has shown definite benefit. In a case report of a COVID-19 patient with respiratory failure and antiphospholipid syndrome, three sessions of TPE led to significant clinical improvement resulting in decreased titers of antiphospholipid antibodies and inflammatory markers, including IL-6.[30]

In a small case series reported from Turkey, of six patients suffering from COVID-19-related autoimmune meningoencephalitis with ARDS requiring mechanical ventilation, four patients recovered well and were discharged. One patient exited from the study, and one was still hospitalized at the time of publication. All these patients had high levels of inflammatory markers such as ferritin, fibrinogen, CRP, IL-6 in sera, and bilateral cerebral inflammation compatible with meningoencephalitis on magnetic resonance imaging (MRI) and were given three to nine sessions of TPE before they recovered.[31]

In a case series of eight patients from Iran, of COVID-19 with septic shock and ARDS, subjected to TPE when they were continuing to be hypoxic despite steroids, only one patient died, that too, attributable to poor general condition and delay in initiation of TPE, while rest all recovered. The survivors received four to five sessions of TPE and were hospitalized between 8 and 22 days after the onset of symptoms.[32]

A few other case studies have indicated that use of TPE in patients of COVID-19 with ARDS and shock resulted in dramatic improvement.

In a somewhat larger case series, of 31 patients from Oman, the TPE group was associated with higher extubation rates (73% vs. 20%; p = 0.018), improvement in laboratory and ventilatory parameters and a lower 14 days (0 vs. 35%; p = 0.033) and 28 days (0 vs. 35%; p = 0.033) postplasma exchange mortality compared to patients not on TPE. However, all-cause mortality was only marginally lower in the TPE group.[33]

Therapeutic plasma exchange has its own share of disadvantages also. It could result in higher risk of bleeding, catheter-related infections, electrolyte imbalances such as hypocalcemia and hypokalemia, and anaphylactic shock. The major limitation is the lack of expertise and infrastructure available to carry out TPE across all centers.

The timing of initiation of TPE is very important. It has been recommended to be started early in patients with respiratory failure requiring mechanical ventilation particularly those with elevated inflammatory biomarkers. TPE may be instituted every day, or on alternate days and may be continued till clinical improvement. In a few studies, on an average, 2–14 daily sessions, were required before recovery.

As for the choice of method, centrifugal one might be preferable, as randomized controlled trials (RCTs) on TPE in septic shock have showed positive results with using centrifugation, although filtration types are also considered useful.[6]

CONCLUSION

Cytokine storm syndrome results from a complex interplay of the various proinflammatory and anti-inflammatory mediators. It is a life-threatening condition, for which no gold standard specific therapy is available yet. Among the various potential modalities, cytokine removal is a promising strategy. Though large scale studies are lacking, yet it could be employed in patients with high cytokine levels, high SOFA score, respiratory failure, and hemodynamic instability. Like most other interventions, early institution of therapy may improve the outcomes further.

REFERENCES

1. Xi Y. COVID-19-associated cytokine storm syndrome and diagnostic principles: an old and new Issue. Emerg Microbes Infect. 2021;10(1):266-76.
2. Kaiafa G, Veneti S, Polychronopoulos G, Pilalas D, Daios S, Kanellos I, et al. Is HbA1c an ideal biomarker of well-controlled diabetes? Postgrad Med J. 2021;97(1148):391-8.
3. Canna SW, Behrens EM. Making sense of the cytokine storm: a conceptual framework for understanding, diagnosing, and treating hemophagocytic syndromes. Pediatr Clin North Am. 2012;59(2):329-44.
4. Fajgenbaum DC, June CH. Cytokine storm. N Engl J Med. 2020;383(23):2255-73.
5. Kim JS, Lee JY, Yang JW Immunopathogenesis and treatment of cytokine storm in COVID-19. Theranostics. 2021;11(1):316-29.
6. Silvester W. Mediator removal with CRRT: complement and cytokines. Am J Kidney Dis. 1997;30(5 Suppl 4):S38-43.
7. Morgera S, Rocktaschel J, Haase M, Lehmann C, von Heymann C, Ziemer S, et al. Intermittent high permeability hemofiltration in septic patients with acute renal failure. Intensive Care Med. 2003;29(11):1989-95.
8. Atan R, Peck L, Prowle J, Licari E, Eastwood GM, Storr M, et al. A double-blind randomized controlled trial of high cutoff

versus standard hemofiltration in critically ill patients with acute kidney injury. Crit Care Med. 2018;46(10):e988-94.
9. Villa G, Chelazzi C, Morettini E, Zamidei L, Valente S, Caldini AL, et al. Organ dysfunc- tion during continuous veno-venous high cut-off hemodialysis in patients with septic acute kidney injury: a prospective observational study. PLoS One. 2017;12(2):e0172039.
10. Alkattan A, OH Hashi K, Kendeel M. Treatment options during cytokine storm. Dr. Sulaiman Al Habib Med J. 2021;3(2):48-52.
11. Mehta Y, Mehta C, Nanda S, Kochar G, George JV, Singh MK, et al. Use of CytoSorb therapy to treat critically ill coronavirus disease 2019 patients: a case series. J Med Case Reports. 2021;15(1):476.
12. Nassiri AA, Hakemi MS, Miri MM. Blood purification with CytoSorb in critically ill COVID-19 patients: A case series of 26 patients. Artif Organs. 2021;45(11):1338-47.
13. Paisey C, Patvardhan C, Mackay M, Vuylsteke A, Bhagra SK. Continuous hemadsorption with cytokine adsorber for severe COVID-19: A case series of 15 patients. Int J Artif Organs. 2021;44(10):664-74.
14. Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine storm in COVID-19: The current evidence and treatment strategies. Front Immunol. 2020;11:1708.
15. Malard B, Lambert C, Kellum JA. In vitro comparison of the adsorption of inflammatory mediators by blood puri- fication devices. Intensive Care Med Exp. 2018;6(1):12.
16. Shum HP, Chan KC, Kwan MC, Yan WW. Application of endotoxin and cytokine adsorption haemofilter in sep- tic acute kidney injury due to Gram-negative bacterial infection. Hong Kong Med J. 2013;19(6):491-7.
17. Schwindenhammer V, Girardot T, Chaulier K, Grégoire A, Monard C, Huriaux L, et al. oXiris(R) use in septic shock: experience of two french centres. Blood Purif. 2019;47(3):1-7.
18. Zhang L, Yan Tang GK, Liu S, Cai J, Chan WM, Yang Y, et al. Hemofilter with adsorptive capacities: case report series. Blood Purif. 2019;47(3):1-6.
19. Lobo VA, Lokhande A, Chakurkar V, D'Costa PM. Continuous hemodiafiltration with the oxiris filter ameliorates cytokine storm and induces rapid clinical improvement in COVID-19 – A case report. Indian J Nephrol. 2021;31(6):555-8.
20. Zhang H, Zhu G, Lee Y, Lu Y, Fang Q, Shao F. The absorbing filter Oxiris in severe coronavirus disease 2019 patients: A case series. Artif Organs. 2020;44(12):1296-1302.
21. Villa G, Romagnoli S, Rosa SD, Greco M, Resta M, Pomarè Montin D, et al. Blood purification therapy with a hemodiafilter featuring enhanced adsorptive properties for cytokine removal in patients presenting COVID-19: a pilot study. Crit Care. 2020;24(1):605.
22. MedRxiv. (2020). Rosalia RA, Ugurov P, Neziri D, Despotovska S, Kostoska E, Veljanovska-Kiridjievska L, et al. Extracorporeal blood purification in moderate and severe COVID-19 patients: a prospective cohort study. [online] Availble from: https://www.medrxiv.org/content/10.1101/2020.10.10.20210096v1. [Last accessed March, 2022].
23. Quenot JP, Binquet C, Vinsonneau C, Barbar SD, Vinault S, Deckert V, et al. Very high volume hemofiltration with the Cascade system in septic shock patients. Intens Care Med. 2015;41(12):2111-20.
24. Ronco C, Bagshaw SM, Bellomo R, Clark WR, Husain-Syed F, Kellum JA, et al. Extracorporeal blood purification and organ support in the critically ill patient during COVID-19 pandemic: Expert review and recommendation. Blood Purif. 2021;50(1):17-27.
25. AL Shareef K, Bakouri M. Cytokine blood filtration responses in COVID-19. Blood Purif. 2021;50(2):141-9.
26. Clark WF, Huang SS, Walsh MW, Farah M, Hildebrand AM, Sontrop JM. Plasmapheresis for the treatment of kidney diseases. Kidney Int. 2016;90(5):974-84.
27. Rimmer E, Houston BL, Kumar A, Abou-Setta AM, Friesen C, Marshall JC, et al. The efficacy and safety of plasma exchange in patients with sepsis and septic shock: a systematic review and meta-analysis. Crit Care. 2014;18(6):699.
28. Knaup H, Stahl K, Schmidt BMW, Idowu TO, Busch M, Wiesner O, et al. Early therapeutic plasma exchange in septic shock: a prospective open-label nonrandomized pilot study focusing on safety, hemodynamics, vascular barrier function, and biologic markers. Crit Care. 2018;22(1):285.
29. Stahl K, Schmidt JJ, Seeliger B, Schmidt BMW, Welte T, Haller H, et al. Effect of therapeutic plasma exchange on endothelial activation and coagulation-related parameters in septic shock. Crit Care. 2020;24(1):71.
30. Ma J, Xia P, Zhou Y, Liu Z, Zhou X, Wang J, et al. Potential effect of blood purification therapy in reducing cytokine storm as a late complication of critically ill COVID-19. Clin Immunol. 2020; 214:108408.
31. Dogan L, Kaya D, Sarikaya T, Zengin R, Dincer A, Akinci IO, et al. Plasmapheresis treatment in COVID-19-related autoimmune meningoencephalitis: Case series. Brain Behav Immun. 2020;87:155-8.
32. Adeli SH, Asghari A, Tabarraii R, Shajari R, Afshari S, Kalhor N, et al. Therapeutic plasma exchange as a rescue therapy in patients with coronavirus disease 2019: a case series. Pol Arch Intern Med. 2020; 130(5):455-8.
33. Khamis F, Al-Zakwani I, Hashmi SA, Dowaiki SA, Bahrani MA, Pandak N, et al. Therapeutic plasma exchange in adults with severe COVID-19 infection. Int J Infect Dis. 2020;99:214-8.

139

CHAPTER

Cough Management in COVID Patients

Vinay Singhal, Amit Gupta, Kunal Sahai

INTRODUCTION

A novel virus SARS-CoV-2 was first detected in Wuhan, China, in December 2019 and from there it spread to rest of the world. It had varied presentation, from asymptomatic cases to patients' mild, moderate, or severe illness. The common symptoms of COVID-19 are fever, dry cough, fatigue, and breathing difficulties. Cough can be most common symptom and it can be distressing to the patient and to the people around. It can increase the transmission by respiratory droplets.[1] Identifying ways to control COVID-19-associated cough would not only relieve the patient but also help to prevent community transmission and disease spread.

HOW TO DEFINE COUGH?

Cough is a natural protective mechanism that allows clearing of the airways of irritants, particles, and microbes by an air expulsion from the lungs with fast speed. Although all coughs are acute at onset, they can be classified according to the duration as acute (<3 weeks), subacute (3–8 weeks), and chronic (>8 weeks) categories. The most common causes of acute cough are respiratory infections (most likely of viral cause), followed by as asthma, chronic obstructive pulmonary disease (COPD), and pneumonia. For subacute cough, they were postinfectious cough and exacerbation of asthma, COPD, and upper airway cough syndrome (UACS). The most common causes for the chronic cough were UACS from rhino sinus conditions, asthma, gastroesophageal reflux disease (GERD), and nonasthmatic eosinophilic bronchitis.[2]

ACUTE COUGH IN COVID-19

Dry cough is a very common initial symptom in 60–70% of COVID-19 symptomatic patients in the acute phase like any other flu infection.[3,4] Cough was reported in 50% of 370,000 confirmed COVID-19 cases with known symptom status reported to the Centers for Disease Control and Prevention (CDC).[5] Cough carries the risk of droplet infection in the community, apart from being distressing and leading to social isolation due to stigmatization in the pandemic. The median time of onset of cough was 1 day from the start of illness and it lasted for an average of 19 days and in 5% of cases persisted >4 weeks.[6]

A complex reflex arc is responsible for cough and this arc is initiated by the trigger of cough receptors existing mainly in the epithelium of the upper and lower respiratory tracts along within the pericardium, esophagus, diaphragm, and stomach by various chemical and mechanical irritants via activation of ion channels.[7] Cough reflex traverse as an afferent pathway via the vagus nerve to the "cough center" in the medulla and then the cough center generates an efferent signal via vagus, phrenic, and spinal motor nerves to expiratory musculature. Initiation of cough may be associated with neuroinflammation due to interaction of virus with airway vagus nerve, this can initiate cough, along with ageusia and anosmia.[8]

The cough during the COVID period can be due to pre-existing conditions or comorbidity having cough as the feature or it can be of COVID itself.

COUGH IN POST-COVID SYNDROME

Cough can persists for long time for weeks to months, referred as post-COVID syndrome or long-COVID. Post-COVID syndrome is there when the COVID symptoms persists for >3 months.[9] Sudre et al.[10] studied two groups of symptoms in people with long COVID, one is fatigue, headache, and upper respiratory complaints (dyspnea, sore throat, persistent cough, and loss of smell) and the other is a multisystem complaints including ongoing fever and gastroenterological symptoms. Cough was present in 16–18% post-COVID patients 60 days after infection[8,11] to 12% patients after 90 days of start of symptoms and 2.5% of patients after 1 year of infection.[12] Lung fibrosis is the feared complication of respiratory infections. Myall et al. report a 4% incidence of post-COVID-19 inflammatory interstitial lung disease (ILD) among a large cohort of patients that

required hospitalization.[13] The presence of fibrotic band-like radiographic abnormalities correlates with decrements in lung function, cough, and frailty.

The persistence of cough was associated with other post-COVID-19 symptoms such as fatigue, dyspnea, and chest pain. These symptoms along with cognitive impairment, including confusion and memory loss (brain fog), are associated with a deleterious effect on activities of daily living. The post-COVID syndrome is pathophysiologically conglomeration of multiple symptoms and signs involving multiple organ systems and occurs due to dysregulated immune response leading to endothelial damage, thrombosis, and organ damage.[14]

Causes of Cough with Post-COVID Syndrome

Cause of cough in post-COVID-19 patient and why it develops in some and not in others is largely unknown. Post-COVID syndrome may be associated with female sex or certain chronic condition such as respiratory comorbidities and severity of acute COVID-19 presentation. However, the persistence of cough was not associated with other post-COVID symptoms such as fatigue, dyspnea, and chest pain. It was also not associated with age, obesity, woman gender, height, weight, being active smoker, or cough as onset symptom of COVID, number of pre-existing medical comorbidities, or with hospitalization variables like the number of symptoms at hospital admission, number of days at hospital, and intensive care unit (ICU) admission.[12] It is usually accompanied by multisystem involvement indicating varying underlying mechanism.

Persistence of Pre-existent or Co-existing Diseases

Cough can present in post-COVID/long COVID syndrome as part of pre-existing comorbidities such as asthma, COPD, ILD, GERD, sinusitis, oral candidiasis, or drug uses such as angiotensin-converting enzyme inhibitors (ACEi). During the management of cough, here we will consider the management of the specific condition by careful history and relevant examination because during COVID-19 management, the necessary treatment of such conditions can be suboptimal.

Persistence of Respiratory Symptoms and Cough Post-COVID-19

COVID-19 illness can cause fibrotic damage to lung parenchyma or damage to the airways. This lung fibrosis or airway damage could increase sensitivity due to any mechanical stimulation for cough as seen in with idiopathic pulmonary fibrosis. In long COVID, the presence of cough with other symptoms of fatigue, dyspnea, chest pain, altered taste, and smell suggests derangement of central nervous system. Song et al.[8] postulated the possibility that SARS-CoV-2 infection leading to neuroinflammation and neuroimmune interactions as mechanisms of cough hypersensitivity by infecting the sensory nerves mediating cough. They also examined whether the neurotropism of SARS-CoV-2 could explain the other symptoms of COVID-19 and post-COVID syndrome. Brain magnetic resonance imaging (MRI) imaging of patients with neurological complications of COVID-19 infection have shown cortical signal abnormalities and neuroinflammatory features with post-COVID syndrome,[15] and positron emission tomography (PET) imaging of brain suggests hypometabolism in the olfactory gyrus and connected limbic-paralimbic regions, extending to the brainstem and the cerebellum in patients with long COVID.[16] Neurotropism associated with COVID-19, activation of vagal sensory neurons with neuroinflammation needs to be studied for better understanding of central cause of COVID-related cough. This may also help us in managing the cough with appropriate use of antiviral, anti-inflammatory, or neuromodulator drugs (e.g., gabapentin and pregabalin) for the treatment of acute or chronic cough associated with COVID-19.

Cough due to Complications of COVID-19 or Pre-existing/Co-existing Illness

Cough can appear or worsen in patients with COVID-19 during treatment. There are instances when worsening occurs as patient acquires secondary bacterial infections. This may be associated with the development of pleuritis and subsequently pleural effusion.

Among the nonpulmonary causes of cough, myocardial injury and heart failure are common. The specific condition must be managed as per with relevant investigations including blood tests, imaging, electrocardiogram, and echocardiography. Tuberculosis should be considered in differential diagnosis in patients with persistent respiratory symptoms in post–COVID-19 as it can occur due to reactivation of latent tuberculosis or new infection secondary to use of immunosuppressive medication or postviral immune function abnormalities.

Barotrauma/air leak syndrome is also seen very often with COVID pneumonia. Forceful coughing with sudden alveolar overdistension can increase intra-alveolar pressure and rupture the alveoli. Air leak syndrome includes pneumomediastinum, pneumopericardium, pneumothorax, or subcutaneous emphysema and has considerable prevalence. It is primarily caused by chest trauma, cardiothoracic surgery, esophageal perforation, and mechanical ventilation. However, spontaneous alveolar air leakage is a rare phenomenon especially following viral pneumonia. Although an incidence of 11.6% previously had been reported concerning the severe acute respiratory syndrome (SARS) outbreak, a much lower incidence (0.72%) has been reported in patients with COVID-19.[17]

MANAGEMENT OF COUGH IN COVID-19

Although it is the assessment of disease severity that becomes very important while managing a case of COVID-19, but at the same time, symptoms of cough, fever, and breathlessness can be highly distressing even in those who do not have severe disease. Treatment of cough in COVID depends upon the patient's presentation (acute or chronic) and availability of the treatment options.

Management includes detailed evaluation of clinical findings to find out the acute cause as well as pre-existing or coexisting diseases behind the cough. The examination should mainly emphasize general examination for pallor, nails for clubbing, cyanosis, lymph nodes swelling, and chest auscultation that can find crepts and rhonchi as well as decreased/altered air entry. The examination of nose should be especially helpful in finding polyps or reddish nasal mucosa (allergic), cobblestone appearance, and secretions in nasopharyngeal mucosa (postnasal drip). Systemic examination should also be done to rule out diseases such as lymphoma, vasculitis, sarcoidosis, and lung cancer.

Investigations

The chest X-ray (CXR) is an integral part to clinch the diagnosis of COVID and non-COVID diseases. Chronic cough with normal CXR is found most commonly in GERD, asthma, postnasal discharge (PND), and drugs such as ACEi. Sputum examination is must in cases of nonresponding cough to find out the cause of secondary infections, especially Grams stain/acid fast bacilli (AFB) stain/KOH mount, and culture. CXR and sputum examination for AFB will determine the diagnosis of tuberculosis. The computed tomography (CT) scan is also useful when the cause of cough remains undiagnosed. Reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 is obviously required to establish the diagnosis of COVID-19.

General Measures

Communication with the patient and family is important. They should be told about the risks, benefits, and possible outcomes of the treatment options. They should also be aware of escalation plans in case of any worsening of symptoms. Treatment plan need to be modified for the patients with older age, pre-existing/co-existing comorbidities, impaired immunity, or the patients who have weak or reduced cough ability.

Although many over-the-counter drugs are available for the relief of cough, but none seems to be effective for the treatment for the cough associated with viral pneumonias. In the UK National Institute for Health and Care Excellence guidelines for managing acute symptoms of COVID-19, only taking honey or opioid-derived antitussives are recommended for cough.[18] Opiates could exert antitussive effects by acting on the cough reflex network in the brainstem, and might have some effects in suppressing cough, particularly in the early stages. However, opiates are not universally effective and have associated risks of dependence, abuse, or central side effects.

Management of Cough with Pre-existing Diseases

Treatment of pre-existing reasons in non-COVID cough obviously starts after a correct diagnosis with the help of examination and investigations. Antihistamines, decongestants, and nasal sprays will relieve allergic and postnasal drip cough. Bronchodilators and steroids are to be given for patients with asthma/cough variant asthma. The infective causes are treated with appropriate antibiotics/antitubercular (ATT) after stain/cultures. Proton pump inhibitors (PPIs) and diet management along with propped up position, while reclining will help majority of GERD patients. The postinfectious cough resolves spontaneously in most of the cases. Switching from ACEi and beta-blockers to other antihypertensives such as calcium channel blockers (CCBs) or angiotensin receptor blockers (ARBs) will help in relieving drug-induced cough.

Lifestyle modification such as cessation of smoking and environmental modifications such as good ventilation that improves air quality along with avoidance of exposure to fumes and smoke from kitchen and fuels are helpful in many patients. The avoidance of triggers and allergens will help in asthma/cough variant asthma.

Management of Cough with Post-COVID Syndrome/Long COVID

Oral corticosteroids are often used for the lower respiratory tract infections other than COVID-19. But their use to treat cough in nonasthmatic patients with lower respiratory tract infection was usually not as effective. Use of corticosteroids for hypoxia with COVID-19 cases can also deal with the pathophysiology for the cough (early inflammatory response and neuroimmune pathology). Though use of dexamethasone decreases the mortality in the hospital treated patients with COVID-19, its effect on the cough was never assessed.[19] Gabapentin and pregabalin, the neuromodulator drugs, had been shown to be effective in chronic cough with long COVID. These drugs can be useful to relieve the other symptom of post-COVID syndrome, such as pain. Antimuscarinic drugs could be used to control COVID-19 cough, because they can decrease cough sensitivity in acute viral upper respiratory tract infection.

According to Swiss Recommendations, there is moderate recommendation for inhaled steroids in persistent cough post-COVID. Recommendation for systemic steroids for interstitial abnormalities post-COVID if there is no active infection is only moderate.

However, there is no recommendation for antifibrotic therapy in signs of pulmonary fibrosis post-COVID.[20]

Investigation of novel therapeutic interventions that interferes with the neuroinflammatory pathways could be advantageous, such as inhibitors of TRP channels, ATP-gated P2X3 receptors, neurokinin-1 receptors (NK1Rs), or sodium channels. Substance P and NK1R might also be a potential target for intervention, because NK1R antagonists such as aprepitant or orvepitant have shown antitussive potential in patients with lung cancer-associated cough or chronic refractory cough, possibly through blocking of central NK1Rs.[21]

CONCLUSION

Cough can be a highly distressing symptom as we manage the case of COVID-19 irrespective of the severity of disease. Though frequency and prevalence of cough are very well studied, but effect of various treatment modalities such as corticosteroids and antivirals (remdesivir) on COVID-19 related cough was not assessed in trials. We need to have better understanding of activation of vagal sensory neurons, neuroinflammation, neuroimmunity, and peripheral and central sensitization for the pathophysiology of acute and chronic cough or cough associated with post-COVID syndrome. Chronic cough should be considered as syndrome and should be considered for the management with other symptoms of post-COVID syndrome.

REFERENCES

1. Dhand R, Li J. Coughs and sneezes: their role in transmission of respiratory viral infections, including SARS-CoV-2. Am J Respir Crit Care Med. 2020;202(5):651-9.
2. Irwin RS, French CL, Chang AB, Altman KW; CHEST Expert Cough Panel*. Classification of cough as a symptom in adults and management algorithms: CHEST Guideline and Expert Panel Report. Chest. 2018;153(1):196-209.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
4. Grant MC, Geoghegan L, Arbyn M, Mohammed Z, McGuinness L, Clarke EL, et al. The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): A systematic review and meta-analysis of 148 studies from 9 countries. PLoS One. 2020;15(6): e0234765.
5. Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, El Burai Felix S, et al. Coronavirus Disease 2019 Case Surveillance - United States, January 22-May 30, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(24):759-65.
6. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.
7. Belvisi MG, Dubuis E, Birrell MA. Transient receptor potential A1 channels: insights into cough and airway inflammatory disease. Chest. 2011;140(4):1040-7.
8. Song WJ, Hui CKM, Hull JH, Birring SS, McGarvey L, Mazzone SB, et al. Confronting COVID-19-associated cough and the post-COVID syndrome: role of viral neurotropism, neuroinflammation, and neuroimmune responses. Lancet Respir Med. 2021;9(5):533-44.
9. Raveendran AV, Jayadevan R, Sashidharan S. Long COVID: An overview. Diabetes Metab Syndr. 2021;15(3):869-75.
10. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of Long-COVID: analysis of COVID cases and their symptoms collected by the Covid Symptoms Study App. medRxiv. 2020.
11. Carfi A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. JAMA. 2020;324(6):603-5.
12. Fernández-de-las-Peñas C, Guijarro C, Plaza-Canteli S, Hernández-Barrera V, Torres-Macho J. Prevalence of Post-COVID-19. Cough one year after SARS-CoV-2 infection: A Multicenter Study. Lung. 2021;199(3):249-53.
13. Myall KJ, Mukherjee B, Castanheira AM, Lam JL, Benedetti G, Mak SM, et al. Persistent post-COVID-19 interstitial lung disease. An observational study of corticosteroid treatment. Ann Am Thorac Soc. 2021;18(5):799-806.
14. Østergaard L. SARS CoV-2 related microvascular damage and symptoms during and after COVID-19: consequences of capillary transit-time changes, tissue hypoxia and inflammation. Phys Rep. 2021;9(3):e14726.
15. Katal S, Gholamrezanezhad A. Neuroimaging findings in COVID-19: a narrative review. Neurosci Lett. 2021;742:135529.
16. Guedj E, Campion J, Dudouet P, Kaphan E, Bregeon F, Tissot-Dupont H, et al. 18 F-FDG brain PET hypometabolism in patients with long COVID. Eur J Nucl Med Mol Imaging. 2021;48(9):2823-33.
17. Eperjesiova B, Hart E, Shokr M, Sinha P, Ferguson GT. Spontaneous pneumomediastinum/pneumothorax in patients with COVID-19. Cureus. 2020;12(7):e8996.
18. National Institute for Health and Care Excellence in collaboration with NHS England and NHS Improvement. Managing COVID-19 symptoms (including at the end of life) in the community: summary of NICE guidelines. BMJ. 2020;369:m1461.
19. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. JAMA. 2020;324(13):1307-16.
20. Funke-Chambour M, Bridevaux PO, Christian F, Soccal PM, Nicod LP, von Garnier C, et al. Swiss Recommendations for the Follow-Up and Treatment of Pulmonary Long COVID. Respiration. 2021;100(8):826-41.
21. Smith J, Allman D, Badri H, Miller R, Morris J, Satia I, et al. The neurokinin-1 receptor antagonist orvepitant is a novel antitussive therapy for chronic refractory cough: results from a phase 2 pilot study (VOLCANO-1). Chest. 2020;157(1):111-18.

CHAPTER 140

Post-COVID Neuropsychiatric Complications

Anand Sanghi, Chirag Matravadia, Rajesh Maniar

INTRODUCTION

Viral infections of the respiratory tract affect all the systems of the body including the central nervous system (CNS). This affection gives rise to many of the psychiatric and neurological problems.[1] Long- and short-term complications of CNS abnormalities have been reported in some of the patients affected with COVID-19 infection, such as stroke and isolated psychiatric syndromes.[2] There was no single wave of COVID-19 infection, but more than one waves are seen. And as the world is going through its second/third wave (varying from country to country), this is a good time to understand about the effects of COVID-19 infection on the acute and chronic neuropsychiatric sequelae and to know its mechanism.

Anxiety, stress, and depression are some of the acute psychiatric manifestations seen in patients with COVID-19 infection.[3] It has been seen that the long-term effects are alone not related to the illness itself, but are also related to stigma or memories and amnesia-associated with the critical care that these patients receive while undergoing treatment.[4] Nearly one-third of the hospitalized patients have reported acute neurological conditions such as headache, sensorium changes, acute cerebrovascular accidents, convulsions, and ataxia.[5] There are also reports of acute cognitive problems such as attention and dysexecutive symptoms.[6] Nevertheless, we can only estimate about COVID-19 infection's long-term neuropsychiatric and cognitive effects.

PATHOPHYSIOLOGY OF NEUROPSYCHIATRIC CONSEQUENCES OF COVID-19

- Neuropsychiatric symptoms of COVID-19 infection are seen due to factors such as electrolyte imbalance, inflammation of the liver, impaired renal function, problems with oxygenation, hyperinflammation,[7] and isolation of the patients due to concerns of spread of the disease to others and these lead to the multifactorial delirium.
- A secondary mode of infection by which COVID-19 infection affects the CNS function is the viral-induced immune reaction and immune response of the body. This can occur both during and after the spell of acute infection. Though the virus is not commonly seen in the cerebrospinal fluid (CSF), but a viral-induced inflammatory response can lead to blood–brain barrier (BBB) dysfunction, resulting in immune cell infiltration and CNS tissue damage.[7]
- COVID-19 infection (SARS-CoV-2) induces coagulopathy, which results in the damage or failure of various organ systems. The viral invasion of vascular endothelium leads to activated thrombotic and inflammatory cascades during the hypercoagulable state, which can lead to cerebrovascular events.[7] Among the hospitalized patients due to COVID-19 infection, the most common neurological finding is that of stroke.[8]
- Apart from the three modes of action mentioned above, another direct mode of action on the CNS was also proposed though less common. Due to high prevalence of loss of taste and smell in these patients, it was thought that the COVID-19 infection directly affects CNS using the olfactory axonal migration. But later studies have confirmed that metabolic support to the olfactory sensory neurons was provided by the olfactory epithelial cells and these neurons were not directly involved in this mechanism.[9] Therefore, it is the BBB where the direct invasion of COVID-19 infection occurs, through (1) transcellular migration (host endothelial cells); (2) paracellular migration (through tight junctions); and (3) an immune system "Trojan Horse" cell passing through the BBB.[8]

NEUROPSYCHIATRIC COMPLICATIONS: ROLE OF ANGIOTENSIN-CONVERTING ENZYME 2 RECEPTORS

Cytokine storm builds up when the coronaviruses attach themselves to the angiotensin-converting enzyme 2 (ACE-2) receptors that are present in the respiratory epithelial

cells causing inflammation and this leads to multiple organ damage and immune-mediated encephalopathies such as delirium and convulsions. These ACE-2 enzymes are present in oronasal, respiratory, cardiovascular, and cerebrovascular and immune systems. SARS-CoV-2 can remain dormant in the neurons of patients recovering from COVID-19's acute effects, raising the likelihood of long-term repercussions by causing demyelination and neurodegeneration.[10]

CYTOKINE STORM AND ITS ROLE IN NEUROPATHOPHYSIOLOGY

The dysregulation of the cytokine network is linked to another pathogenic mechanism. It has been demonstrated that during cytokine storm, there is upregulation of proinflammation cytokines, such as interleukin 10 (IL-10), tumor necrosis factor α (TNF-α), IL-6, IL-2R, and CCL2 (C–C motif chemokine ligand 2).[11] Due to this, the organs already damaged by the COVID-19 infection continue to produce endogenous substances that are capable to generating chronic and systemic inflammation. Furthermore, the "cytokine storm" raises crucial questions concerning the degenerative chronicity of the CNS in particular, given that other neurodegenerative pathologies, such as Parkinson, Alzheimer, Huntington disease, and amyotrophic lateral sclerosis, are caused by a similar process. Since SARS-CoV-1 and MERS-CoV offer descriptions related with autoimmune neurodegenerative disorders,[11] highlight the heightened inflammatory reaction and its relationship with autoimmune mechanisms by COVID-19.

NEUROPSYCHIATRIC EFFECTS OF CORONAVIRUS INFECTION

Nonspecific Neurological Symptoms

Patients with COVID-19 may experience nonspecific neurological symptoms such as disorientation and headache.[12] Headache, myalgia, dizziness, and exhaustion are the most commonly reported nonspecific symptoms[13] found that 36.4% of COVID-19 patients admitted at the Hospital of Huazhong University of Science and Technology in Wuhan, China, showed neurological symptoms.

Delirium

Delirium, along with agitation and altered awareness, is the most common neuropsychiatric presentation in patients with COVID-19, with clinical expression in 65% of patients in the critical care unit.[6] With the growth in delirium rates as a sign of COVID-19, it is time to consider if mental status changes should be included in the test criteria. The pathophysiology of this mechanism is unknown; however, it could be a primary symptom induced by the virus infecting the nervous system, or a secondary manifestation caused by encephalopathy caused by inflammation or other virus-related systemic consequences.

Depression

COVID-19 infection results in a hyperinflammatory state marked by an elevation in C-reactive protein, ferritin, and IL-6 levels, which, despite being a transient state, is likely to be linked to psychiatric issues.[6] C-reactive protein, a peripheral inflammatory marker, was found to be linked with depressive symptoms in patients. Thus, it is discovered that COVID-19 patients suffer from psychological distress, and that inflammatory indicators are linked to the degree of depressive symptoms in these individuals.[14] Post-COVID depressive symptoms are more likely seen in females,[15] postinfection physical discomfort, severe infection,[15] elevated inflammatory markers,[14] and prior psychiatric illness.

Anxiety

Studies show that as dangerous infectious disease spreads, social levels of anxiety symptoms rise, such as the psychological load produced by SARS-CoV-1, in which a significant portion of the sample had anxiety problems. Hypochondriac fears and anxieties could be a contributing factor.[16] Fear and confusion regarding COVID-19 are among the many effects of the virus, and they can lead to diseases like anxiety. It has been observed that the pandemic has a greater impact on people who have previously experienced psychiatric illnesses, which could be linked to proinflammatory cytokines in these patients.

Post-traumatic Stress Disorder

With a prevalence of over 40% (postdischarge period of 1–6 months) prior coronavirus epidemics,[17] post-traumatic stress disorder (PTSD) was one of the most prevalent psychiatric illnesses diagnosed among SARS and MERS survivors. To date, the prevalence of PTSD in COVID-19 patients appears to range between 20 and 30%, while the prevalence of less precisely defined post-traumatic stress symptoms (PTSS) varies substantially.[18] Younger age, female gender,[18] requirement for intensive care unit (ICU)-level care,[18] and having a previous psychiatric history are the most common risk factors for PTSD/PTSS following SARS-CoV-2 infection found so far. Many risk variables for COVID-19 are also risk factors for PTSD, which is interesting. Patients with PTSD have higher incidence of obesity, diabetes, metabolic syndrome, cardiovascular illness, and autoimmune disease. Delirium and ICU-level treatment, which are both typical COVID-19 sequelae,[19] also are the risk factors for PTSD/PTSS, with >20% of critical care survivors reporting PTSS 12 months after discharge.

Psychosis

Higher incidences of psychosis have been recorded during many pandemics or epidemics since the 1918 Spanish influenza pandemic. An observational study from China found a 25% increase in psychotic illnesses early in the COVID-19 pandemic.[20] This link has been

linked to the pandemic's significant mental stress, but, as previously mentioned, more direct processes have also been suspected.[21] Although there is not enough information to define a typical COVID-19 psychotic presentation, considerable disorganization and confusional signs have been described.[22] COVID-19 therapy has been linked to the onset of psychosis. Chloroquine and hydroxychloroquine, which were once the cornerstones of COVID-19 treatment, have been linked to hallucinations and other psychotic symptoms.[22] Due to CYP3A4 suppression, this risk is increased in patients receiving lopinavir/ritonavir combination therapy.[23] High-dose corticosteroids, which are still one of the only effective therapies for severe COVID-19 infection, can elicit psychotic symptoms, which have also been reported in the context of viral disease therapy.

NEUROPSYCHIATRIC INTERVENTIONS

Unspecific Neurological Complications

Because several medications utilized as a therapeutic resource in normal settings can aggravate the acute respiratory crisis associated with COVID-19, treating individuals with neurological issues caused by SARS-CoV-2 necessitates extra vigilance. Immunosuppressive treatments for autoimmune neurological disorders and corticosteroid medications stand out among them.

Delirium

The majority of cases of delirium caused by the COVID-19 infection have been hyperactive or mixed variations with high levels of anxiety, which makes treatment more difficult. Low-potency antipsychotics, especially second-generation antipsychotics such as olanzapine and quetiapine, should be preferred in such circumstances. Furthermore, despite the lack of evidence to support the use of any therapies in COVID-19-related hyperactive delirium, most psychiatrists believe haloperidol to be the best agent for managing agitation in delusional patients.[24] Melatonin or melatonin receptor agonists (ARM) treatment has also been linked to a lower occurrence of delirium in studies. Melatonin, in this sense, should be considered a first-line medication for treating sleep-wake rhythm and awareness abnormalities, as well as reducing the usage of chemicals that can cause central respiratory depression, such as benzodiazepines.[25] As a result, health workers must adhere to local rules and regulations for the monitoring and management of delirium. It is also vital to implement simple delirium screening procedures, especially given the high workload during the COVID-19 crisis.

Depression

COVID-19 clinical management should always be careful, and this is the key. Immune modulation medicines, such as IL-6 inhibitors and melatonin, are being studied for the treatment of depression caused by infection-induced hyperinflammation, and other therapy, such as cytokine blocking medications and Janus kinase inhibitors (JAK), have also been suggested.[26]

Anxiety

COVID-19 patients with anxiety or panic symptoms, as well as breathing problems, may be evaluated and managed by a psychiatrist. Although the use of lower dosages of benzodiazepines may be suitable in some circumstances, it is crucial to note the risk of respiratory depression. As a result, clinicians must weigh the disadvantages and advantages of prescribing benzodiazepines to patients who have severe respiratory symptoms. Depending on the conditions and symptoms of each patient, other medications such as gabapentin, buspirone, hydroxyzine, or a low dose of selective serotonin reuptake inhibitors (SSRIs) may be used. Other nonpharmacological and psychological therapies, such as psychotherapy, should also be investigated.[24]

Post-traumatic Stress Disorder

While there is evidence to support the use of the serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine and selective serotonin reuptake inhibitors (SSRIs) for PTSD in medically sick patients, possible dangers should be carefully considered on a case-by-case basis. The α-1 receptor blocker prazosin has been demonstrated in several studies to reduce nightmare frequency and intensity, as well as improve other PTSD symptoms in patients.[27] Although limited Internet connection and poor health state in many afflicted patients make in-person psychological interventions preferable when available, there is some evidence that psychoeducational services delivered online to COVID-19 survivors with PTSS have been effective. Supportive counselling, resilience training, and psychological first aid have some evidence in treating PTSD. Exposure-based cognitive behavioral treatment (CBT) has the highest level of evidence in persons with PTSD.

Psychosis

Patients hospitalized for severe COVID-19 may present to primary care settings on antipsychotics that were started during the acute period,[21] and patients hospitalized for severe COVID-19 may present to primary care settings on antipsychotics that were started during the acute period.[22] It is crucial to remember that antipsychotics can cause QT prolongation and Torsades de Pointes, especially when used with other QT prolonging drugs (e.g., azithromycin). Furthermore, COVID-19 infection is proarrhythmogenic in and of itself.

CONCLUSION

The severe acute respiratory syndrome is primarily responsible for the clinical deterioration of COVID-19 infection;

nevertheless, understanding the atypical consequences, particularly psychiatric and neuropsychiatric ones, is critical for mitigating the direct and indirect effects of this pandemic event. Depression, anxiety, post-traumatic stress disorder, psychosis, nonspecific neurological symptoms, delirium, and cerebrovascular problems, were the most common mental and neuropsychiatric consequences. Acute respiratory disorders can cause mental and neuropsychiatric symptoms during or after the infectious period. As a result, therapeutic intervention, both pharmacological and nonpharmacological, is required in the treatment of such illnesses; nonetheless, it is still vital to monitor the psychological effects of the medications used to treat COVID-19. Healthcare practitioners will be able to plan proper healthcare delivery and allocate resources with the use of robust neuropsychiatric and cognitive monitoring. For many COVID-19 survivors, early intervention for emergent cognitive deficits will be important for independent functioning and enhanced quality of life.

REFERENCES

1. Kępińska AP, Iyegbe CO, Vernon AC, Yolken R, Murray RM, Pollak TA. Schizophrenia and influenza at the centenary of the 1918-1919 Spanish influenza pandemic: mechanisms of psychosis risk. Front Psychiatry. 2020;11:72.
2. Butler M, Watson C, Rooney A, Badenoch J, Cross B, Butler M, et al. The neurology and neuropsychiatry of covid-19. BMJ Opinion. 2020;92(9).
3. Asmundson GJG, Taylor S. Coronaphobia: Fear and the 2019-nCoV outbreak. J Anxiety Disord. 2020;70:102196.
4. Jones C, Humphris GM, Griffiths RD. Psychological morbidity following critical illness-the rationale for care after intensive care. Clinical Intensive Care. 1998;9(5):199-205.
5. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020;77(6):683-90.
6. Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry. 2020;7(7):611-27.
7. Achar A, Ghosh C. COVID-19-Associated neurological disorders: the potential route of CNS invasion and blood-brain barrier relevance. Cells. 2020;9(11):2360.
8. Jain R, Young M, Dogra S, Kennedy H, Nguyen V, Jones S, et al. COVID-19 related neuroimaging findings: a signal of thromboembolic complications and a strong prognostic marker of poor patient outcome. J Neurol Sci. 2020;414:116923.
9. Gupta K, Mohanty SK, Mittal A, Kalra S, Kumar S, Mishra T, et al. The Cellular basis of loss of smell in 2019-nCoV-infected individuals. Briefings in bioinformatics. 2021;22(2):873-81.
10. Lippi A, Domingues R, Setz C, Outeiro TF, Krisko A. SARS-CoV-2: at the crossroad between aging and neurodegeneration. Mov Disord. 2020;35(5):716.
11. Troyer EA, Kohn JN, Hong S. Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. Brain Behav Immun. 2020;87:34-9.
12. Asadi-Pooya AA, Simani L. Central nervous system manifestations of COVID-19: a systematic review. J Neurol Sci. 2020;413:116832.
13. Carod-Artal FJ. Complicaciones neurológicas por coronavirus y COVID-19. Rev Neurol. 2020;70(9):311-22.
14. Guo Q, Zheng Y, Shi J, Wang J, Li G, Li C, et al. Immediate psychological distress in quarantined patients with COVID-19 and its association with peripheral inflammation: a mixed-method study. Brain Behav Immun. 2020;88:17-27.
15. Ma Y-F, Li W, Deng H-B, Wang L, Wang Y, Wang P-H, et al. Prevalence of depression and its association with quality of life in clinically stable patients with COVID-19. J Affect Disord Elsevier. 2020;275:145-8.
16. Furer P, Walker JR, Chartier MJ, Stein MB. Hypochondriacal concerns and somatization in panic disorder. Depress Anxiety. 1997;6(2):78-85.
17. Han RH, Schmidt MN, Waits WM, Bell AK, Miller TL. Planning for mental health needs during COVID-19. Curr Psychiatry Rep. 2020;22(12):1-0.
18. Halpin SJ, McIvor C, Whyatt G, Adams A, Harvey O, McLean L, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. J Med Virol. 2021;93(2):1013-22.
19. Garcez FB, Aliberti MJ, Poco PC, Hiratsuka M, Takahashi SF, Coelho VA, et al. Delirium and adverse outcomes in hospitalized patients with COVID-19. J Am Geriatr Soc. 2020;68(11):2440-6.
20. Hu W, Su L, Qiao J, Zhu J, Zhou Y. COVID-19 outbreak increased risk of schizophrenia in aged adults. Chinaxiv. [online] Available from: https://www.clinicaltmssociety.org/system/files/2020.02.29-chinaxiv-covid-19-outbreak-increased-risk-of-schizophrenia-in-aged-adults.pdf. [Last accessed March 2022].
21. Brown E, Gray R, Monaco SL, O'Donoghue B, Nelson B, Thompson A, et al. The potential impact of COVID-19 on psychosis: a rapid review of contemporary epidemic and pandemic research. Schizophr Res. 2020;222:79-87.
22. Parra A, Juanes A, Losada CP, Álvarez-Sesmero S, Santana VD, Martí I, et al. Psychotic symptoms in COVID-19 patients. A retrospective descriptive study. Psychiatry Res. 2020;291:113254.
23. Mascolo A, Berrino PM, Gareri P, Castagna A, Capuano A, Manzo C, et al. Neuropsychiatric clinical manifestations in elderly patients treated with hydroxychloroquine: a review article. Inflammopharmacology. 2018;26(5):1141-9.
24. Bilbul M, Paparone P, Kim AM, Mutalik S, Ernst CL. Psychopharmacology of COVID-19. Psychosomatics. 2020;61(5):411-27.
25. Zambrelli E, Canevini M, Gambini O, D'Agostino A. Delirium and sleep disturbances in COVID-19: a possible role for melatonin in hospitalized patients? Sleep Med. 2020;70:111.
26. Ferrando SJ, Klepacz L, Lynch S, Tavakkoli M, Dornbush R, Baharani R, et al. COVID-19 psychosis: A potential new neuropsychiatric condition triggered by novel coronavirus infection and the inflammatory response? Psychosomatics. 2020;61(5):551-5.
27. Raskind MA, Peskind ER, Chow B, Harris C, Davis-Karim A, Holmes HA, et al. Trial of prazosin for post-traumatic stress disorder in military veterans. N Engl J Med 2018;378(6):507-17.

CHAPTER 141

Constipation and Diarrhea in COVID Patients: Management

Mansi Dandnaik, Ripal Patel Shah, Tejash Parikh

INTRODUCTION

Constipation is a major problem among bedridden patients. The prevalence of constipation in severe COVID-19 patients is estimated to be at least one in three patients. Immobility and medications are more important risk factors than COVID-19 itself. It becomes very important to identify and address this issue not only for patient comfort but for patient safety. Constipated patient can never be happy and concentrate on breathing. Further uncorrected constipation leads to respiratory distress.

Similarly, diarrhea is also seen in as much as 30% of the patients of COVID-19 as it is seen in other viral illnesses. It is usually self-limiting but antiviral helps in early resolution. Diarrhea is also disastrous for a breathless patient and it adds to overall morbidity. Overuse of laxatives, antibiotic-associated diarrhea (*Clostridioides difficile*), and cytomegalovirus (CMV) colitis are not unusual causes of diarrhea in patients who are sick enough to require either mechanical ventilation or extracorporeal membrane oxygenator.

CONSTIPATION IN COVID PATIENTS

The routine definition of constipation includes objective parameters such as less than three stool frequency per week, requires manual maneuvers to clear bowel, and subjective like straining while passing, hard stools, or incomplete bowel movement, etc. In critically ill individuals, subjective symptoms are difficult to assess so have to decide on the absence of defecation, the described time duration differs among studies. In view of inconclusive definition, European Intensive Care Medicine Society recommends to use the term "paralysis of the lower gastrointestinal tract" instead of "constipation." They defined this as "the inability of the bowel to pass stool due to impaired peristalsis" and suggested that clinically absence of stool for 3 or more days in the absence of mechanical obstruction irrespective of bowel sounds.[1]

Incidence of constipation in critically ill varies from 5 to 90% in various studies depending on study population and criteria used for defining constipation. More sick patients those requiring mechanical ventilation has higher incidence. Underlying etiology responsible for intensive care admission also impacts the incidence. Similar experiences related to bowel hypomotility are being reported from COVID care centers.

Nearly half of the COVID-19 patients had gastrointestinal (GI) symptoms on hospital presentation which includes diarrhea, vomiting, abdominal pain, etc. Among all hospitalized individuals with COVID-19, nearly 74% had at least one GI complication which includes hepatobiliary, hypomotility, bowel ischemia, and others. Hypomotility of the gut is seen more commonly with severe COVID-related illness. Gastric feeding intolerance for >24 hours, clinical and/or radiological ileus was seen in 46.2 and 55.8% patients, respectively.

Various hypotheses proposed for hypomotility issues related to COVID-19 which includes:

- Pharmacological adverse events, e.g., opioids as cough suppressant and sedation, and neuromuscular blocking agents
- Metabolic and electrolyte disorders, e.g., hyperglycemia, hypokalemia, and hypoxia
- Corona virus-induced small vessel thrombosis
- Viral enter neuropathy
- Critical illness, e.g., sepsis, use of vasopressor agents.

Clinical Impact

Impact from constipation varies from mild abdominal distention to increasing mortality and ventilator days **(Box 1)**. There are various studies suggesting days from early first passage of stool early (<6 days) compared to late is associated with reduced bacterial intensive care unit (ICU)-acquired infections.[2]

Management

The potential issues related to constipation described above, appropriate and early management of constipation should be done.

BOX 1: Possible complications associated with constipation in intensive care unit (ICU) patients.

- Abdominal distention and discomfort
- Delayed gastric emptying and intolerance to enteral feeding
- Vomiting
- Increased intra-abdominal pressure
- Colonic pseudo-obstruction
- Intestinal ischemia or perforation
- Pulmonary aspiration
- Bacterial translocation and overgrowth
- Prolonged mechanical ventilation and ICU length of stay

- Treating the underlying cause
- Treating constipation (1) laxatives and enemas and (2) neostigmine
- Prophylaxis for constipation.

TABLE 1: Laxative classification.

Types of laxative	*Example*	*Description*
Stool softener	Docusate sodium	Reduce the surface tension of the oil–water interface of the stool, allowing incorporation of water and fat into the stools with resultant softening
Bulking agents	Bran	Increase stool bulk and frequency
Stimulant laxative	Senna	Increase water and electrolyte secretion by the intestinal mucosa and stimulate peristalsis
Osmotic laxatives	Lactulose and polyethylene glycol (PEG)	Poorly absorbed by the gut and act as hyperosmolar agents, increasing the water content of stool and making the stool softer

Treating the Underlying Cause

Detailed physical examination, reviewing drug history, and laboratory and imaging modalities, sometimes even endoscopy are required to confirm the etiology for constipation. Primary purpose of the workup is to rule out mechanical obstruction and acute colonic pseudo-obstruction (Ogilvie syndrome). Electrolyte imbalances should be corrected and fluid therapy to be optimized. COVID-related treatment sometime has strong cough suppressant including ethylmorphine or codeine-like opioids. Sedation and analgesia in ICU patients do receive fentanyl, morphine, etc. If possible withdraw opioids and add laxatives. If not possible to withdraw completely than selective opioids receptors antagonist such as methyl naltrexone which does not cross blood–brain barrier should be given. Another recently proposed alternative, lubiprostone, is a selectively activated chloride channel-2. It acts locally in the small bowel which improves gut motility and increases fluid secretion.[3,4]

Laxatives and Enemas

Two types of management options for constipation are available commonly, oral laxatives and enemas or suppositories. Oral laxatives are again further divided into stool softeners, bulking agents, stimulant, and osmotic laxatives **(Table 1)**. The preference of laxative is usually a matter of personal choice and availability due to hardly any published recommendation for critically ill population. Lactulose is most widely used. Recommendation is to start with dose of 10 mL two times a day and then increase it up to maximum of 20 mL thrice daily. Lactulose can produce intestinal gases in some patients which can cause uncomfortable bloating. Senna (10 mL/day) and polyethylene glycol (PEG) are other common alternatives. Van der et al.[5] compared different laxative administration which included PEG, lactulose, or placebo in critically ill patients with mechanical ventilation, multiorgan dysfunction on circulatory support, and who had not passed stool by day 3 postadmission. They concluded that PEG and lactulose were more efficient in causing early defecation than placebo. Lactulose found to be associated with increased incidence of acute intestinal pseudo-obstruction, possible explanation is due to increased gas production. PEG appeared to be more efficient than lactulose particularly for patients on opioids.[5] Enemas are usually preferred for those patients who do not have optimum response to orally administered laxatives.

Neostigmine

Neostigmine, an acetyl cholinesterase inhibitor, should be considered to promote gut motility and increase peristalsis for severe functional colonic pseudo-obstruction once other correctable causes ruled out. There are studies available showing the effectiveness of neostigmine in such scenario, which includes the study by Ponec et al.[6] In that study, 21 patients with acute colonic pseudo-obstruction with no improvement postconservative treatment for 24 hours were included and randomized to receive intravenous saline or single-dose intravenous 2 mg neostigmine. 10 of the 11 patients which means almost all who received neostigmine had rapid passage of stool or flatus, with rapid response in just 4 minutes, as compared none in placebo group. Another study of 24 multiple organ failure patients with mechanical ventilation was done by Van der Spoel et al.[7] In the particular study, colonic ileus is related to critically ill patients randomized to placebo versus a continuous infusion of neostigmine intravenously in dose of 0.4–0.8 mg/h over 24 hours. This also showed good response with 11 out of 13 patients in neostigmine group passed stools, compared to none in placebo group (p <0.001). Major concern with neostigmine use is low heart rate and rarely reported cardiac

arrest so care should be taken. Atropine or glycopyrrolate are to be given either as premedication or as treatment in patients with poor cardiocirculatory reserve. Colonic perforation is also a rare association with neostigmine.

SUGGESTED APPROACH FOR PREVENTING AND TREATING CRITICALLY ILL PATIENTS

On admission:

- Take relevant history of usual bowel movement routine—daily, weekly, etc.
- Inquire about time of last stool (when possible)
- If patient already taking laxative medication
- Underlying bowel disease (inflammatory bowel disease, IBS…)
- Identify possible risk factors (prolonged immobilization, opiate use…)
- Prescribe preemptive laxative agents, specifically if patient already taking laxatives prior to hospitalization or in case of risk factors.

If no bowel movement within 24 hours postadmission:

- Correct abnormal electrolyte
- Ensure adequate hydration
- Evaluate and try to omit opiate and other "constipating" drugs
- Rectal and abdominal examination for nature and presence of stools if required disimpact
- Patient if not on laxative than start lactulose, PEG, docusate, senna, etc…and if taking then increase the dose
- Re-evaluate daily if no movement, then add a second agent. If there is no bowel movement after 24 hours, redo rectal examination and give enema.
- Do X-ray of the abdomen to rule out pseudo-obstruction or ileus impaction…

COVID-19 AND DIARRHEA

Epidemiology of COVID-19-associated Diarrhea

Whole world is facing pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2/COVID-19). COVID-19 patients have a wide range of symptoms outlined from mild symptoms to severe illness. Symptoms may present within 2–14 days with the exposure to the corona family virus. Any patient can have mild-to-severe symptoms. People present with fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, diarrhea, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting. COVID-19 affects different people in different ways. Most infected people will recover without hospitalization. Some of the patients will become severely ill and require urgent medical attention and treatment. Geriatric people and those with underlying clinical conditions such as coronary artery disease, diabetes mellitus, chronic respiratory disease, or cancers are prone to develop consequential diseases. Any individual can get illness with COVID-19 and become seriously ill or die at any age.[8]

Diarrhea is a common symptom with varying frequency in COVID-19 patients. A diarrhea incidence among various studies was found to be between 3.8 and 37.1% of cases.[9]

Initially found in a small percentage of cases, an increasing number of patients present with diarrhea. Diarrhea was detected in up to 30% of patients with MERS-CoV and 10.6% of patients with SARS-CoV symptoms may have COVID-19.[10]

Diseases caused by coronavirus family have the respiratory system symptoms along with intestinal involvement and development of diarrhea without blood or mucus.[3] In 2003, study conducted at Hong Kong evaluated the gastrointestinal symptoms of patients with SARS in Hong Kong in 2003.[11]

Pathophysiology

Involvement of intestine and diarrhea pathogenesis in COVID-19 are not entirely known, an alteration in intestinal porousness may occur in coronavirus infection, showed in enterocyte malabsorption. Also intestinal angiotensin-converting enzyme 2 (ACE2) is necessary for taking up of dietary amino acids, modulating antimicrobial peptides expression and gut microbiome homeostasis development. Accordingly to Mouse models, colitis was correlated with the presence of ACE2 alterations, that suggests that coronavirus actions may do enzyme alteration and responsible for development of the susceptibility to intestinal inflammation and diarrhea. The intestinal epithelium is in direct contact with exogenous microbes and coronavirus affects first small intestinal epithelial cell. Diarrhea may be the vital sign of corona infection and clinical manifestation.[12,13]

Gut microbiota **(Fig. 1)** affects both lungs through an important cross talk between these microbiota and lungs which is known as the "gut-lung-axis." This axis between microbiota and lungs is expected to be bidirectional which means microbial metabolite can results the pulmonary health (lungs) and the gut microbiota may be affected with inflammatory reaction in the lung.[14]

Various research studies showed that in COVID-19-infected excreta sample, viral nucleic acid is detected even after being cleared from respiratory airways of patients, but persistence in excreta of COVID-19 patients was not known yet.[9]

Prevention and Management of Diarrhea in COVID-19

Based on etiopathogenesis of diarrhea and on the important role of enzyme (ACE2), the use of ACE or angiotensin receptor blockers should be researched first, mainly in elder

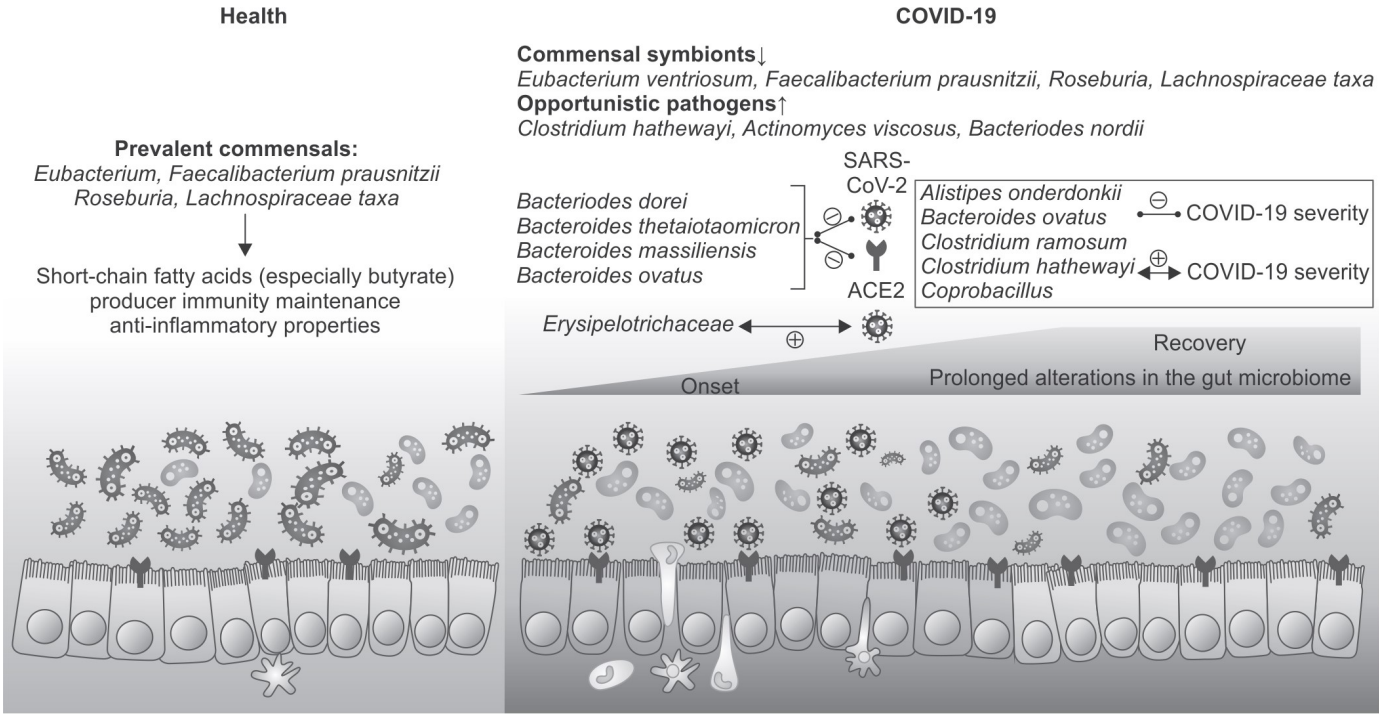


Fig. 1: The gut microbiome alterations in COVID-19.[15]

age group or patients having coronary vascular diseases, as it may lead to a great risk of developing diarrhea among COVID-19 patients.[15]

Presently, there is no specific drug and treatment for COVID-19 and its management is mainly symptomatic as a supportive care. There is no evidence available on the efficacy of antidiarrheal drugs across the globe, but with the fluids, an adequate rehydration can be maintained in all COVID-19 patients having diarrhea and monitoring of electrolyte (potassium) should be performed.[10]

Antibiotics (azithromycin) and antivirals (remdesivir) are often used for COVID-19 treatment, involving a likely alteration of the gut microbiota and causing diarrhea. The gut microbiota could be a newer therapeutic agent and that probiotics could have a role in the treatment and management of COVID-19 patients.[10]

A quick improvement in diarrhea among COVDI-19 patients has been seen after initiating treatment of antiviral drugs.[16] No any antiviral therapy is specifically made for the management of diarrhea in COVID-19, various molecules could have successful outcome. Some monoclonal antibodies have the role of inhibiting the contact between the virus and ACE2 through receptor-binding domain of the spike protein.[17] In addition to that, a TMPRSS2 inhibitor approved for clinical use and might constitute a vital role as treatment option.[18] Commercial approved serine protease inhibitor (camostat mesylate), a recognized effective inhibitor of TMPRSS2, and is in use in many countries such as Japan for the management of noninfectious conditions such as chronic pancreatitis and reflux esophagitis.[19]

The identified coronavirus in the stool sample and its long fecal persistence from days to months suggest that orofecal transmission may be possible directly from person to person, leading to several implications and requiring further standard precautions for preventing the disease. There should be avoidance of contact with possible sources of contamination like saliva, vomiting, and feces through practicing proper hygiene.[10] There should be modified plan of management for outpatient. Deferrable gastroenterological conditions and endoscopic procedures which are not urgently required should be postponed and according to the existing symptoms or based on possible exposure to COVID-19 infected patients or illness originating from high-risk areas of transmission, every patient should be stratified.[10]

In conclusion, COVID-19 patients may develop various gastrointestinal symptoms mainly diarrhea. Early investigation and follow-up are required for these patients to reach out the diagnosis of COVID-19 disease.

CONCLUSION

Motility-related gastrointestinal issues are very common daily issues not just for COVID patients but all critically ill patients. There are very few published data to guide real incidence and impact on clinical practice. So both constipation and diarrhea need attention from clinician so that morbidity of the patient is minimized.

REFERENCES

1. Reintam Blaser A, Malbrain ML, Starkopf J, Fruhwald S, Jakob SM, De Waele J, et al. Gastrointestinal function in intensive care patients: Terminology, definitions and management. Recommendations of the ESICM Working Group on Abdominal Problems. Intensive Care Med. 2012;38(3): 384-94.
2. Gacouin A, Camus C, Gros A, Isslame S, Marque S, Lavoué S, et al. Constipation in long-term ventilated patients: Associated factors and impact on intensive care unit outcomes. Crit Care Med. 2010;38(10):1933-8.
3. Kumar L, Barker C, Emmanuel A. Opioid-induced constipation: Pathophysiology, clinical consequences, and management. Gastroenterol Res Pract. 2014;2014:141737.
4. Jamal MM, Adams AB, Jansen JP, Webster LR. A randomized, placebo-controlled trial of lubiprostone for opioid-induced constipation in chronic noncancer pain. Am J Gastroenterol 2015;110(5):725-32.
5. van der Spoel JI, Oudemans-van Straaten HM, Kuiper MA, van Roon EN, Zandstra DF, van der Voort PHJ, et al. Laxation of critically ill patients with lactulose or polyethylene glycol: A two-center randomized, double-blind, placebo-controlled trial. Crit Care Med. 2007;35(12):2726-31.
6. Ponec RJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. N Engl J Med. 1999;341(3):137-41.
7. van der Spoel JI, Oudemans-van Straaten HM, Stoutenbeek CP, Bosman RJ, Zandstra DF. Neostigmine resolves critical illness-related colonic ileus in intensive care patients with multiple organ failure—a prospective, double-blind, placebo-controlled trial. Intensive Care Med. 2001;27(5):822-7.
8. World Health Organization. Coronavirus n.d. [online] Available from: https://www.who.int/health-topics/coronavirus#tab=tab_1 [Last accessed March 2022].
9. Luo S, Zhang X, Xu H. Don't overlook digestive symptoms in patients with 2019 novel coronavirus disease (COVID-19). Clin Gastroenterol Hepatol. 2020;18(7):1636-7.
10. Kanwal F, D'amico F, Baumgart DC, Danese S, Peyrin-Biroulet L. Diarrhea during COVID-19 infection: Pathogenesis, epidemiology, prevention, and management. Clin Gastroenterol Hepatol. 2020;18(8):1663-72.
11. Leung WK, To K-F, Chan PKS, Chan HLY, Wu AKL, Lee N, et al. Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection. 2003;125(4):1011-7.
12. Hashimoto T, Perlot T, Rehman A, Trichereau J, Ishiguro H, Paolino M, et al. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. Nature. 2012;487:477-81.
13. Gu J, Han B, Wang J. COVID-19: Gastrointestinal manifestations and potential fecal–oral transmission. Gastroenterology. 2020;158(6):1518-9
14. El Hiba O, Radhakrishnan J, Balzano T, Isbaine F, (eds). Handbook of Research on Pathophysiology and Strategies for the Management of COVID-19 2022. Pennsylvania: IGI Global; 2022.
15. Zuo T, Zhang F, Lui GCY, Yeoh YK, Li AYL, Zhan H, et al. Alterations in gut microbiota of patients with COVID-19 during time of hospitalization. Gastroenterology. 2020;159(3):944-55.e8.
16. Song Y, Liu P, Shi XL, Chu YL, Zhang J, Xia J, et al. SARS-CoV-2 induced diarrhea as onset symptom in patient with COVID-19. Gut. 2020;69(6):1143-4.
17. Tian X, Li C, Huang A, Xia S, Lu S, Shi Z, et al. Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. Emerging Microbes & Infections. 2020;9(1):382-5.
18. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-80.e8.
19. Kawase M, Shirato K, van der Hoek L, Taguchi F, Matsuyama S. Simultaneous treatment of human bronchial epithelial cells with serine and cysteine protease inhibitors prevents severe acute respiratory syndrome coronavirus entry. J Virol. 2012;86(12):6537-45.

142

CHAPTER

Diabetic Ketoacidosis in COVID New Onset Patients

Banshi Saboo, Jigar Mehta, Subhajyoti Ghosh, Jothydev Kesavade

INTRODUCTION

Globally only 5% of known diabetes is diagnosed to be type 1 diabetes but the incidence is increasing at about 3% every year.[1] The studies have correlated that the severity of developing COVID-19 and related complications amongst the obese and diabetes is high.[2] Even the reports had documented COVID-19-induced severe metabolic decompensation as diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS), of which SARS-CoV-2 is characteristically linked with new onset of type 1 diabetes.[3] The past experience from severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) have taught the fact Coronavirus-mediated islet cell damage is not a novel phenomenon, may be because *Coronaviridae* family to inherited a genetic predisposition for islets cell damage.[4]

DIABETIC KETOACIDOSIS AND COVID

An important finding was high levels of inflammatory markers, same can be seen in DKA. Interleukin 6 (IL-6) has been highlighted as the main culprit for maladaptive immune response to the SARS-CoV-2 virus.[5] IL-6 is also elevated in DKA which hypothesized to be the driver of ketosis, but it is still a matter of debate.[6] The hormonal system responsible for maintaining blood pressure is called renin–angiotensin–aldosterone system (RAAS), which exerts its effect on vascular tone and aldosterone secretion. The RAAS is also found in the pancreas. The pancreatic cells express both angiotensin I and II receptor and prorenin genes.[7] **Figure 1** explains the role of amplification of angiotensin-converting enzyme 2 (ACE-2) at pancreatic islets and the kidney.[8]

Etiology and Pathogenesis of Type 1 Diabetes

Type 1 diabetes is an autoimmune condition executed through autoreactive $CD4^+$ and $CD8^+$ T cells lysis of β-cells. The regional differences are quite evident with known North–South gradient, having higher figures in northern latitudes showing the influence of environmental factors, hence seasonality in the new-onset type 1 diabetes mellitus (T1DM) has been linked with viral etiology.[9] The association of viral infections and T1DM is complex. The Mouse models reveal that while certain viruses could be harmful to the β-cells and begin autoimmunity, others could prove to be having both protective and preventive effects. Although one needs to stay cautious while extrapolating these findings to human subjects.[10]

Pathogenesis of β-cells Damage

Evidence of fulminant T1DM from Japan predominantly in adults had shown that to be preceded by minor upper respiratory or gastrointestinal infections mainly of viral etiology as mumps, human herpesvirus 6 (HHV6), Coxsackie B3, B4, herpes simplex virus (HSV), hepatitis A, influenza-B, and parainfluenza. This fulminant T1DM called as type 1 B diabetes, characterized by acute onset of ketoacidosis with very short (1 week) duration of osmotic symptoms, absence of islet-related autoantibodies, extremely low C-peptide levels, elevated serum pancreatic enzyme levels, and a HbA1c <8.5% on the first visit.[11,12]

Hence, it was stated that β-cell damage due to viral infection can be due to either:

- Direct lytic effects of viral replication
- Host inflammatory response-mediated damage by autoreactive CD^+ T cells, leading to autoimmunity **(Fig. 2)**.

The pathological processes for chronic β-cell damage are varied as:

- Molecular mimicry
- T-cell activation
- Chronic β-cell infection leading to major histocompatibility complex 1 (MHC-1) overexpression.

The Associated Viruses which may Cause β-cell Damage

The enterovirus infection has shown significant association with type 1 diabetes and related autoimmunity.[13] The TEDDY study (The Epidemiological Determinants of Diabetes

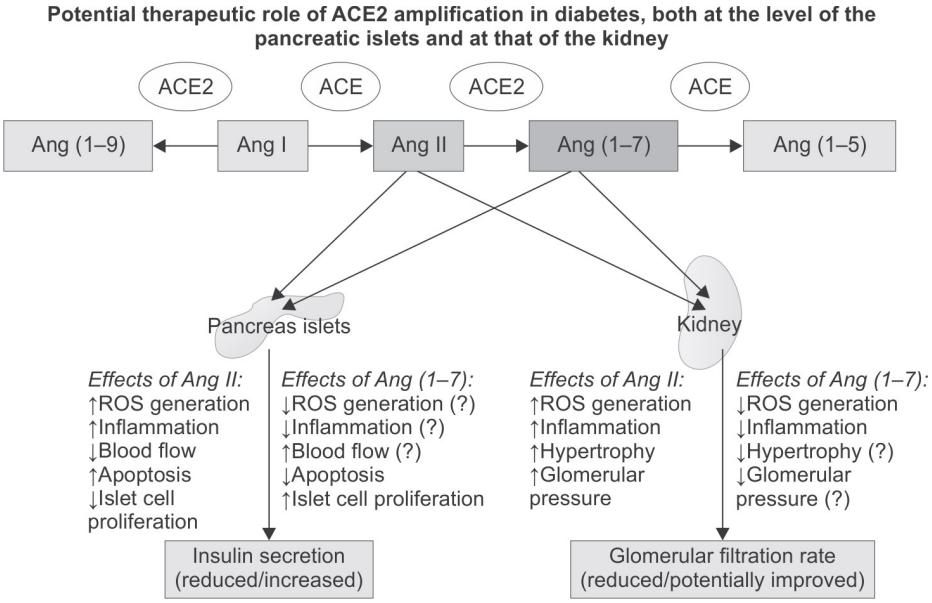


Fig. 1: Role of amplification of angiotensin-converting enzyme 2 (ACE-2) at pancreatic islets and the kidney.

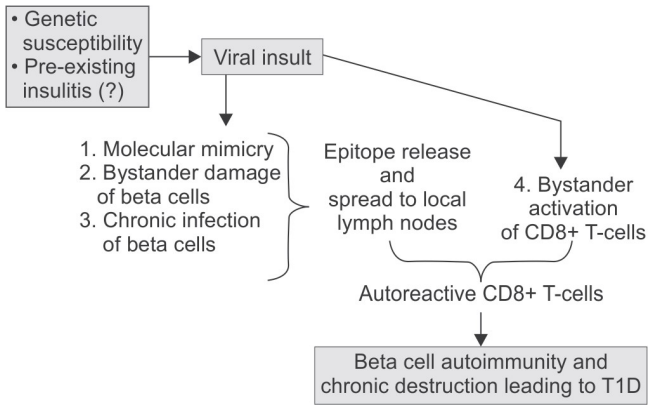


Fig. 2: Host inflammatory response-mediated damage by autoreactive CD+ T cells, leading to autoimmunity.
(Adapted from Boddu SK, Aurangabadkar G, Kuchay MS. New onset diabetes, type 1 diabetes and COVID-19. Diabetes Metab Syndr. 2020;14(6):2211-7)

in Young) confounded that several respiratory infection occurring till 9-month postnatal period is associated with subsequent risk of type 1 diabetes autoimmunity, and interestingly coronavirus was one of the identified pathogens. With due time and research, many viruses came to be associated with T1DM, especially listed as, *Enteroviruses* (especially Coxsackie B1, B4), mumps, cytomegalovirus (CMV), rubella, etc. Even studies had substantial data to contradict the relationship between β-cell autoimmunity due to viral origin.

EPIDEMIOLOGY OF DIABETIC KETOACIDOSIS: AN UPDATE

The data from US and the UK has reported that hospitalization from DKA had increased in the last decade.[14,15]

From 2000, two subtypes being identified are as follows:

1. *Ketosis-prone diabetes*: Recognized from early 2000s amongst type 2 diabetes mellitus (T2DM) with obesity presented in DKA, they had impaired insulin levels but still negative for T1DM autoimmune markers.[16]
2. *Euglycemic diabetic ketoacidosis (euDKA)*: This group accounts for up to 10% of DKA. It is characterized by metabolic acidosis along with increased total body ketone level, but having glucose levels ≤250 mg/dL.[17,18] It was first described by Munro et al. in 1972.

SARS CoV-1 and Diabetes

The studies had shown that ACE-2 is the functional receptor for both SARS-CoV-1 and SARS-CoV-2.[19] ACE-2 is mainly found abundantly in the lung and small intestine, hence becomes the routes of entry for the SARS-CoV-1 and SARS-CoV-2.[20] Studies during 2003 SARS-CoV-1 epidemic had documented that those who did not receive glucocorticoid medications for milder SARS symptoms even had raised fasting blood sugar (FBS) which in turn was an independent predictor of higher mortality and morbidity.[21] During the follow-up in 2010 for investigating any pancreatic lesions, they were found to be strongly immune positive for ACE-2 in pancreatic islets but only weakly positive for exocrine pancreases. Insulin-dependent diabetes was observed in 20 of the 39 patients (age: 47.2 ± 2.2 years) during hospitalization. At 3 years of follow-up, two still persisted with diabetes, hypothesizing that the damage on β-cells can only be acute and transient in nature.

COVID-19 and Pancreatitis

There is no report or documented case of acute pancreatitis with the SARS-CoV-1 in 2003. However, during COVID-19,

SARS-CoV-2 had many cases documented of acute pancreatitis.[22] A researcher at Liverpool, UK observed that 10 out of 35 patients with acute pancreatitis during the period March/April 2020 were positive for SARS-CoV-2. 3 of the 10 had new-onset diabetes managed with insulin.[23]

COVID-19 and New-onset Diabetes

According to data from Hoffmann et al.[24] and Zhou et al.,[25] SARS-CoV-2 and SARS-CoV-1 use the same ACE-2 receptor. More intriguingly, recent reports show that newly diagnosed diabetes is commonly observed in COVID-19 patients.

The association between COVID-19 infections with new-onset hyperglycemia amongst people with no history of diabetes is increasing along with raised risk of mortality and morbidity. The phenomenon of infection leading to inflammation and cytokine storm resulting to insulin resistance and stress hyperglycemia is well known and that maybe a phenomenon resulting in hyperglycemia following COVID-19 infections.

During the recent pandemic of COVID-19 in Italy, those presented with more severe DKA was 44.3% in 2020 in compared with 36% in 2019 which was higher than 23% of annual cases of new childhood diabetes.[26] A similar observation was reported from Germany, i.e., twofold increase in DKA and severe ketoacidosis amongst children and adolescents during the pandemic of COVID-19 when diagnosis of diabetes was made, hence new-onset diabetes.[27]

A multicenter study had reported an increase in new-onset T1DM in children from UK, during COVID-19 pandemic. 21 out of 30 children presented with DKA of which 52% with severe DKA. Amongst them 2 of 21 tested positive for SARS-CoV-2 and 3 of 16 tested positive for SARS-CoV-2 antibody [immunoglobulin G (IgG)].[3]

The conclusion from meta-analysis by Sathish et al. where >3,700 patients from eight studies had shown a pooled proportion of 14.4% for newly diagnosed diabetes amongst patients hospitalized for COVID-19.

Euglycemic Diabetic Ketoacidosis

During the COVID-19 pandemic, a cluster of cases and reports of euglycemic DKA was reported across the globe. Especially in those presenting were mainly on sodium-glucose cotransporter 2 inhibitors (SGLT2i) where presenting blood glucose level <300 mg/dL, later they were managed with intravenous (IV) insulin infusion to treat DKA.

A case was reported by Oriot and Hermans about euDKA in T1DM patient with SARS-CoV-2 pneumonia.[28] Li et al. suggest that COVID-19 might accelerate fat breakdown and induce ketosis, with further development of ketoacidosis.[29] Overall, the mechanisms linking COVID-19 with ketosis, ketoacidosis, or DKA need further research.

IMPACT OF COVID-19 AMONGST YOUTH AND PEDIATRICS

The impact of COVID-19 on diabetes is mainly adult centric, but impact of the same on pediatric diabetes still remains an ambiguous area. According to Chao et al., as quoted *"Spike in Diabetic Ketoacidosis Rates in Pediatric Type 2 Diabetes during the COVID-19 Pandemic."* They observed persistently increase in trend of new-onset type 2 diabetes cases for three consecutive years during the same 6 months of the year. During the same pandemic period, a spike in DKA is noted mainly among new-onset diabetes. Interestingly none had active SARS-CoV-2 infection, of which two new-onset diabetes were serology positive (IgG) for SARS-CoV-2.[30]

CONSIDERATIONS IN THE GENERAL MANAGEMENT OF DIABETIC KETOACIDOSIS

The main tenets of DKA management have not changed in decades and include the triad of *fluid resuscitation*, *potassium repletion*, and *insulin replacement.*

For fluid resuscitation, isotonic saline (0.9% NaCl) is often the preferred along with close monitoring and potassium repletion may be needed.

The major pitfalls of DKA treatment are as follows:[31]

- Inadequate potassium supplementation
- Failure to prevent hypoglycemia
- Recurrence of ketoacidosis due to ineffective transitioning from IV route to subcutaneous (SC) insulin therapy.

Management of euDKA is similar to classical DKA, but only difference is that dextrose-containing fluids may be required as an *initial step* during fluid resuscitation rather than adding later during when level of glucose declines. The other point is that glycosuria may last for days if DKA is due to SGLT2i use,[32] hence there may be extended phase of fluid resuscitation.

Assessing Diabetic Ketoacidosis Severity

The American Diabetes Association (ADA) classification is shown in **Table 1**.

Management of Uncomplicated Diabetic Ketoacidosis in Patient with COVID-19

Diabetic Ketoacidosis Management at Home

The point-of-care ketones testing kit is imprecise,[33] hence any patient having raised ketones should be looked for other signs of DKA. If clinically stable and taking oral fluids, should consult their care team. However, any patient with rapid decline in clinical parameter be urgently referred to nearby health facilities.

TABLE 1: Classification of hyperglycemic crisis severity and insulin treatment options.

	Mild DKA	*Moderate DKA*	*Severe DKA*	*HHS*	*HONK*
Blood glucose mg/dL (mmol/L)	>250 (>13.8)	>250 (>13.8)	>250 (>13.8)	>600 (>33.3)	>600 (>33.3)
pH	7.25–7.30	7.00–7.24	<7.00	>7.30	
HCO_2 (mmol/L)	15–18	10–14	<10	>18	
Urine/serum ketones	+	+	±	±	+
Serum osmolality (Osm_{eff})				320	320
Anion gap	Elevated	Elevated	Elevated	Elevated	Elevated
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma	Stupor/coma
Insulin therapy	SC/IV	SC/IV	IV	IV	IV
Frequency of glucose monitoring	every 1–2 hours	every 1–2 hours	every 1 hour	every 1 hour	every 1 hour
Location of care	Intermediate care unit	Intermediate care unit/ICU	ICU	ICU	ICU

(DKA: diabetic ketoacidosis; HCO_2: bicarbonate; ICU: intensive care unit; IV: intravenous; Na^+, sodium; SC: subcutaneous ; HHS: hyperglycemic hyperosmolar syndrome; HONK: hyperosmolar nonketotic coma)

Role of Subcutaneous Insulin Use in Diabetic Ketoacidosis

In context of pandemic along with available evidence, SC insulin therapy proves to be useful for mild/moderate uncomplicated DKA. From the Cochrane review (2016) assessing IV insulin versus SC rapid-acting insulin protocol found that the effects of SC versus IV insulin (rapid-acting insulin analogues) are comparable for treating mild or moderate DKA.[34]

Summary of SC insulin randomized controlled trials (RCTs) in DKA and potential strategies in COVID-19 is given in **Table 2**.

One study was assessing the impact of adding early basal insulin within the first 12 hours at the dose of 0.25 unit/kg. The authors observed reduction in rebound hyperglycemia [33.3% in the intervention group versus 93.5% in the control ($P < .001$)].

Even though SC protocol is useful but still not recommended for:

- Severe DKA
- Other complicated illness (end-stage renal disease, severe AKI, pregnancy, concomitant myocardial infarction, or stroke)
- Any patients requiring intensive care unit (ICU) care for mechanical ventilation and/or vasopressor support.

Management of Severe and/or Complicated Diabetic Ketoacidosis in Patients with COVID-19

Any patients presented with severe DKA should be managed in an ICU with IV access for fluid resuscitation along with SCII along with frequent monitoring of either venous blood or capillary glucose (e.g., every 1–2 hours). Also frequent monitoring for potassium and electrolytes to be done. The respiratory support and cardiac monitoring may be needed. The insulin requirement may be as high as needs 4 units/kg/day with critically ill patients with COVID-19.[35] The concomitant usage of corticosteroids and/or vasopressors also had an impact insulin requirement.[17]

The resolution from DKA leads to rapid increase in insulin sensitivity, mainly in severe DKA. Hence, insulin rate should adjust hourly.

PREVENTION OF DIABETIC KETOACIDOSIS DURING COVID-19

It is been observed that majority of people with diabetes and COVID-19 infection may not require hospitalization. The self-care of these categories of patient includes continuing insulin at home insulin and to reassess their oral hypoglycemic agent (OHA), especially those taking SGLT2i.

Most of the professional societies are doing advocacy to follow "sick day rules" which include at least 3-month supply of medications, all necessary supplies for insulin therapy and point-of-care ketones bodies (blood or urine) testing kit.[36]

Telemedicine is useful modality for adolescents in preventing DKA.[37]

Lastly, insulin initiation and proper behavioral change communication program should not be postponed during the pandemic. BCC can be achieved by either face to face counseling or, via video teleconferencing.

CONCLUSION

In this regard, the establishment of the CoviDiab Registry (covidiab.e-dendrite.com) 2 is timely and should provide valuable insights into issues regarding COVID-19-related diabetes. These pandemics provide us a classic example of a lethal intersection about the burden of a noncommunicable disease on communicable disease. Most of the DKA in T1DM is precipitated by omission of insulin, hence rationalization of insulin therapy is of paramount importance for which clinicians, clinical programs; along with insurers as well as manufacturers should come together with program for sustainable insulin regimens at an affordable cost.

TABLE 2: Summary of subcutaneous insulin randomized controlled trials (RCTs) in DKA and potential strategies in COVID-19.

	Population	***Intervention versus conventional IVI protocol***	***Outcomes measured***	***Key findings***	***Notes for use in COVID-19***
Della Manna et al. (2005)	Pediatric and adolescent patients with DKA (n = 60)	SC lispro 0.15 units/kg every 2 hours until BG <13.8 mmol/L (250 mg/dL) then interval increased to every 4 hours until resolution of DKA	Time to resolution of DKA	Both groups reached BG <13.8 mmol/L (<250 mg/dL) within 6 hours Metabolic acidosis and ketosis resolved faster in control group (IVI) 95% (57/60) patients were treated in ED and did not require admission	Every 2–4 hours insulin dosing outside of ICU was effective but slightly slower to resolution
Ersöz et al. (2006)	Patients with mild/moderate DKA (n = 20)	Single bolus injection of 0.15 U/kg IV regular insulin then 0.075 units/kg every 1 hour until resolution of DKA	Time to resolution of DKA, amount of insulin used, mortality, hypoglycemia rate	No differences between groups with respect to time of resolution of DKA, amount of insulin use, rate of hypoglycemia or mortality	Every 1 hour monitoring used in both groups
Hsia et al. (2012)	Patients with DM1 or DM2 (n = 61)	Glargine 0.25 units/kg within 12 hours of initiation of IV insulin	Rates of rebound hyperglycemia (BG >180 mg/dL) within 12 hours of discontinuation of IVI	• Rebound hyperglycemia 33.3% in intervention group versus 93.5% in control (P <0.001) • Average lower glucose levels in intervention group (P <0.01)	SC basal insulin during IVI can improve overall glucose control post-DKA; may reduce rebound DKA
Karoli et al. (2011)	Patients with mild/moderate DKA (n = 50)	SC lispro initially 0.3 units/kg, followed by 0.2 units/kg 1 hour later then subsequently treated with 0.2 unit/kg every 2 hours until BG <250 mg/dL, then dose reduced to 0.1 unit/kg every 1 hour	Duration of treatment and resolution of hyperglycemia and ketoacidosis *Other endpoints*: Total length of hospitalization, amount of insulin administration, hypoglycemia rate	• No difference in the mean duration of treatment and amount of insulin required for correction of hyperglycemia and ketoacidosis • No differences in mortality or LOS	Could be adapted to allow every 2 hour monitoring and dosing until DKA resolution
Umpierrez et al. (2004)	Patients with mild/moderate DKA (n = 45)	SC aspart every 1 hour or every 2 hours 1-hour group: Initial dose of 0.3 units/kg followed by 0.1 units/kg every 1 hour until BG <250 mg/dL dose reduced to 0.05 units/kg 2-hour group: Initial dose of 0.3 units/kg followed by 0.2 units/kg every 2 hours until BG <250 mg/dL dose reduced to 0.1 units/kg	Duration of treatment and resolution of hyperglycemia and ketoacidosis *Other endpoints*: Total length of hospitalization, amount of insulin administration, hypoglycemia rate	No difference in mean duration of treatment until resolution of hyperglycemia or ketoacidosis or rate of hypoglycemia between group	Every 2 hours dosing was safe and effective
Umpierrez et al. (2004)	Patients with uncomplicated DKA (n = 40)	SC lispro, managed on medicine ward (n = 10) or an intermediate care unit (n = 10) initial dose of 0.3 units/kg followed by 0.1 units/kg every 1 hour until BG <250 mg/dL dose reduced to 0.05 units/kg	Duration of treatment and resolution of hyperglycemia and ketoacidosis *Other endpoints*: Total length of hospitalization, amount of insulin administration, hypoglycemia rate	• No difference in mean duration of treatment until resolution of hyperglycemia or ketoacidosis or rate of hypoglycemia between group • Treatment in ICU was associated with 39% higher hospitalization charges than was treatment with subcutaneous lispro in a nonintensive care setting ($14,429 ± $5,243 vs. $8,801 ± $5,549, P <.01)	Medical ward can be a safe environment for intensive SC protocol though every 1 hour monitoring used in all groups

(DM1: diabetes mellitus type 1; DM2: diabetes mellitus type 2; DKA: diabetic ketoacidosis; LOS: length of stay IV: intravenous; IVI: intravenous insulin; SC: subcutaneous)

REFERENCES

1. DIAMOND Project Group. DIAMOND Project Group Incidence and trends of childhood type 1 diabetes worldwide 1990-1999. Diabet Med. 2006;23(8):857-66.
2. Docherty AB, Harrison EM, Green CA, Hardwick H, Pius R, Norman L, et al. Features of 16,749 hospitalised UK patients with COVID-19 using the ISARIC WHO clinical characterisation protocol. medRxiv. 2020.
3. Unsworth R, Wallace S, Oliver NS, Yeung S, Kshirsagar A, Naidu H, et al. New-onset type 1 diabetes in children during COVID-19: multicenter regional findings in the UK. Diabetes Care. 2020;43(11):e170-1.
4. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damage islets and cause diabetes. Acta Diabetol. 2010;47(3):193-9.
5. Chen X, Zhao B, Qu Y, Chen Y, Xiong J, Feng Y, et al. Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely correlated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. Clin Infect Dis. 2020:ciaa449.
6. Stentz FB, Umpierrez GE, Cuervo R, Kitabchi AE. Proinflammatory cytokines, markers of cardiovascular risks, oxidative stress, and lipid peroxidation in patients with hyperglycemic crises. Diabetes. 2004;53(8):2079-86.
7. Andraws R, Brown DL. Effect of inhibition of the renin-angiotensin system on development of type 2 diabetes melitus (meta-analysis of randomised trials). Am J Cardiol. 2007;99(7):1006-12.
8. Batlle B, Soler MJ, Ye MACE2 and diabetes: ACE of ACEs?. Diabetes. 2010;59(12):2994-96.
9. Filippi CM, von Herrath MG.. Viral trigger for type 1 diabetes: pros and cons. Diabetes. 2008;57(11):2863-71.
10. Coppieters KT, Boettler T, von Herrath M. Virus infections in type 1 diabetes. Cold Spring Harb Perspect Med. 2012;2(1):a007682.
11. Imagawa A, Hanafusa T, Miyagawa J, Matsuzawa Y. A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence of diabetes related antibodies. N Engl J Med. 2000;342(5):301-7.
12. Hwang YC, Jeong IK, Chon S, Oh S, Ahn KJ, Chung HY, et al. Fulminant Type 1 diabetes mellitus associated with acute hepatitis A. Diabet Med. 2010;27(3):366-7.
13. Yeung WC, Rawlinson WD, Craig ME. Enterovirus infection and type 1 diabetes mellitus: systematic review and meta-analysis of observational molecular studies. BMJ. 2011;342:d35.
14. Zhong VW, Juhaeri J, Mayer-Davis EJ. Trends in hospital admission for diabetic ketoacidosis in adults with type 1 and type 2 diabetes in England, 1998–2013: a retrospective cohort study. Diabetes care. 2018;41(9):1870-77.
15. Vellanki P, Umpierrez GE. Increasing hospitalizations for DKA: a need for prevention programs. Diabetes Care. 2018;41(9):1839-41.
16. Umpierrez GE. Ketosis-prone type 2 diabetes: time to revise the classification of diabetes. Diabetes Care. 2006;29(12):2755-57.
17. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, et al. American Association of Clinical Endocrinologists; American Diabetes Association. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care. 2009;32(6):1119-31.
18. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32(7):1335-43.
19. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003;426(6965):450-4.
20. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004. 2004;203(2):631-7.
21. Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med. 2006;23(6):623-8.
22. Jin X, Lian JS, Hu JH, Gao J, Zheng L, Zhang YM, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut. 2020;69:1002-9.
23. Szatmary P, Arora A, Raraty MGT, Dunne DFJ, Baron RD, Halloran CM. Emerging phenotype of SARS-CoV2 associated pancreatitis. Gastroenterology. 2020;159(4):1551-4.
24. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitors. Cell. 2020;181(2):271-80.
25. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science. 2020;367(6485):1444-8.
26. Rabbone I, Schiaffini R, Cherubini V, Maffeis C, Scaramuzza A; Diabetes Study Group of the Italian Society for Pediatric Endocrinology and Diabetes. Has COVID-19 delayed the diagnosis and worsened the presentation of type 1 diabetes in children? Diabetes Care. 2020;15(6):1377-81.
27. Basatemur E, Jones A, Peters M, Ramnarayan P. Paediatric critical care referrals of children with diabetic ketoacidosis during the COVID-19 pandemic. Arch Dis Child. 2020;106(4):e21.
28. Oriot P, Hermans MP. Euglycemic diabetic ketoacidosis in a patient with type 1 diabetes and SARS-CoV-2 pneumonia: case report and review of the literature. Acta Clin Belg. 2020;16:1-5.
29. Li J, Wang X, Chen J, Zuo X, Zhang H, Deng A. COVID-19 infection may cause ketosis and ketoacidosis. Diabetes Obes Metab. 2020;22(10):1935-41.
30. Chao LC, Vidmar AP, Georgia S. Spike in diabetic ketoacidosis rates in pediatric type 2 diabetes during the COVID-19 pandemic. Diabetes Care. 2021;44(6):1451-3.
31. Karajgikar ND, Manroa P, Acharya R, Codario RA, Reider JA, Donihi AC, et al. Addressing pitfalls in management of diabetic ketoacidosis with a standardized protocol. Endocr Pract. 2019;25(5):407-12.
32. Alhassan S, Rudoni M, Alfonso-Jaume MA, Jaume JC. Protracted glycosuria after discontinuation of sodium-glucose cotransporter 2 inhibitors: implications for weekly dosing and extended risk of euglycemic diabetes ketoacidosis. J Diabetes. 2019;11(5):410-1.
33. Misra S, Oliver NS. Utility of ketone measurement in the prevention, diagnosis and management of diabetic ketoacidosis. Diabet Med. 2015;32(1):14-23.
34. Andrade-Castellanos CA, Colunga-Lozano LE, Delgado-Figueroa N, Gonzalez-Padilla DA. Subcutaneous rapid-acting insulin analogues for diabetic ketoacidosis. Cochrane Database Syst Rev. 2016;(1):CD011281.
35. Korytkowski M, Antinori-Lent K, Drincic A, Hirsch IB, McDonnell ME, Rushakoff R, et al. A pragmatic approach to inpatient diabetes management during the COVID-19 pandemic. J Clin Endocrinol Metab. 2020;105(9):dgaa342.
36. Laffel LM, Limbert C, Phelan H, Virmani A, Wood J, Hofer SE. ISPAD Clinical Practice Consensus Guidelines 2018: Sick day management in children and adolescents with diabetes. Pediatr Diabetes. 2018;19(Suppl 27):193-204.
37. McDonnell ME. Telemedicine in complex diabetes management. Curr Diab Rep. 2018;11(3):42.

CHAPTER 143

Unexplained Deterioration in COVID-19 Patients

Amitkumar Prajapati, Harendra Thakker, Minesh Mehta

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a brand-new disease. It has changed our understanding of pathophysiology. Management is still an open debate with limited number of randomized controlled studies. Global connectivity has put the world population in danger. The highly contagious nature of the disease and asymptomatic carrier leads to a very high number of patients. An overwhelming influx of patients to hospitals, prolonged stay in the intensive care unit (ICU), high mortality, depleted resources, limited manpower, and multi-organ failure management has made it still more complicated.

While treating patients of COVID-19 in large numbers during this pandemic, we all have come across scenarios where we have seen unexplained deterioration in COVID patients. Sudden death of COVID-19 patients who looked all right before sometime have been noted by all treating clinicians. Apart from lungs, brain and heart must be focused on as the patient is suddenly crashing. It is their comorbid conditions that leads to rapid deterioration.

There are certain prehospitalization risk factors which have been found to be associated with sudden deterioration in COVID-19 patients:

- Age > 50 years
- Male
- Incubation period > 8 days
- Diabetes mellitus
- Hypertension
- Cardiovascular disease
- Cerebrovascular (CV) disease
- Chronic kidney disease
- Chronic obstructive pulmonary disease (COPD)
- History of cancer
- Dementia
- Organ transplant
- Chronic obstructive lung disease
- Sickle cell disease
- Immunocompromised status [human immunodeficiency virus (HIV), on steroid, etc.]
- Pregnancy

There are several studies which revealed that prognosis was worse in older patients with clinical symptoms such as fever (38.5°C) cough, and shortness of breath. Lymphopenia, neutrophil-lymphocyte ratio, and peak platelet/lymphocyte ratio may have prognostic value in serious disease. Elevated D-dimer, C-reactive protein (CRP), ferritin, and lactate dehydrogenase (LDH) levels have consistently been reported to be associated with severe disease.

Multicenter study in China involving 1,168 patients in 32 hospitals of moderate disease of COVID-19 was carried out to describe clinical characteristics of disease deterioration in moderate disease, time window, and risk factor for disease deterioration and order of organ damage when patient deteriorates. Of 1,168 patients, 148 (13%) deteriorated to severe (130) and critical (18). The median time for deterioration was 11 days after onset (range 9–14 days). Respiratory dysfunction and hypoxia were major manifestations as disease deteriorates. 52% of deteriorated patients had respiratory rate > 30 breaths per minute, 80% had SaO_2 < 93%, 67% had PaO_2/FiO_2 between 200 and 300, 19% had lactate level > 2 mmole/liter. In view of multiple organ dysfunction, 87% had acute respiratory distress syndrome (ARDS), 20% had acute kidney injury (AKI), 7% had coagulopathy, 9% had acute heart failure (AHF), 3–4% had acute hepatic injury (AHI), and 5.4% had shock. Organ injury occurred in the following sequence: ARDS, AKI, AHF, coagulopathy, AHI, and shock.

The most common cause of deterioration in COVID-19 patients is when severe COVID patients suddenly become breathless, tachypnic and hypoxic, and are later diagnosed with ARDS. It is common and is responsible as the main cause of death in COVID-19 patients. Incidence in different studies is found to be between 65 and 85% in severe COVID patients.

Pulmonary embolism is one of the common causes of unexplained deterioration in COVID patients. The incidence ranges between 2.6 and 8.9% hospitalized and up to one-third of those requiring ICU admissions, despite standard prophylaxis of anticoagulation.

Tertiary care hospital in Pakistan has reported 10 cases of surgical emphysema and pneumomediastinum in COVID-19 patients possibly due to risk of positive pressure ventilation and is found to be associated with poor outcome. Spontaneous pneumomediastinum in COVID-19 patients is seen without history of smoking and positive pressure ventilation. A unique feature of COVID-19 interstitial pneumonia is abrupt progression to respiratory failure. This abrupt deterioration may be caused by sudden shift in the spread of virus laden bioaerosols through the airways to many different regions of lungs from the initial site of infection, and is usually seen after 1 week of illness onset.

Sudden cardiac arrest (prehospital and in hospital) without any definitive cause is known in severe COVID-19 patients where prognosis is very poor.

Any unexplained hemodynamic failure with rise in cardiac biomarkers should make you suspect acute coronary syndrome/myocarditis/pericarditis with or without pericardial tamponade.

COVID-19-associated myocarditis is known and pathophysiology is thought to be due to a combination of virus injury and cardiac damage due to host immune response.

Similarly coronary artery disease may be due to hypoxia, inflammatory myocarditis, microvascular dysfunction or thrombosis due to hypercoagulability or systemic inflammation which destabilized coronary artery plaque.

Diabetic patients with moderate COVID, sometimes suddenly becomes tachypnic. While investigating many of these patients, they were found to have diabetic ketoacidosis possibly due to uncontrolled diabetes, use of steroids, and severe dehydration.

Invasive aspergillosis has been reported in moderate to severe ARDS. Incidence ranges around 10–11% of patients in ICU with mortality of >50%. COPD, use of steroid, and old age are possible risk factors.

Sudden loss of vision in COVID patients due to blocking of blood vessels, secondary herpes infection, and most commonly mucormycosis which was seen in large number of patients in second wave of COVID-19. Risk factors for mucormycosis were found to be uncontrolled diabetes, use of steroid, and immunosuppressive state because of various causes.

Many patients present with CV stroke (ischemic/hemorrhagic) and are later detected to be COVID-19 positive. In multicenter study of 8,163 patients of COVID, total 103, i.e., 1.3% patients developed acute ischemic stroke with high number of patients having hypertension, diabetes, hyperlipidemia, CHF (chronic heart failure), and AF (atrial fibrillation). These patients had high incidence of multisystem involvement and in hospital mortality.

Apart from CV stroke, many patients suddenly deteriorated with history of weakness in both lower limbs followed by respiratory failure and were later on diagnosed with demyelinating neuropathy GBS (Guillain-Barré syndrome). More than 220 patients of GBS have been reported so far in various studies.

Case report of young women presented with altered sensorium and random rhythmic movement of bilateral upper limb and lower limb having COVID-19 were later on diagnosed with meningoencephalitis.

Headache, dysgeusia, and anosmia have been reported as common nonspecific manifestations of COVID-19 infection.

Many COVID-19 patients had sudden hemodynamic instability with severe pallor and later on were found to have gastrointestinal (GI) bleeding. However, in 11,158 hospitalized patients of COVID-19, 314 patients (3%) had GI bleeding, but use of anticoagulant and antiplatelet agents were not associated with increased incidence of GI bleeding. Patients who had GI bleeding had increased in hospital mortality rate.

Few patients of COVID-19 had unexplained severe abdominal pain and were later on diagnosed with acute pancreatitis, however there is no definite correlation found between the COVID virus and pancreatitis.

CONCLUSION

Beyond the life-threatening pulmonary complications of severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), the widespread organ-specific manifestations of COVID-19 can cause sudden worsening of patients. One study states that in 10–35% of cases, the cause of mortality is unknown.

BIBLIOGRAPHY

1. Finsterer J, Scorza FA. GBS in 220 patients with Covid-19. Egypt J Neural Psychiatr Neurosurg. 2021;57(1):55.
2. Franki R. Comorbidities, the rule in New York's covid 19 deaths Hospitalist. 2020.
3. Hafizi F, Kherani S, ShamsM. Meningoencephalitis in SARS-CoV-2 infection. IDCases. 2020;21:e00919.
4. Mitaka H, Kuno T, Takagi H, Patrawalla P. Incidence and mortality of COVID-19-associated pulmonary aspergillosis: a systematic review and meta-analysis. Mycoses. 2021;64(9):993-1001.
5. Qu R, Ling Y, Zhang YH, Wei LY, Chen X, Li XM, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. J Med Virol. 2020;92(9):1533-41.
6. Selvaraj V. Dama sachetti Archives IMJ (August 2020).
7. Sethi SM, Ahmed AS, Hanif A, Aqeel M, Zubairi ABS. Subcutaneous emphysema and pneumomediastinum in patients with COVID-19 disease; case series from a tertiary care hospital in Pakistan. Epidemiol Infect. 2021;149:e37.
8. World Health Organization. Coronavirus disease (COVID-19) pandemic. [online] Available from https://www.who.int/emergencies/diseases/novel-coronavirus-2019 [Last accessed March, 2022].
9. Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, et al. Association of blood glucose control and outcome in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab. 2020;31(6):1068-77.e3.
10. Zhao Q, Meng M, Kumar R, Wu Y, Huang J, Lian N, et al. Impact of COPD and smoking history on severity of Covid 19: a systemic review and meta-analysis. J Med Virol. 2020.

CHAPTER 144

Autopsies Findings in SARS-CoV-2 Patients

Quirino Piacevoli

INTRODUCTION

The autopsy management in the course of a pandemic was characterized by two different moments: In the first phase, the lack of knowledge of the virus and of the dynamics of its spread also meant that it was not possible to perform autopsies on deceased patients.

Subsequently it was understood from the biopsies that were made to the sick, but also from the first autopsies that came from other parts of the world, that instead it was a fundamental moment from a diagnostic point of view. With the autopsies, it was possible to understand what were the physiopathological mechanisms that sustained organ damage during infection. Such as, for example, what sustained lung damage, or the initial cause of progressive respiratory failure that led to death. Progressively, at the autopsy table, very important diagnostic values were given and it was finally understood what should also be done from a therapeutic point of view. The analysis of the different organ's patients suffering from SARS-CoV-2, may help to understand pathogenesis and clinical outcome and to improve the therapeutic strategies. The need to better define the pathogenesis of coronavirus disease 19 (COVID-19) as well as to provide the correct statistical records concerning deaths related to this virus inevitably involves the role of forensic pathology and routine autopsy practice. In light of the ongoing health emergency, we have launched a preliminary investigation into the alleged correlation between COVID-19 and all the other clinical manifestations in the early days of February 2019. The first SARS-CoV-2 outbreak in Italy was discovered on February 20, 2020 in Codogno (Lodi). Since then, our country has known millions of infected people and 78,371 deaths (data updated in December 2020). From the 32,792 published articles, it emerged that SARS-CoV-2 not only causes damage to the respiratory system, but also to the cardiovascular system with arrhythmic, thromboembolic complications, heart failure, myocarditis, and disseminated intravascular coagulopathy, dermatitis, and many other neurological complications, such as dizziness, headache, ataxia epilepsy, and dysgeusia.[1]

Cellular and humoral innate immunity represent a first line of resistance to most infectious agents. Evidence from SARS-CoV-1 suggests that these viruses may block interferon-mediated antiviral immunity. CD8 cytotoxic T cells play a fundamental role in antiviral resistance. Evidence suggests that during COVID-19 infection, T cells undergo functional exhaustion as evidenced by lymphopenia, skewing toward a T17 phenotype, inappropriate for antiviral immunity and suppression.

COVID-19: PNEUMONIA PATHOPHYSIOLOGY FINDINGS

One of the main findings was an increase in pulmonary compliance of >50 up to 80. Therefore, the compliance is more severe in these patients compared with those with ARDS. Moreover, the shunt fraction in these patients is >50, thus leading to tremendous hypoxemia. The virus enters the epithelial–endothelial receptor and so we have an interstitial inflammation and a space with edema that appears as ground-glass opacities.

At the beginning, they are mostly at the periphery, because the different elasticity between pleura and alveoli makes this a weak point to stress and pressure.

The X-ray shows characteristically peripheral density of the lungs. Ventilation-induced lung injury (VILI) starts developing in <40 hours.

At this point we have lung "vasoplegia" (undetermined mechanism), i.e., if the lungs are full of gas with a "normal compliance" and perfusion is in another place, the problem is the perfusion.

This is evidence of a vascular disease. The lungs are no more able to direct the blood flow where it is necessary, except for gravity. Vasoplegia is increased by nitric oxide that causes vasodilation acting on cyclic guanosine monophosphate (cGMP) receptors and phosphorylated myosin. At the same time, these patients show a decreased level of

angiotensin I and angiotensin II that are vasoconstrictors. Final result is vasodilation.

Gravity dependent V/A mismatch means that ventilation goes in one direction and perfusion in a different one. In this case, blood goes down into the lungs where there is no ventilation, thus causing hypoxemia.

This report wants to describe the findings of the autopsies of infected patients in order to improve the therapy for patients and to have a better outcome.

Pathological Anatomy Services have started in March 2020, performing autopsies on COVID-19-positive patients after some initial hesitation. To date, we have totaled about 150 autopsies, almost entirely targeted to the lungs. We have waited for a special suit to be able to perform the autoptic examination safely on the brain.

Ours is the largest case study in the world, since the Chinese have published the results of only three "minimally invasive" autopsies (+ an isolated case report) and another one from New Orleans whose authors have published only other three cases. The only other Italian hospital that performs autopsies is "Sacco" that reports about 20 cases).

Here is what we learnt from the first group of anatomical-pathological dissertations and the most significant interventions are here presented.

Already macroscopically, the lungs appear "spotty," with hyperemic/hemorrhagic areas alternating with rosy areas. From a histological point of view, some areas are severely emphysematous, with enormously dilated blood vessels (up to 20 times the norm) often full of microthrombi. In many cases, diffuse alveolar damage (DAD) is evident, with desquamation of pneumocytes, formation of hyaline membranes, and a fibrotic exudate (as in ARDS). It appears as a high-flow syndrome, with hepatomegaly and dilated portal vessels and diffuse thrombosis at all levels. Even the heart appears enlarged, always with a hydropericardium and a marked left ventricular hypertrophy (but some of them were hypertensive patients).[2]

Just in one case, a thrombus was found almost completely obstructing the superior vena cava and the right atrium. It has often been noticed the ascent of the diaphragm, indicating that at a certain point the lungs no longer expand, associated with hepatomegaly. Waiting for data on central nervous system (CNS) samples, biopsies of the olfactory mucosa were performed. COVID-19 classically gives anosmia and ageusia: The virus could reach the brainstem trans-synaptically, starting from the peripheral nerve endings of the olfactory or lingual nerve (as well as from the innervation of the lungs). In this scenario, part of the respiratory failure could be caused by the direct damage of the virus on the nuclei of the brainstem (ambiguous nucleus, of the solitary tract ...).

As concerns the cells of the immune system, many macrophages but very few lymphocytes intervene in the interstitial what. The pathologists point out that in the blood of patients with COVID-19 infection, there is a very high number of endothelial cells (expression of the endothelial damage caused directly by the virus) and that these cells trigger a cytokine storm that mainly recruits macrophages. It is also for this reason that a high dose of cortisone may be effective. In conclusion: The pathologists tell us to freely ask for the autopsies that we deem appropriate (especially sudden deaths, or deaths in relatively young or otherwise healthy patients), accompanied by as much information as possible (comorbidity, date of onset of symptoms, therapies carried out, O_2 support system, transfer to TI). This is to understand how much "past" there is in the disastrous lungs that have been examined and to explain some anomalous findings (for example, a case of amyloidosis or an abnormal thickening of the myocardium which, according to Dr Senni, cannot be traced back to an acute myocarditis ...).

During the initial phase of the pandemic, Professor Gattinoni also reported that, perhaps, the classic ventilation of the acute respiratory distress syndrome (ARDS) at high pressures and the same prone-supination were in many cases useless when not harmful and underlined the utility of critically reviewing this attitude, marrying a ventilation as "gentle" as possible, so as not to add iatrogenic damage to a disease devastating for itself ... What appeared was not a classic ARDS.

At the same time, an increasing number of "sudden" deaths and more and more patients arriving exhausted from 15 to 20 days of serious home illness and with catastrophic intra hospital course accumulated in our unfortunate hospitals.

From the anatomic-pathological data already described, it was possible to deduce some details that well explained why it was so difficult to ventilate lungs apparently affected by pneumonia in the ARDS phase (more than the classic ARDS): It was found, together with widespread alveolar damage with hyaline membranes, an important proliferation and exfoliation of type II pneumocytes and presence of infiltrating inflammation mostly due to the monocyte-macrophage type. Important early fibrosis phenomena, induced by at least two different factors, were also found: On the one side, transformation in the fibrous sense of the pneumocytes and fibroblastic induction from the monocytes-macrophages; on the other side, the presence of thrombotic (or thrombotic-hemorrhagic) microangiopathy phenomena. The presence of lymphocytes was mostly scarce or in any case poorly represented. This means that patients have a so called "innate immunity," i.e., a primary immunity and not a little specific "secondary immunity."

This phase is a so-called "hyper-inflammation" characterized by an important elevation of the inflammation indexes with an impressive release of cytokines, high D-Dimer rates, etc. We could place at this level the invasion

and macrophage activation that generates, on the one hand, the destruction of functional lung tissue, and, on the other hand, extremely active "repair"-proliferation processes that lead to progressive fibrosis and the endothelial (-vascular) one. It can also be witnessed the progression of obliterating microangiopathy toward a form of proliferative thrombus angiitis with promotion of thrombosis of the arterioles and then of the degree vessels themselves. The phenomenon is, at this point, (and can also be from the beginning but more rarely) systemic, so that extensive venous and arterial thrombotic phenomena can occur, concomitantly with changes also in the spontaneous coagulation and platelet profile, if not hindered in some way by direct action of drugs or measures. In short, what we often radiologically [computed tomography (CT)] refer to as diffuse interstitial pneumonia is already widely remodeled, functionally inert, often not vascularized due to the presence of multiple previous thromboembolic phenomena observed during the autopsies.

As the hub of cardiovascular emergencies [ST-elevation myocardial infarction (STEMI)-not STEMI], our hospital has performed numerous autopsies that revealed frequent, even more than expected, coronary thromboses, in the absence of significant atherosclerosis, as well as numerous associated peripheral arterial thromboses. Deep venous thrombosis (DVT) and thromboembolic phenomena (TEP) were also found, even though to a lesser extent. Isolated hemorrhagic events apparently were not related to the disease. In fact, bleeding is easily a macrophage direct activity of the mucous membranes after endothelial damage, at a relatively early stage (and sudden death was seen immediately after hospitalization for prolonged fever of a 43-year-old young woman due to gastroduodenal bleeding) or it may be a late manifestation from a more complex thrombohemorrhagic vascular process, as we have seen in a case of collateral pancreatic-duodenal bleeding aneurysm of arcuate collateral ligament stenosis of the celiac tripod. At the end of a long COVID pneumonia that mainly occurred at home, this was resolved with success through embolization in urgency because the patient (a dear and very good anesthesiologist and intensivist colleague, one of the best in our hospital) had returned to hospital for intractable abdominal pain.

Just one last consideration, I personally consider extremely important: I think that much of what has been exposed is potentially usable at home, with few tools and above all with better understanding of clinical questions; this could drastically reduce the arrival of patients to hospitals and, above all the late arrival that is often without real chances of recovery.

Clinical News about another group of patients: They presented bilateral interstitial pneumonia from COVID-19, ARDS, kidney failure, severe sepsis, heart failure, and hypertension in some. One of these patients returned from Padua on March 6, 2020. Fever worsened on March 9, 2020. Admitted to our hospital, a chest CT scan was performed that highlighted multiple areas of bilateral interstitial infiltration.

MACROSCOPIC DESCRIPTION

Asymmetry of the upper limbs with edema of the right upper limb continuous solution of the central region of the body as for tracheotomy.

Chest

Bilateral pleural effusion of about one litre on the left and about 500 cc on the right.

Pericardium

Opaque surface of the parietal sheet of the pericardium with growths referable to fibrin deposits as for fibrous pericarditis.

Heart

Heart of shape and volume preserved, *concentric hypertrophy of both cardiac cavities was observed, with reduction of the lumen of the cavities*. Thickening of the left ventricle wall of 2 cm and thickening of the wall of the right ventricle of 0.8 cm; the myocardium appeared pale, diminished in consistency and flabby; the atrial cavities appeared dilated. Nothing to detect for the valve system. Ectasia of the ascending aorta.

Lungs

Both lungs appeared increased in volume and consistency; on the hilum the bronchi had hyperemic mucosa with catarrhal content, and pulmonary arteries free of thrombi. Small bilateral hilar lymph nodes were observed. On the cutting surface, the lung parenchyma of both lungs had a compact appearance, an increased consistency, reddish complexion with areas of thickening of the interstitial bronchial vessel plot; when squeezed, frothy liquid flowed out. In correspondence with the upper portion of the lower lobe of the left lung, a circumscribed area of compact hemorrhagic appearance was observed, well delimited with respect to the neighboring pulmonary parenchyma which normally takes on a relationship with the bronchial structures of the peripheral branches to be histologically ascertained.

INTERNATIONAL FINDINGS

Thus the Washington Post headlines an article dedicated to the testimony of some pathologists who in recent months have been involved in performing autopsies on the bodies of people who have disappeared due to the coronavirus.

Autopsies have always been a source of discovery for the understanding of new diseases: From HIV/AIDS (human immunodeficiency virus/acquired immunodeficiency

syndrome), through Ebola, to COVID-19. The WP states that "thanks to the autopsy tests conducted on COVID patients, confirmation has come that the lungs are the organs most affected by the virus. But damage was also found in the brain, kidneys, liver, gastrointestinal tract, spleen and endothelial cells that line the blood vessels." As already mentioned, the researchers also found a widespread alteration of coagulation. Dr Amy Rapkiewicz, a pathologist at NYU Langone Health Academic Medical Center said "As already mentioned, the researchers also found a widespread alteration of coagulation".

Dr Richard Vander Heide of LSU in New Orleans also claims to have performed autopsies on patients who had suffered cardiac arrest in hospital but who, once examined, had no primary damage to the heart but to the lungs. One of the first US surveys released on April 10 involved a 44-year-old patient who had been treated at LSU Health. Vander Heide, who has been operating since 1994, on the pages of the WP recalls having dissected the lung and having probably discovered hundreds or thousands of microclots: "I will never forget the day. I had never seen something like this." Autopsy after autopsy, Vander Heide says he found the same troubling picture.

A preliminary study conducted in China, published in the BMJ's Journal of Neurology, Neurosurgery and Psychiatry in March 2020, found that 22% of 113 patients experienced neurological problems ranging from excessive sleepiness to coma. In June 2020, points out the WP, some French researchers reported that "84% of patients in intensive care had neurological problems and that, at the time of discharge, a third was confused or disoriented."

Isaac Solomon, a neuropathologist at Brigham and Women's Hospital in Boston, conducted 18 autopsies, examining particular areas of the brain: "the cerebral cortex (the gray matter responsible for processing information), the thalamus (which modulates sensory input), the basal ganglia (responsible for motor control), etc." The expert stressed that he found only small pockets of inflammation, while there were signs of damage caused by the lack of oxygen.

CONCLUSION

The fight against SARS-Cov-2 and its different variants is still ongoing and we need to know much more. Postmortem swabs could be used as a valuable tool in preventive evaluation of the risks–benefits ratio associated with autopsy execution. SARS-CoV-2 RNA postmortem detection could have a key diagnostic role in deaths lacking medical assistance, unattended deaths, and patients with multiple comorbidities. Based on the present report, staged postmortem swabs should be performed even after a long postmortem interval.

REFERENCES

1. Salerno M, Sessa F, Piscopo A, Montana A, Torrisi M, Patanè F, et al. No Autopsies on COVID-19 Deaths: A Missed Opportunity and the Lockdown of Science. J Clin Med. 2020;9(5):1472. doi: 10.3390/jcm9051472. PMID: 32422983; PMCID: PMC7291342.
2. Pomara C, Li Volti G, Cappello F. COVID-19 Deaths: Are We Sure It Is Pneumonia? Please, Autopsy, Autopsy, Autopsy! J Clin Med. 2020;9(5):1259. doi: 10.3390/jcm9051259. PMID: 32357503; PMCID: PMC7287760.

CHAPTER 145

Perioperative Concerns in COVID

Pradeep Bhatia, Sadik Mohammed, Shilpa Goyal

INTRODUCTION

According to the World Health Organization (WHO) statistics on Coronavirus disease 2019 (COVID-19), >200 million cases have been reported till September 2021 with >4.8 million deaths.[1] In India, alone >33 million cases have been reported with around 0.5 million death by the end of September 2021.[2] The affected individual exhibits variable presentation ranging from asymptomatic to critical illness and more than two-third of those who recover may have long-term health consequences.[3] It is not surprising that these individuals may present with emergency or elective surgery and their perioperative management requires a thorough understanding of every aspect of the care.

Over the hundreds of years, the healthcare workers (HCWs) have been playing important roles in fighting against many deadly epidemics. This is also true for the current pandemic, i.e., COVID-19. The close contact with the infected patients makes HCWs vulnerable for getting infected. Although the exact number of the HCWs infected with COVID-19 is yet unknown, it has been estimated that several hundreds of the HCWs have been infected while providing the care to the hospital admitted COVID-19 patients. Among them, anesthesiologists and intensivists remain at the highest risk for getting infected as operating rooms (ORs) and intensive care units (ICUs) are busy environment. Strict adherence to the safe medical practices and infection prevention protocols during perioperative management of patients with COVID-19 is of utmost importance.

In this chapter, the perioperative concerns for patients with COVID-19 (active COVID, post-COVID and long COVID) is discussed. The acute phase extends up to 4 weeks in asymptomatic patients while it may extend up to 6–8 weeks in symptomatic patients.[4] Long COVID and post-COVID are considered if signs and symptoms persist for 4–12 weeks and for >12 weeks, respectively, after acute phase.[5,6] The content of the chapter is based on position statements from Indian Society of Anaesthesiologists[6] and Indian Society of Critical Care Medicine,[7] WHO[8] guidelines for the prevention and treatment of COVID-19, and a comprehensive review of updated literature on the perioperative management of infectious patients.[9-12]

PERIOPERATIVE CONCERNS FOR PATIENTS WITH ACTIVE COVID-19

The causative organism for COVID-19, i.e., severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can be transmitted to HCWs involved in their care mainly during aerosol-generating procedures (laryngoscopy, endotracheal intubation, extubation, and bronchoscopy). Therefore, infection control measures to limit spread of the virus are essential component of the perioperative care of these patients.

Infection Control

Based on the experience from other infectious agents (Ebola, SARS-CoV, etc.) and guidance from the Centers for Disease Control and Prevention (CDC), various other societies have published recommendations for infection control during anesthesia for patients with COVID-19.[6,13,14] Goals are to prevent infection transmission to HCWs and to prevent contamination of the anesthesia machine and other anesthesia equipment. Similar infection control measures should be employed while caring for both suspected or confirmed COVID-19 cases and include handwashing with soap or hand hygiene with chlorhexidine, universal precaution including use of personal protective equipment (PPE), standard handling of medical waste disposal, and environment and equipment disinfection.

Although the available literatures on the use of PPE during aerosol generating procedures and risk of infection transmission showed conflicting results, it is prudent to use the PPE while caring for all COVID-19 suspected or confirmed cases.[15-17] The extended or level III PPE which include reinforced fluid-resistant long-sleeved surgical gown with attached hood, full length disposable plastic apron, filtering face piece 3 (FFP3) respirator or powered

hood respirator, disposable full face visor, pair of disposable gloves, and dedicated shoes with shoe covers should be worn for all aerosol-generating procedures. Level 2 airborne precaution which include disposable apron, disposable gloves, FFP3 respirator, and eye protection should be used by all other HCWs while caring for the patients who do not undergo aerosol-generating procedures.

Another area which need distinct consideration is donning (putting on) and doffing (putting off) of PPE. It is suggested that donning and doffing should be monitored by a trained observer as error during these are common which may lead to contamination of HCWs with pathogens.[18,19] Used PPE must be removed slowly and deliberately in the correct sequence to reduce the possibility of self-contamination. After removing gloves and other PPE, a thorough hand hygiene should be performed before touching any body parts.

Preoperative Evaluation and Preparation

There is increased risk of perioperative morbidity (pulmonary complications) and mortality in patients with COVID-19, therefore the preoperative evaluation should focus on risk assessment.[20,21] This risk should be balanced against the risks of delaying or avoiding the planned procedure before deciding to perform surgery. The reported odds for 30-day mortality after surgery is >5.[22] The overall mortality with emergency surgery was reported to be higher compared with elective surgery (26 vs. 19%).[20] There is consensus that in confirmed or suspected COVID-19 patients, elective procedures should be postponed till 8 weeks after symptom resolution.[23]

During the transport within a medical facility, a surgical mask should be used by the patient and they should be directly transported to dedicated OR without holding in the preoperative area. A protective barrier with slits for easy patient access may be fitted on the transport trolley **(Fig. 1)**. If possible portable tent system with high-efficiency particulate air (HEPA) filtration should be used during transport for patients with COVID-19.[24] A high-quality heat and moisture exchanging (HME) filter should be used between patient and breathing circuit while transporting the intubated patient. Similarly, during recovery patients should be transported directly to an airborne infection isolation room without keeping them in the postanesthesia care unit (PACU).

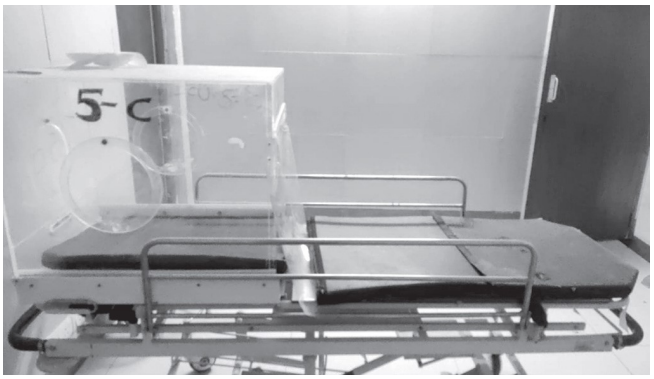


Fig. 1: A dedicate transport trolley fitted with protective barrier.

Avoiding Contamination of Anesthesia Equipment

A dedicated OR with appropriate operation of laminar flow and the functional HEPA filter with limited entry (only personnel involved in direct care of the patient) should be used for COVID-19 patients undergoing surgery. For preventing contamination and need for disinfection of the anesthesia equipment, only necessary equipment should be kept in the OR particularly during aerosol-generating procedures. Other equipment should be kept ready outside the OR and brought in when required. Preventing contamination of all the component of anesthesia workstation is critical.[25] The surface contamination of the outer parts of the anesthesia workstation and other reusable equipment (multipara monitor, ultrasound machine, etc.) can be prevented by covering it with plastic covers. During removal of these covers after use, similar care should be taken as during doffing of PPE. The contamination of internal components of the anesthesia workstation can be prevented by putting HME filters rated for viral filtration efficiency between both limbs of breathing circuit and anesthesia workstation as well as between patient's airway interface and breathing circuit. These filters should be replaced between two cases. For decontamination of the anesthesia workstation and reusable equipment, cleaning should be performed according to manufacturer's recommendations while disposables items should be bagged for disposal as contaminated waste.[26]

When the HME filters are placed as recommended, there is no need to replace the water trap that receives the gas sampling line and the carbon dioxide absorber, however, the gas sampling tubing should be replaced between two cases. Similarly, the internal components of the anesthesia workstation and breathing system do not need cleaning or decontamination when HME filters are used as recommended. Between the two cases, the OR should remain closed to allow adequate air exchanges for removing aerosolized pathogens and then the OR should undergo a thorough deep terminal cleaning using guidelines from CDC. Enhanced environmental cleaning and disinfection of the OR using ultraviolet C (UV-C) light and/or hydrogen peroxide vapor is encouraged.[26]

Anesthesia Management

Selection of anesthetic technique (general vs. regional) for confirmed or suspected COVID-19 patients should take into consideration both the patient factors as well

as the procedure. As there are risk and benefit to both the techniques, selection of one technique over the other has no advantage when either would be appropriate. The general principles to be followed for both the techniques are as mentioned below.

General Anesthesia

Induction of general anesthesia should be performed using rapid sequence induction and intubation. The selection of induction agent should take in to consideration the patient factor. Adequate preoxygenation should be performed and volume status should be optimized (intravenous fluids or vasopressor) particularly in critically ill patients as they may become even more hypoxemic and hypotensive after induction and during intubation. Consideration should be given for using ketamine, etomidate, or a combination of ketamine and propofol rather than propofol alone.[27] If bag mask ventilation is required, low pressure small volume breath should be delivered maintaining a tight seal between face and mask. For securing the airway, the endotracheal intubation should be preferred over a supraglottic airway to prevent leak around the airway device and to prevent viral spread. The airway must be secured rapidly and repeated attempts at intubation must be avoided to reduce aerosolization of respiratory secretions.[28-30] Videolaryngoscopy has distinct advantage as it may increase the first attempt success rate and also allows the clinician to remain at distance from the patient's airway during the procedure.[31] Further it also ensures adequate depth under direct vision eliminating chest auscultation to confirm the equal air entry on both sides of the chest.

The other aerosol-generating procedures during anesthesia care include bag mask ventilation, jet ventilation with an open airway, open suctioning of airways, airway endoscopy/bronchoscopy, noninvasive ventilation, high-flow oxygen, nebulized medications, tracheostomy, and transesophageal echocardiography. During the intubation, attention should be paid to reduce coughing and/or bucking. It was suggested that intubation should be performed in a negative pressure room outside the OR as most ORs use positive pressure air flow; however, recent simulation-based studies suggest that air exchange rate and other factors may affect aerosol distribution.[32] Double gloves should be used during intubation and outer gloves should be removed immediately after securing the airway. After the successful intubation, the cuff should be inflated before connecting the breathing circuit. Disconnection should be avoided as much as possible and if required the viral filters should be left on the endotracheal tube (ETT). Alternatively, a clamp can be placed on the ETT with the ventilator on standby if viral filters are not on place. A closed suction system can be placed for tracheal suctioning before extubation and when required.

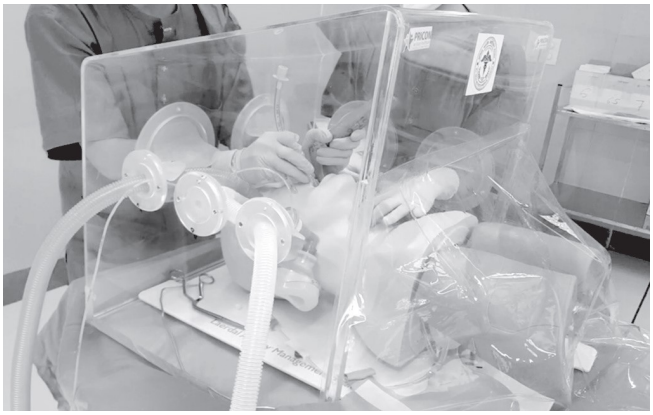


Fig. 2: A protective barrier provided with arm sheaths or slits to allow access to the patient airway during intubation and extubation.

Variety of protective barrier devices have been developed to protect the anesthesiologist from droplet or aerosol contamination during intubation and extubation.[33,34] These devices are provided with arm sheaths or slits to allow access to the patient airway during intubation and extubation **(Fig. 2)** and may have incorporated continuous suction to vent aerosols.[35,36] The concerns with these devices are that these have not been critically evaluated in humans, they may prolong the intubation and adequate view of the patient's airway may be compromised. Because of the concern that these devices may increase exposure of healthcare providers, the Food and Drug Administration (FDA) has issued an alert recommending against the use of passive protective barriers (those without negative pressure) for use when caring for patients with known or suspected COVID-19.[37]

Similar to the endotracheal intubation, the tracheal extubation is also considered as a high-risk procedure for aerosolization of respiratory secretions, therefore all the precautions should be followed. Care must be taken to avoid coughing to prevent spread of secretions during extubation. A surgical mask, wet gauze, or clear plastic drape may be placed over the patient's mouth and nose while the ETT is still in place just prior to extubation.

For management of the difficult airway, the basic principles for management of the difficult airway also apply to patients with COVID-19. In general, awake fiberoptic intubation should be avoided and if it is required, the airway should be anesthetized using topical local anesthetic ointment or gel, and/or nerve blocks. Nebulized and transtracheal injection of local anesthetic should be avoided.

Regional Anesthesia

The advantage of regional anesthesia over general anesthesia in COVID-19 patients is that risk of aerosolization of respiratory secretions can be avoided and it should be used for lower extremity and lower abdominal surgery if not contraindicated. A few small randomized controlled studies suggest better outcome with neuraxial technique

compared to general anesthesia.[38] Many COVID-19 patients are receiving anticoagulants which affect the timing of or decision to use neuraxial anesthesia or deep peripheral nerve blocks. If the procedure is decided to be performed under regional anesthesia alone, a surgical mask should be placed on patient's mouth and nose at all times. For the patients requiring oxygen supplementation, minimal possible flow to maintain the oxygen saturation of around 94% should be used. The oxygen face mask should be placed over the surgical mask, while the nasal prongs under a surgical mask.

PERIOPERATIVE CONCERNS FOR PATIENTS WITH LONG COVID AND POST-COVID

As the wrath of the pandemic is on the declining phase, lots of population is waiting for the elective surgeries. But, these patients who were tested positive for COVID-19 previously need to be evaluated thoroughly before taking the patient under anesthesia. Various anesthesia societies have suggested thorough preanesthetic check-up for ruling out all the risks associated with respiratory, cardiac, renal, and neurological complications in the perioperative period. Clinical systemic manifestations in post-COVID phase are as follows:

- *Pulmonary*: After recovery from the acute phase, the degree of lung involvement varies from minimal lung involvement to restrictive lung disease. The degree of lung involvement depends on the age of the patient, severity of illness, duration of ICU stay, and mechanical ventilation.[22,39] Airway hyper-reactivity may persist for 2–6 weeks following acute infection. Therefore, pulse oximetry, 6-minute walk test, and screening pulmonary function tests should be done prior to taking patients for surgery under anesthesia. High-resolution computed tomography (HRCT) of the thorax and pulmonary angiography may be warranted in some patients to see whether lungs have progressive disease or recovered from the insult.
- *Cardiac*: Direct damage to myocardium has been reported during the acute phase which may have prolonged effects in few patients. This may present with varied symptoms such as chest pain, palpitations owing to dysrhythmia, and cardiomyopathy. Decreased perfusion may be evident on cardiac magnetic resonance imaging (MRI). Routine electrocardiography (ECG) and transthoracic echocardiography are advisable in patients presented for surgery 2–6 months after acute phase.[40,41] ECG may reveal ST-T changes, inversions of T wave, and abnormalities in PR intervals. Echocardiography will help differentiate myocarditis from myocardial infarctions and regional wall motion abnormalities. N-terminal pro-brain natriuretic peptide (NT-pro-BNP) was considered mandatory for all minor and major surgeries in a few studies.[42]
- *Renal*: The kidney insult due to the virus may be due to direct inflammation and injury and due to direct viral injury through angiotensin-converting enzyme 2 (ACE-2) receptors. Preoperative evaluation of kidney functions such as serum creatinine and blood urea nitrogen is advised to rule out the degree of kidney damage.[40]
- *Neurological*: Due to direct damage to the olfactory nerves, the patients might have persistent loss of smell (11–13%) and taste (7–9%).[3] Patient may present with other neurological clinical manifestations such as encephalitis, convulsions, stroke, and demyelinating neuropathy. Patients who present with demyelinating neuropathy requiring anesthesia are tough to manage. Optimal use of opioids and neuromuscular blockers is needed. Quantitative neuromuscular monitoring should be done intraoperatively to guide about the appropriate timing of administering neuromuscular blockers and reversal of neuromuscular blockade. Regional anesthesia is well avoided in these subsets of patients.[40]
- *Hematological system*: COVID-19 infection is a prothrombotic state. These patients are prone to develop thrombosis due to the ongoing inflammation and immobility associated with the disease state. They may present with ischemic strokes and limb ischemia. Thromboprophylaxis should be taken into consideration if started, both mechanical and pharmacological. Early mobilization should be encouraged as per enhanced recovery after surgery (ERAS) protocol.[40] Coagulation profile should be assessed preoperatively.
- *Decreased functional status*: 59–81% patients showed weakness, fatigue, and decreased mobility even after 6 months of acute infection.[3,4] They may also present with psychological distress symptoms such as anxiety and depression. Professional rehabilitation programs are being planned for these patients, but due to lack of awareness, less of the people can take its advantage.[4]

A new health hazard has been reported in post-COVID phase as large number of patients are presenting with rhinocerebral mucormycosis. Those patients having a history of reverse transcription polymerase chain reaction (RT-PCR) tested positive for COVID-19, immunocompromised, or raised sugar levels are prone to it. It was declared as epidemic and a notifiable disease in many states of India. Its management became more complicated due to scarcity of relevant antifungal drugs and their side effects.[43] They are being regularly posted for debridement of the affected area and the surgery is quite debilitating. Besides, other complications which are common to other type of surgeries post-COVID, the anesthesiologists may face an additional challenge of difficult airway.[43] There is high likelihood of these patients going for postoperative mechanical ventilation.

TABLE 1: Suggested timing for elective surgeries after diagnosis of COVID.

S. No.	Patients condition during acute phase	Suggested wait time from the date of COVID diagnosis and surgery
1.	Asymptomatic or mild nonrespiratory symptoms	4 weeks
2.	Symptomatic but did not require hospitalization (mild COVID illness)	6 weeks
3.	Symptomatic who require hospitalization (moderate COVID illness)	8–10 weeks
4.	Patient who require ICU admission (severe COVID illness)	12 weeks

(ICU: intensive care unit)
Adapted from: American Society of Anesthesiologists and Anesthesia Patient Safety Foundation joint statement on elective surgery and anesthesia for patients with COVID-19

Recommendations[44]

- The timing for elective surgery in post and long-COVID is summarized in **Table 1**.
- There should be a multidisciplinary discussion and decision regarding taking up the patient for elective surgery at 7 weeks post-COVID. All the factors regarding clinical status, symptoms, degree of systemic involvement, and urgency of surgery depending on the disease progression should be taken under consideration.
- Elective surgery done within 7 weeks of contracting the disease has high mortality rates. It should only be done in cases of disease progression with calculated risk.
- Those patients who are symptomatic need special consideration after 7 weeks.
- The patients who are symptomatic even till 7 weeks have high mortality rate, so they should be taken for surgery only if necessary.
- Vaccinations given to patients a few weeks before planned surgery might be protective for the patient and limit spread of nosocomial infection to other people.

Hence, patients with COVID-positive status (present or past) and scheduled for surgery (elective or emergency) pose challenge to the anesthesiologists. A thorough understanding of the associated pathophysiology of the disease process and infection control practices are of utmost importance while caring for these patients. A multidisciplinary team approach is required for adequate perioperative management of these patients.

REFERENCES

1. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard with Vaccination Data. [online] Available from: https://www.who.int/ [Last accessed March, 2022].
2. Ministry of Health and Family Welfare, Government of India. Homepage. [online] Available from: https://www.mohfw.gov.in/ [Last accessed March, 2022]
3. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021;397(10270):220-32.
4. The Lancet. Understanding long COVID: a modern medical challenge. Lancet. 2021;398(10302):725.
5. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med. 2021;27(4):601-15.
6. Malhotra N, Bajwa SJ, Joshi M, Mehdiratta L, Hemantkumar I, Rani RA, et al. Perioperative management of post-COVID-19 surgical patients: Indian Society of Anaesthesiologists (ISA National) Advisory and Position Statement. Indian J Anaesth. 2021;65(7):499-507.
7. Mehta Y, Chaudhry D, Abraham OC, Chacko J, Divatia J, Jagiasi B, et al. Critical care for COVID-19 affected patients: Position statement of the Indian Society of Critical Care Medicine. Indian J Crit Care Med. 2020;24(4):222-41.
8. WHO. Infection prevention and control during health care when novel coronavirus disease (COVID-19) is suspected or confirmed. [online] Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-IPC-2021.1 [Last Accessed March, 2022].
9. Wax RS, Christian MD. Practical recommendations for critical care and anesthesiology teams caring for novel Coronavirus (2019-nCoV) patients. Can J Anesth. 2020;67(5):568-76.
10. Park J, Yoo SY, Ko JH, Lee SM, Chung YJ, Lee JH, et al. Infection prevention measures for surgical procedures during a Middle East Respiratory Syndrome outbreak in a tertiary care hospital in South Korea. Sci Rep. 2020;10:325.
11. Missair A, Marino MJ, Vu CN, Gutierre J, Missair A, Osman B, et al. Anesthetic implications of Ebola patient management: A review of the literature and policies. Anesth Analg. 2015;121(3):810-21.
12. Chen Y, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. J Med Virol. 2020;92(4):418-23.
13. Perioperative considerations for the 2019 Novel Coronavirus (Covid-19). Anesthesia Patients Safety Foundation Newsletter; February 2020. [online] Available from: https://www.apsf.org/news-updates/perioperative-considerations-for-the-2019-novel-coronavirus-covid-19/ [Last accessed March, 2022].
14. American Society of Anesthesiologists Committee on Occupational Health: Coronavirus Information for Health Care Professionals (Clinical FAQs). [online] Available from: https://www.asahq.org/about-asa/governance-and-committees/asa-committees/committee-on-occupational-health/coronavirus/clinical-faqs [Last accessed March, 2022].
15. El-Boghdadly K, Wong DJN, Owen R, Neuman MD, Pocock S, Carlisle JB, et al. Risks to healthcare workers following tracheal intubation of patients with COVID-19: a prospective international multicentre cohort study. Anaesthesia. 2020;75(11):1437-47.
16. Liu M, Cheng SZ, Xu KW, Yang Y, Zhu Q, Zhang H, et al. Use of personal protective equipment against coronavirus disease 2019 by healthcare professionals in Wuhan, China: cross sectional study. BMJ. 2020;369:m2195.

17. Cook TM, Lennane S. Occupational COVID-19 risk for anaesthesia and intensive care staff - low-risk specialties in a high-risk setting. Anaesthesia. 2021;76(3):295-300.
18. Okamoto K, Rhee Y, Schoeny M, Lolans K, Cheng J, Reddy S, et al. Impact of doffing errors on healthcare worker self-contamination when caring for patients on contact precautions. Infect Control Hosp Epidemiol. 2019;40(5): 559-65.
19. Tomas ME, Kundrapu S, Thota P, Sunkesula VC, Cadnum JL, Mana TS, et al. Contamination of health care personnel during removal of personal protective equipment. JAMA Intern Med. 2015;175(12):1904-10.
20. COVIDSurg Collaborative. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. Lancet. 2020;396(10243):27-38.
21. Doglietto F, Vezzoli M, Gheza F, Lussardi GL, Domenicucci M, Vecchiarelli L, et al. Factors associated with surgical mortality and complications among patients with and without coronavirus disease 2019 (COVID-19) in Italy. JAMA Surg. 2020;155(8):691-702.
22. COVIDSurg Collaborative, GlobalSurg Collaborative. Timing of surgery following SARS-CoV-2 infection: an international prospective cohort study. Anaesthesia. 2021;76(6):748-58.
23. American Society of Anesthesiologists. COVID-19 and Elective Surgery. [online] Available from: https://www.asahq.org/in-the-spotlight/coronavirus-covid-19-information/elective-surgery [Last accessed March, 2022].
24. United States Food and Drug Administration. Letter. [online] Available from: https://www.fda.gov/media/137856/download. [Last accessed March, 2022].
25. FAQ on Anesthesia Machine Use, Protection, and Decontamination during the COVID-19 Pandemic. American Society of Anesthesiologists Committee on Occupational Health: Coronavirus. Information for Health Care Professionals (Clinical FAQs). [online] Available form: https://www.apsf.org/faq-on-anesthesia-machine-use-protection-and-decontamination-during-the-covid-19-pandemic/ [Last accessed March, 2022].
26. Dexter F, Parra MC, Brown JR, Loftus RW. Perioperative COVID-19 defense: An evidence-based approach for optimization of infection control and operating room management. Anesth Analg. 2020;131(1):37-42.
27. Yao W, Wang T, Jiang B, Gao F, Wang L, Zheng H, et al. Emergency tracheal intubation in 202 patients with COVID-19 in Wuhan, China: lessons learnt and international expert recommendations. Br J Anaesth. 2020;125(1):e28-e37.
28. Orser BA. Recommendations for endotracheal intubation of COVID-19 patients. Anesth Analg. 2020;130(5):1109-10.
29. Cook TM, El-Boghdadly K, McGuire B, McNarry AF, Patel A, Higgs A. Consensus guidelines for managing the airway in patients with COVID-19: Guidelines from the Difficult Airway Society, the Association of Anaesthetists the Intensive Care Society, the Faculty of Intensive Care Medicine and the Royal College of Anaesthetists. Anaesthesia. 2020;75(6):785-99.
30. Cook TM, McGuire B, Mushambi M, Misra U, Carey C, Lucas N, et al. Airway management guidance for the endemic phase of COVID-19. Anaesthesia. 2021;76(2):251-60.
31. Hall D, Steel A, Heij R, Eley A, Young P. Videolaryngoscopy increases 'mouth-to-mouth' distance compared with direct laryngoscopy. Anaesthesia. 2020;75(6):822-23.
32. Tsui BCH, Pan S. Are aerosol-generating procedures safer in an airborne infection isolation room or operating room? Br J Anaesth. 2020;125(6):e485-87.
33. Canelli R, Connor CW, Gonzalez M, Nozari A, Ortega R. Barrier enclosure during endotracheal intubation. N Engl J Med. 2020;382(20):1957-58.
34. Malik JS, Jenner C, Ward PA. Maximising application of the aerosol box in protecting healthcare workers during the COVID-19 pandemic. Anaesthesia. 2020;75(7):974-75.
35. Hellman S, Chen GH, Irie T. Rapid clearing of aerosol in an intubation box by vacuum filtration. Br J Anaesth. 2020;125(3): e296-e99.
36. Tsui BCH, Deng A, Lin C, Okonski F, Pane S. Droplet evacuation strategy for simulated coughing during aerosol-generating procedures in COVID-19 patients. Br J Anaesth. 2020;125(3):e299-301.
37. United States Food and Drug Administration. Protective barrier enclosures without negative pressure used during the COVID-19 pandemic may increase risk to patients and health care providers - Letter to health care providers. [online] Available from: https://www.fda.gov/medical-devices/letters-health-care-providers/protective-barrier-enclosures-without-negative-pressure-used-during-covid-19-pandemic-may-increase [Last accessed March, 2022].
38. Elsharydah A, Li FC, Minhajuddin A, Gabriel RA, Joshi GP. Risk score for major complications after total hip arthroplasty: the beneficial effect of neuraxial anesthesia. A retrospective observational study. Curr Orthop Pract. 2020;31(2): 156-61.
39. Ojo AS, Balogun SA, Williams OT, Ojo OS. Pulmonary Fibrosis in COVID-19 Survivors: Predictive Factors and Risk Reduction Strategies. Pulm Med. 2020;2020:6175964.
40. Hoyler MM, White RS, Tam CW, Thalappillil R. Anesthesia and the "post-COVID syndrome": Perioperative considerations for patients with prior SARS-CoV-2 infection. J Clin Anesth. 2021;72:110283.
41. Davido B, Seang S, Tubiana R, de Truchis P. Post-COVID-19 chronic symptoms: a postinfectious entity? Clin Microbiol Infect. 2020;26(11):1448–9.
42. Bui N, Coetzer M, Schenning KJ, O'Glasser AY. Preparing previously COVID-19-positive patients for elective surgery: a framework for preoperative evaluation. Perioper Med. 2021;10(1):1-4.
43. Gupta KK, Singh A, Kalia A, Kandhola R. Anaesthetic considerations for post-COVID-19 mucormycosis surgery- A case report and review of literature. Indian J Anaesth. 2021; 65(7):545-7.
44. El-Boghdadly K, Cook TM, Goodacre T, Kua J, Blake L, Denmark S, et al. SARS-CoV-2 infection, COVID-19 and timing of elective surgery: A multidisciplinary consensus statement on behalf of the Association of Anaesthetists, the Centre for Perioperative Care, the Federation of Surgical Specialty Associations, the Royal College of Anaesthetists and the Royal College of Surgeons of England. Anaesthesia. 2021;76(7):940-46.

CHAPTER

146

Prolong Sedation, Analgesia, and Paralysis in COVID-19—Adverse Outcome

Palepu B Gopal, VVSSD Prasanthi

INTRODUCTION

Severe COVID-19 pneumonia patients with acute respiratory distress syndrome required prolonged period of sedation in high doses and continued paralyzing agents for endotracheal intubation and controlled ventilation.[1] The clinical practice guidelines from the Society of Critical Care Medicine (SCCM) recommend a strategy of light sedation rather than deep sedation and utilization of nonbenzodiazepines for mechanical ventilation to decrease ventilator days, tracheostomy rate, and intensive care unit (ICU) length of stay.[2] But deep sedation and continued paralysis were favored by ICU staff for controlled ventilation of COVID-19 patients in view of the unique pathophysiology of COVID-19 which includes high respiratory drive, impaired lung compliance, intense inflammatory response linked to tolerance to sedative agents,[3] and severe ventilator dyssynchrony. Many patients required prone ventilation to improve gas exchange and the number of patients who required extracorporeal membrane oxygenation (ECMO) increased during COVID-19 pandemic. Severity of respiratory failure requiring prolonged mechanical ventilation median duration of 7–12 days, high workload on healthcare workers, reduced bedside availability of critical care staff, shortages of personal protective equipment (PPE), increased risk of accidental self-extubation, and risk of infection transmission to healthcare workers resulted in deep and prolonged sedation and paralysis.

Each of these barriers, and several others, have led to increased and prolonged sedation use and requirement of combinations of multiple agents thereby increasing potential risks of side effects such as drug accumulation (midazolam), tolerance, tachyphylaxis (dexmedetomidine), hypertriglyceridemia (propofol), QT interval prolongation (haloperidol), psychotomimetic effects (ketamine), hyperalgesia, opioid dependence (fentanyl and/or hydromorphone), and delirium (midazolam). Prolonged and high-dose usage of sedative and paralyzing drugs gave rise to shortage of these agents, potential for increased rate of physical and psychological dependence, acute brain dysfunction, and intensive care unit-acquired weakness (ICUAW).

SEDATION IN NONINVASIVE VENTILATION

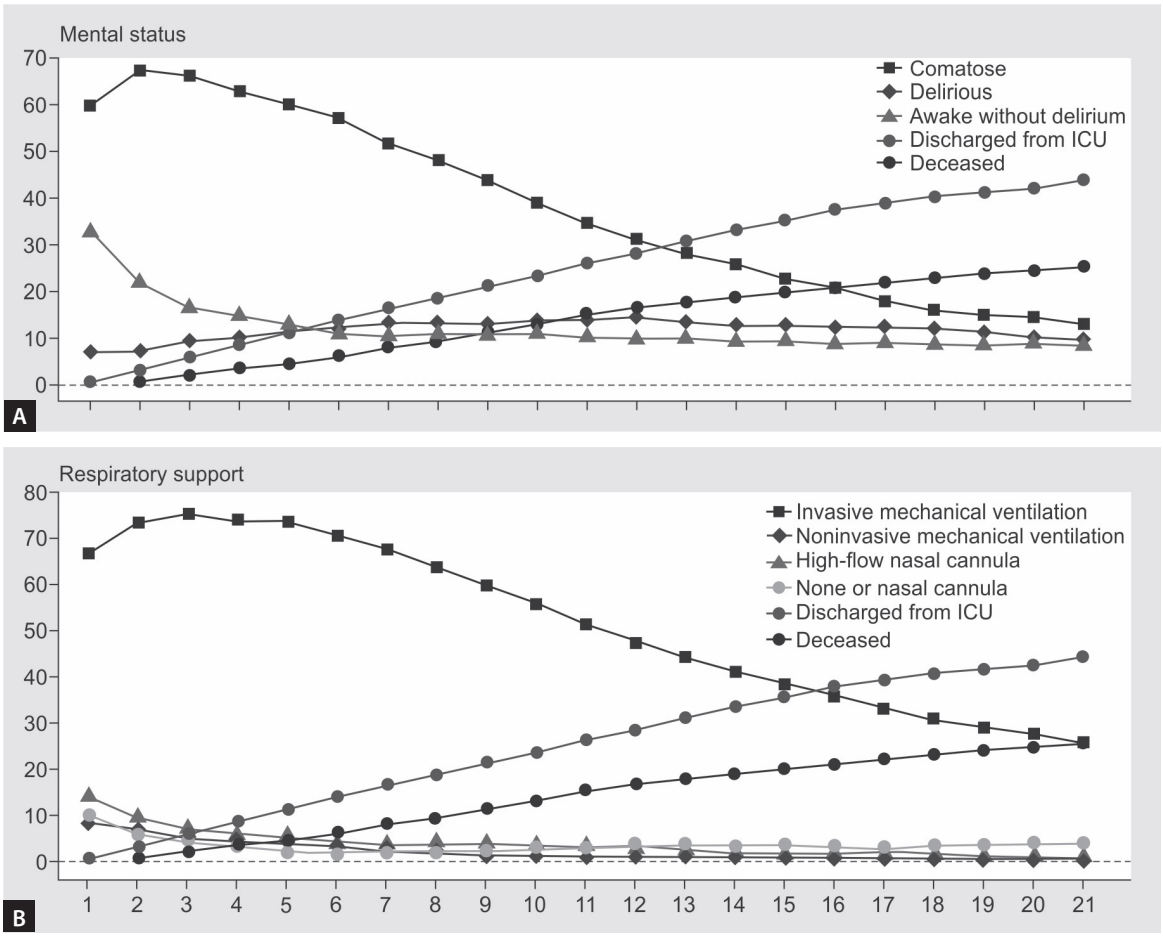
Sedation can typically decrease the respiratory drive in young COVID-19 patients who have high respiratory drive and no dyspnea when breathing spontaneously. Muriel et al. in 2015 compared three group of patients with no sedation, only analgesia, and sedation plus analgesia for outcome of noninvasive ventilation (NIV) failure and 28-day mortality rate. They found that these two outcome measures were increased with use of sedation and/or analgesia. Therefore, sedation in COVID-19 patients during NIV was not recommended. If the patient's condition worsens, the only solution is to intubate and initiate invasive mechanical ventilation.

BRAIN AND SEDATION

Acute Brain Dysfunction

Delirium prevalence is reported up to 11–12% among COVID-19 hospitalized patients.[4] Acute brain dysfunction in COVID-19 patients occurs due to neuroinflammation, possibly due to viral invasion through olfactory nerves, systemic brain injury related to hypoxia, endotheliitis, multiorgan involvement, procoagulant nature of the disease, and the effects of heavy sedative strategies, especially benzodiazepines. Other factors such as immobilization, prolonged mechanical ventilation, and social isolation from families[4] also added to this dysfunction.

In a cohort study, mechanically controlled and ventilated COVID-19 patients had a median Richmond Agitation Sedation Scale (RASS) of –4 [interquartile range (IQR), –5 to –3] and, during the 21-day study period, the median number of days alive and free of coma or delirium were only 5 days (IQR, 0.0–14.0).[4] Additionally, approximately about two-third of patients received benzodiazepines for a median of 7.0 days (4.0–12.0) **(Figs. 1A and B)**. Controlled ventilation, use of restraints, and sedatives were the factors associated with a higher risk of delirium the next day.



Figs. 1A and B: Level of sedation, respiratory support, mortality, and intensive care unit (ICU) discharge in COVID-19 patients. (*Source:* Pun BT, Badenes R, Heras La Calle G, Orun OM, Chen W, Raman R, et al. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): A multicentre cohort study. Lancet Resp Med. 2021;9(3):239-50).

The potential significant adverse outcomes included prolonged controlled ventilation, delirium, increased morbidity and mortality, and long-term sequelae of the post-intensive care syndrome (PICS), which included cognitive impairment.

Delayed Emergence of Consciousness

Sustained high levels of sedation and neuromuscular paralysis facilitate lung protective ventilation and ventilator synchrony in COVID-19 patients with acute respiratory distress syndrome, but may delay recovery of consciousness and impair neurologic outcome.[5] The consequences of sedatives on cognition dysfunction are well-established.[5]

Neurological examination alone cannot guide sedative dosing because comatose patients who are adequately sedated appear identical on examination to those who are highly sedated. This can be guided by electroencephalogram (EEG) examination which appear as slow delta oscillations in adequate sedation and burst suppression in high levels of sedation. Continuous EEG monitoring in COVID-19 patients is practically not possible for obvious reasons.

Iatrogenic Withdrawal Syndrome

The prolonged use of opioids and benzodiazepines during the ICU stay and pre-existing comorbidities results in iatrogenic withdrawal syndrome, which is defined as "a constellation of signs and symptoms that can be induced by abruptly stopping or reducing the dose of a sedative, reducing plasma concentration, and administering an antagonist of that drug."[6]

Tolerance is defined as a decrease in the pharmacological action of a drug after its continuous use **(Table 1)**.[6] Opioid-induced hyperalgesia (OIH) is a different phenomenon and is defined as paradoxically exaggerated response to pain due to continuous use of an opioid.[7] Prolonged benzodiazepines use increased risk of withdrawal and prolonged mechanical ventilation, especially in elderly patients. Prolonged therapy with opioids can cause physiological and psychological dependence.

CARDIOVASCULAR COMPLICATIONS

Sedatives such as dexmedetomidine cause exaggerated hemodynamic instabilities, such as hypotension,

TABLE 1: Definitions of withdrawal syndromes.[6]

Term	*Definition*
Tolerance	A decrease in response to a drug dose that occurs with continued use; increasing doses are needed to achieve the effect originally produced by regular doses
Physical dependence	A state of adaptation that manifests through a drug class-specific withdrawal syndrome
Psychological dependence	A subjective sense of need for a specific psychoactive substance, either to obtain its positive effects or to avoid negative effects associated with abstinence

bradycardia, and heart block in critically ill COVID patients. Propofol induces a dose-dependent decrease in the systemic vascular resistance and myocardial contractility,[8] which may worsen the pre-existing hemodynamic instability in COVID-19 patients with septic shock or cardiogenic shock. Morphine has potential of histamine release leading to hypotension. Patients with COVID-19 are known to develop myocardial injury, viral myocarditis, and stress cardiomyopathy.[8] Further sedatives induced decrease in myocardial contractility, hypotension, and heart block leads to decreased end-organ perfusion which may not be well-tolerated in these patients.

PULMONARY COMPLICATIONS

At high doses and rapid infusion, fentanyl is associated with chest wall rigidity, which can decrease compliance and lead to inappropriate ventilation which can be a potentially devastating complication in the critically ill patient with COVID-19.[9]

NEUROMUSCULAR COMPLICATIONS

Critical care management grabs the attention of intensivist during the acute phase of illness and neuromuscular complications such as ICUAW and positioning-related peripheral nerve injuries are less taken care.

Muscle atrophy starts within 4 hours of inactivity due to degradation and programmed myocyte death. Prolonged sedation and paralysis lead to immobility and muscle inactivity leading to disuse atrophy which is the major cause for critical illness neuromyopathy. Critical illness polyneuropathy and myopathy were predominant in severe COVID-19 who required mechanical ventilation. ICUAW is caused by either critical illness polyneuropathy or critical illness myopathy.[10] Respiratory muscles weakness can lead to difficult weaning from mechanical ventilation. ICUAW is associated with prolonged stays in the ICU and a major contributor for physical impairment and dysfunction following ICU stay.[10] ICUAW is potentiated by the other risk factors associated with COVID-19 which include drugs such as corticosteroids and aminoglycosides, and hyperglycemia, which is an invariable consequence of steroid usage. The long-term consequences of ICUAW are indistinguishable from several features of postcritical care myoneural and pathological syndromes such as postinfective polyneuropathy. These will have significant effect on recovery and quality of life and may necessitate long-term neurorehabilitation with attendant complications **(Fig. 2)**.

GASTROINTESTINAL EFFECTS

COVID-19 patients have virus attaching to angiotensin-converting enzyme 2 (ACE-2) receptors expressed on gut causing activation of inflammation and paralytic ileus. This is aggravated by opioid sedation induced risk of hypomotility, abdominal distention, and other related complications increasing risk of pulmonary aspiration impairing ventilation. Prone ventilation further augments this risk by increasing intra-abdominal pressure due to physical compression. Hypomotility leads to intolerance to feeds and malnutrition in prolong ICU stay. Prolonged and high-dose propofol infusions can independently result in elevated levels of triglycerides, thereby increasing the risk of pancreatitis.

DRUG-RELATED ADVERSE EFFECTS

Seizures

Prolonged and higher doses of sedatives such as lorazepam lead to propylene glycol toxicity. Intravenous (IV) lorazepam has a solvent named propylene glycol (1,2-propanediol). Propylene glycol has been associated with toxicity in high-dose and/or prolonged lorazepam therapy. This is clinically characterized by cardiac arrhythmia, seizures, lactic acidosis, hypotension, and agitation. Propylene glycol toxicity should be considered whenever a patient has an unexplained anion gap metabolic acidosis in patients receiving high doses of IV lorazepam.

Propofol-related Infusion Syndrome

Propofol-related infusion syndrome is a rare condition that may occur with prolonged (>48 hours) and higher-dose (>4–5 mg kg^{-1} h^{-1}) of propofol infusions.[8] It is manifested with refractory bradycardia, metabolic acidosis, rhabdomyolysis, hyperlipidemia, enlarged liver, and hyperkalemia. This should be treated by stopping the infusion and providing supportive measures. Some patients may require hemodialysis, or even ECMO in severe cases. Inability to stop or lower the dose of propofol while supporting adequate sedation becomes problematic in patients presenting with COVID-19.

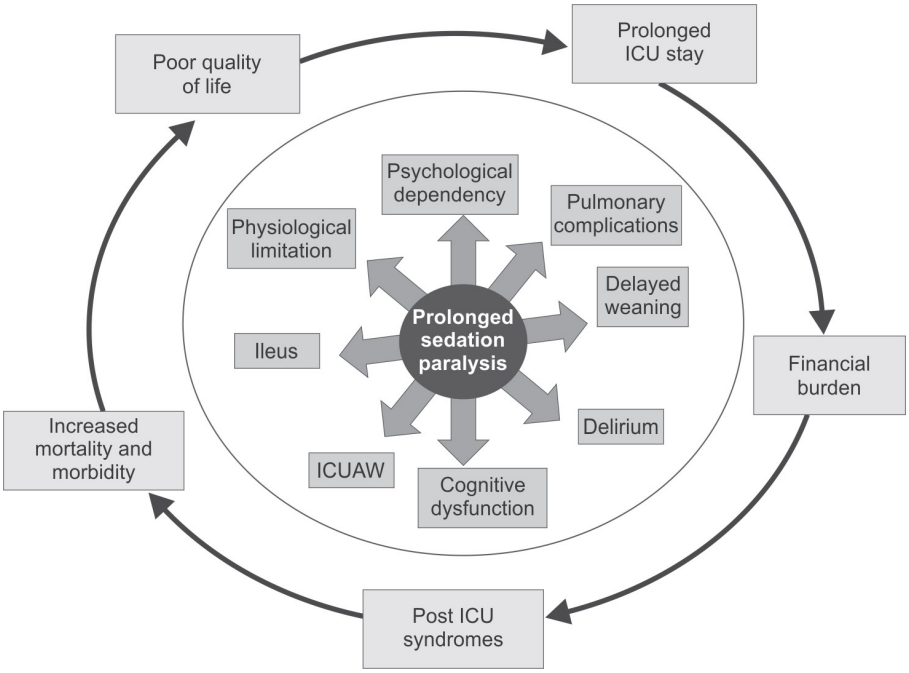


Fig. 2: Adverse events vicious cycle secondary to prolonged and high-dose sedation and paralysis. (ICU: intensive care unit; ICUAW: intensive care unit-acquired weakness)

Hypertriglyceridemia

COVID-19 may increase potential risk factors for triggering hemophagocytic lymphohistiocytosis (HLH).[11] Concomitant use of sedatives such as propofol for prolonged period results in hypertriglyceridemia and cytokine storm in a subset of COVID-19 patients deviating the intensivist in the diagnosis of HLH. The HLH presenting features are fever, cytopenia, hypertriglyceridemia, elevated ferritin, elevated lactate dehydrogenase (LDH), and abnormal liver function tests. Hypertriglyceridemia, defined as a blood level >150 mg/dL, is a major risk factor for cardiovascular events,[12] leading healthcare providers to choose sedatives other than propofol for sedation.

Drug Shortages and Sustained Utilization of Intensive Care Unit Resources

Drug shortages have resulted in usage of alternative sedation strategies and agents apart from regular sedation strategies thereby increasing drug interactions and associated side effects. Increased use of sedatives in pandemic has led to worsening shortages, ultimately forcing some hospitals to ration supplies and others to go without the same. Propofol has been listed as a drug in shortage since 2018, has seen an enhanced usage during the COVID-19 pandemic. Food and Drug Administration (FDA) and American Society of Health-System Pharmacists cited 10 sedative and analgesic agents shortage in their databases including propofol and dexmedetomidine.[13]

Ketamine has wide variety of advantages in critical illness, including in pain management, in postoperative analgesia, in refractory status epilepticus, and as adjunctive sedation. Ketamine will have an opioid-sparing effect owing to its analgesic property. Although ketamine is associated with hypertension and tachycardia, it may also decrease cardiac function in some subsets of critically ill patients, including those with septic shock. It is also associated with psychotomimetic effects which should be addressed.

Drug Interactions

Attention must be paid to the potential interaction between sedative agents and other drugs administered as part of treatment and about 300 international clinical trials are currently underway. Hydroxychloroquine and haloperidol combination can cause significant QT prolongation. Metabolism of hydroxychloroquine is increased with concomitant administration of barbiturates. In patients with high fever, dexmedetomidine may need to be stopped to understand the cause of the fever. Barbiturates may increase metabolism of other drugs as they are P450 enzyme inducers.

Drug Accumulation

Polypharmacy in COVID-19 patients along with multi-organ dysfunction leads to significant pharmacokinetic and pharmacodynamic (pK/pD) alterations. Prolonged infusions may also lead to drug accumulation which is significant in critically ill COVID-19 patients. Fentanyl undergoes CYP3A4 metabolism, the derangement of which in hepatic dysfunction can lead to its accumulation.

Morphine has active metabolites such as morphine 6 glucuronide that can accumulate in the setting of renal failure, leading to neurotoxicity. The incidence of acute kidney injury (AKI) has been reported recently to be around 25% in COVID-19 patient who are critically ill. Hence, drug accumulation and associated side effects are common with prolonged infusions of high doses of sedatives and analgesics such as 1-hydroxymidazolam, active metabolite of midazolam, which is eventually excreted by the kidneys and can accumulate during prolonged infusions in AKI.

Sedation-induced Intensive Care Unit-acquired Infections

Prolonged duration of therapy may also result in development of long-term adverse effects including B and T cell-mediated immune dysfunction. Prolongation sedation and paralysis in the presence of risk factors for infection, microaspiration, gastrointestinal motility disturbances, microcirculatory effects, and immunomodulatory effects increase the incidence of infection in critically ill COVID-19 patients.[14]

Venous Thromboembolism

Neuromuscular blockade in conjunction with deep sedation presents added risk for COVID-19 patients due to its hypercoagulable state. Since patients are immobilized, there is the potential for increased rates of deep venous thromboembolism,[15] primary pulmonary artery thrombosis, and arterial thrombosis. This along with a hypercoagulable state has led to various grades of pulmonary embolism with an incidence of 16.7%,[16] with attendant morbidity and mortality in COVID-19 patients.

Difficult Weaning

Sedatives with longer half-life cause delay in extubation especially in patients with proximal muscle weakness, diaphragmatic weakness, and decreased respiratory reserve. This is further complicated by delayed excretion of drugs depending on renal and hepatic metabolism, which is commonly deranged in these patients.

Microcirculatory Effects of Sedation

Sedation may alter tissue perfusion when already compromised, as in septic patients, and contributes to the development of multiorgan failure.[17] Benzodiazepines can induce an increase in cutaneous blood flow secondary to vasodilation, a decrease in reactive hyperemia, and alterations of vasomotion. It has been proved in clinical studies that alterations of normal microcirculatory control mechanisms may contribute to the development of organ failure in septic patients through compromise in the tissue nutrient blood flow.[17,18]

Quality of Life

Over sedation synergistically acts with other risk factors such as pulmonary impairment, ICUAW, cognitive dysfunction, physical impairment, and psychiatric dysfunction leading to poor functional outcomes. Critically ill patients with COVID-19 will likely have delayed recovery from physical and cognitive impairment which may significantly impact the quality of life.

Increased Mortality and Morbidity

Deep and prolonged sedation associated with longer time to extubate, and prolonged ICU stay leads to higher mortality rate at 3 months after ICU discharge. Prolonged sedation and paralysis can be one of the attributable factors for increased mortality and morbidity.

CONCLUSION

Prolong sedation, analgesia, and paralysis in COVID-19 patients have been a necessary evil with inevitable attendant adverse consequences. Some of these adverse consequences were quite troublesome, even after successful recovery from COVID-19 and continued to haunt the patient long after necessitating prolonged rehabilitation. This phase was not without complications, some of which added to morbidity and mortality. Clear understanding of etiopathogenesis of these syndromes and strategies to mitigate the same will lessen the incidence of the syndromes and complications in these patients and reduce the burden on healthcare systems.

REFERENCES

1. Kapp CM, Zaeh S, Niedermeyer S, Punjabi NM, Siddharthan T, Damarla M. The use of analgesia and sedation in mechanically ventilated patients with COVID-19 ARDS. Anesth Analg. 2020:10.1213/ANE.0000000000005131.
2. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med. 2018;46(9):e825-73.
3. Martyn JAJ, Mao J, Bittner EA. Opioid tolerance in critical illness. N Engl J Med. 2019;380(4):365-78.
4. Pun BT, Badenes R, Heras La Calle G, Orun OM, Chen W, Raman R, et al. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): A multicentre cohort study. Lancet Respir Med. 2021;9(3):239-50.
5. Edlow BL, Claassen J, Victor JD, Brown EN, Schiff ND. Delayed reemergence of consciousness in survivors of severe COVID-19. Neurocrit Care. 2020;33(3):627-9.
6. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) national practice guideline for the use of medications in the treatment of addiction involving opioid use. J Addict Med. 2015;9(5):358-67.
7. Carullo V, Fitz-James I, Delphin E. Opioid-induced hyperalgesia: A diagnostic dilemma. J Pain Palliat Care Pharmacother. 2015;29(4):378-84.

8. Karamchandani K, Dalal R, Patel J, Modgil P, Quintili A. Challenges in sedation management in critically ill patients with COVID-19: A brief review. Curr Anesthesiol Rep. 2021;1-9.
9. Roan JP, Bajaj N, Davis FA, Kandinata N. Opioids and chest wall rigidity during mechanical ventilation. Ann Intern Med. 2018;168(9):678.
10. Hermans G, Van den Berghe G. Clinical review: Intensive care unit acquired weakness. Crit Care. 2015;19(1):274.
11. Henderson LA, Canna SW, Schulert GS, Volpi S, Lee PY, Kernan KF, et al. On the alert for cytokine storm: Immunopathology in COVID-19. Arthritis Rheumatol. 2020;72(7):1059-63.
12. Thompson WG, Gau GT. Hypertriglyceridemia and its pharmacologic treatment among US adults—invited commentary. Arch Intern Med. 2009;169(6):578.
13. Hubmayr RD, Abel MD, Rehder K. Physiologic approach to mechanical ventilation. Crit Care Med. 1990;18(1):103-13.
14. Nseir S, Makris D, Mathieu D, Durocher A, Marquette CH. Intensive care unit-acquired infection as a side effect of sedation. Crit Care. 2010;14(2):R30.
15. Murray MJ, Deblock H, Erstad B, Gray A, Jacobi J, Jordan C, et al. Clinical Practice Guidelines for Sustained Neuromuscular Blockade in the Adult Critically Ill Patient. Crit Care Med. 2016;44(11):2079-103.
16. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: A multicenter prospective cohort study. Intensive Care Med. 2020;46(6):1089-98.
17. De Backer D, Cortes DO, Donadello K, Vincent JL. Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. Virulence. 2014;5(1):73-9.
18. Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL. Persistent-microcirculatory alterations are associated with organ failure and death in patients with septic shock. Crit Care Med. 2004;32(9):1825-31.

CHAPTER 147

Multisystem Inflammatory Syndrome in Adults

Yatindra Dube, Akshaykumar Chhallani, Nirmal Jaiswal

INTRODUCTION

In April 2020, few previously healthy pediatrics patients were identified suffering from clinical syndrome similar to Kawasaki disease and toxic shock syndrome.[1] Shock, GI (gastrointestinal) abnormality, and cardiac dysfunction were the predominant symptoms in those patients. This was latter labeled as multisystem inflammatory syndrome-children (MIS-C). Centers for Disease Control and Prevention (CDC) reported 3,185 similar cases in April 2020.[2] Similar to these cases, various case reports and case series were published in adult population and were labeled as multisystem inflammatory syndrome-adults (MIS-A).[3] Unfortunately, as in pediatrics, there is lack of high-quality data to guide diagnosis and treatment of MIS-A and most of the management is guided either by experiences from case reports or small case series.

ETIOPATHOGENESIS

Although pathogenesis of MIS-A is not very clear, virus-induced endothelial dysfunction and coagulopathy are the main identified pathological features. Endothelialitis and complement deposition in the vessels of affected organ have been found to be pathognomonic feature of MIS-A. This deposition causes cardiac dysfunction, skin rash, and gastrointestinal symptoms.[4]

DIAGNOSIS

Contrary to MIS in children, diagnostic criteria in adults lack a clarity. Septic shock and flare of collagen vascular disease are very close differential diagnosis for MIS-A. The potential role of procalcitonin as a rapid diagnostic marker to differentiate between sepsis and MIS-A which have two different mechanism of systemic inflammatory response remains vital.

Centers for Disease Control and Prevention has recommended following clinical criteria to diagnose MIS-A.[2]

- A severe illness requiring hospitalization—aged ≥21 years.
- A positive test result of SARS-CoV-2 infection either by polymerase chain reaction (PCR) or antigen or serology during admission or in the previous 12 weeks.
- Severe dysfunction of one or more extrapulmonary organ systems (e.g., hypotension or shock, cardiac dysfunction, arterial or venous thrombosis or thromboembolism, or acute liver injury).
- Laboratory evidence of severe inflammation as evidenced by abnormally high values of CRP [C-reactive protein, ferritin, D-dimer, interleukin (IL)-6].
- Absence of severe respiratory illness (to exclude patients in which inflammation and organ dysfunction might be attributable simply to tissue hypoxia).
- There should not be alternative diagnosis and no obvious microbiological cause.

In MIS-C, skin manifestations were more common in the younger cohort, while myocarditis and gastrointestinal symptoms were more frequent in older children. Similar findings were noted by Davogustto et al. who identified GI symptoms were more common in adults.[4]

TREATMENT

High-quality evidence for an optimal treatment strategy for MIS-A is lacking. Good supportive medical management is mainstay in treating MIS-A and close monitoring of affected patients is very important.[5,6] Though definitive evidence is lacking; intravenous immunoglobulins 2 g/kg and intravenous (IV) methylprednisolone 1–2 mg/kg/day can be tried. There are few case reports treated successfully with IL-1 receptor antagonist (anakinra) or high-dose methylprednisolone 10–30 mg/kg/day in refractory patients. This treatment is extrapolated from successful outcomes in MIS-C.

Vaccination following Multisystem Inflammatory Syndrome—Adults

A conversation between the patient, their guardian(s), and their clinical team or a specialist (e.g., specialist in

infectious diseases, rheumatology, or cardiology) is strongly encouraged to assist with decisions about the use of COVID-19 vaccines as there is lack of data in this regard.[7]
CDC recommends vaccination in patients after MIS-A if:

- Clinical recovery has been achieved, including return to normal cardiac function.
- It has been ≥90 days since their diagnosis of MIS-C.
- They are in an area of high or substantial community transmission of SARS-CoV-2 or otherwise have an increased risk for SARS-CoV-2 exposure and transmission.
- Onset of MIS-C occurred before any COVID-19 vaccination.

Additional factors when considering individual benefits and risks may include:

- An increased personal risk of severe COVID-19 (e.g., age and underlying conditions).
- Timing of immunomodulatory therapies [Advisory Committee on Immunization Practices (ACIP)'s general best practice guidelines for immunization can be consulted for more information].

CONCLUSION

- MIS-A is a potentially fatal clinical condition after SARS-CoV-2 infection which is delayed hyperinflammatory immunological response.
- It needs high clinical suspicion, acumen, and timely actions to diagnose and treat these patients in small window of opportunity to avoid fatalities.
- Further research, encouragement to enroll in clinical trials, data sharing, and collaborations are needed to know utility of immunoglobulins, steroids, and other potential available treatment in the management protocol.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

1. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem inflammatory syndrome in children in New York State. N Engl J Med. 2020;383(4):347-58.
2. Centers for Disease Control and Prevention. (2020). Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). CDC Health Alert Network. [online] Available from: https://www.mayoclinic.org/diseases-conditions/mis-c-in-kids-covid-19/symptoms-causes/syc-20502550. [Last accessed March, 2022].
3. Morris SB, Schwartz NG, Patel P, Abbo L, Beauchamps L, Balan S, et al. Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection—United Kingdom and United States, March–August 2020. Morb Mortal Wkly Rep. 2020;69(40):1450.
4. Davogustto GE, Clark DE, Hardison E, Yanis AH, Lowery BD, Halasa NB, et al. Characteristics associated with multisystem inflammatory syndrome among adults with SARS-CoV-2 infection. JAMA Netw Open. 2021;4(5):e2110323.
5. Chow EJ. The multisystem inflammatory syndrome in adults with SARS-CoV-2 infection—another piece of an expanding puzzle. JAMA Netw Open. 2021;4(5):e2110344.
6. Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: Version 1. Arthritis Rheumatol. 2020;72(11):1791-805.
7. Centers for Disease Control and Prevention. (2021). Interim clinical considerations for use of COVID-19 vaccines currently authorized in the United States. [online] Available from: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html. [Last accessed March, 2022].

148

CHAPTER

Lung Transplant Success Stories in COVID

Vijil Rahulan, Unmil Shah, Sharanya Kumar

INTRODUCTION

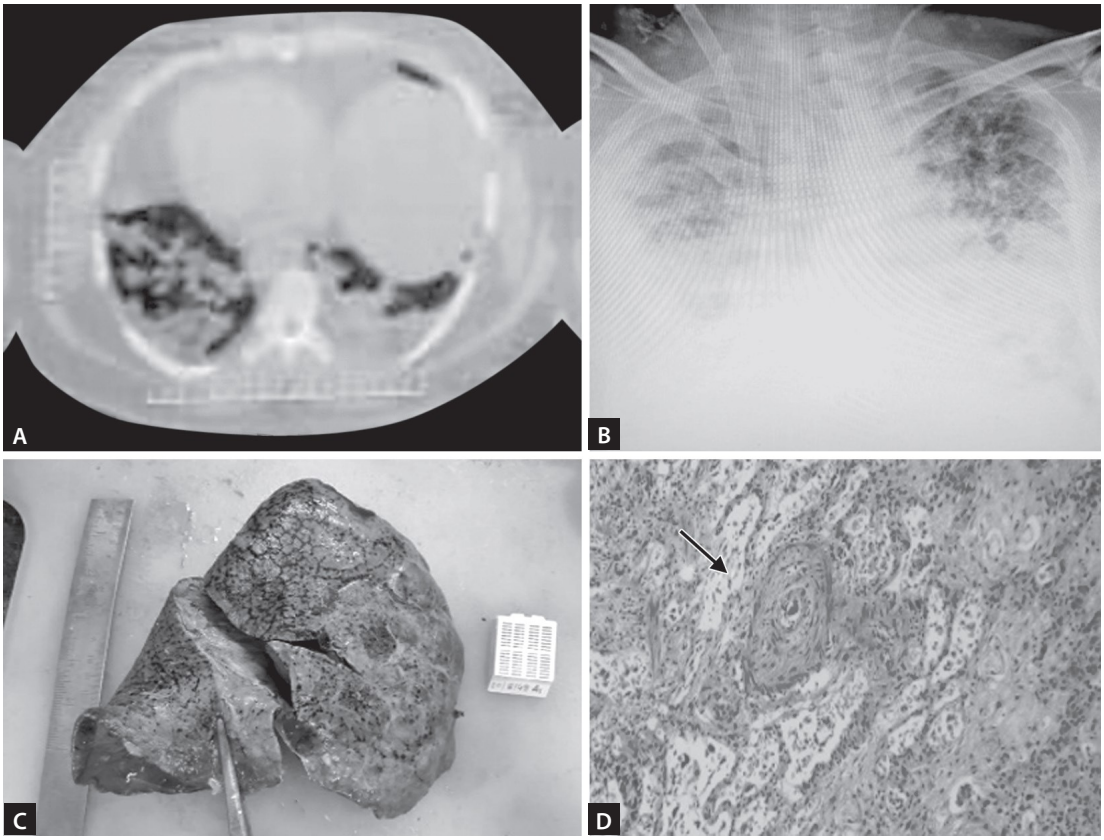
Novel coronavirus was declared a pandemic by WHO (World Health Organization) on 11 March 2020.[1] At time of writing this article, WHO has recorded 240,940,937 SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) cases and 490,3911 fatalities across the globe.[2] SARS-CoV-2 infection can lead to severe respiratory failure and acute respiratory distress syndrome (ARDS) requiring mechanical ventilation. The mortality of patients with critical coronavirus disease 2019 (COVID-19) is strikingly high, ranging between 15 and 74%, particularly when invasive mechanical ventilation (IMV) has been required.[3] Some patients would require extracorporeal membrane oxygenation (ECMO) as a bridge to recovery (if initiated early) or as a bridge to lung transplantation. Estimated in-hospital mortality 90 days after ECMO initiation was 37.4%.[4] Lung transplantation becomes the only life-saving option at that time for such post-COVID end-stage lung disease. Worldwide, lung transplantation has been performed for such severe post-COVID-19 fibrosis demonstrating irreversible lung damage, with acceptable early post-transplant outcomes. Between May 2020 and September 2021, our center has performed 25 lung transplants for post-COVID ARDS-related end-stage fibrosis who met the criteria for candidacy for transplantation. 24 were bridged with ECMO and 1 patient was a known case of interstitial lung disease who became COVID-19 positive and worsened, requiring continuous noninvasive ventilatory (NIV) support. We will briefly describe clinical summary of three such successful transplantation and discuss our standard of practice in perioperative management of these patients.

CASE #1

A 30-year-old previously healthy male was tested COVID-19 positive and was admitted in a local hospital in Punjab. His computed tomography (CT) score was 22 on admission and he received steroid, tocilizumab, antibiotics, oxygen, and other supportive therapies. In view of increasing oxygen requirement, he was intubated and ventilated 10 days later. Despite high ventilatory settings and prone position, he developed mixed respiratory failure and was put on VV-ECMO (venovenous extracorporeal membrane oxygenation) the next day. He was airlifted to our center the following day. He was admitted in our respiratory intensive care unit (ICU) and was treated as per standard protocol for COVID ECMO and ARDS ventilation and underwent tracheostomy on 5th day of admission. His respiratory compliance was poor and continued to be dependent of ECMO support. He had two episodes of gram-negative sepsis requiring low-dose pressors but responded well to appropriate antibiotics. After 4 weeks of ECMO and ventilatory assist, he could not be weaned and his CT chest displayed parenchymal damage, fibrosis, cystic changes, and traction bronchiectasis. After several rounds of discussion with team, the patient and family members, decision to proceed with lung transplantation was made. He was evaluated by multidisciplinary team and was registered at state's cadaveric transplantation program. He received suitable organ call and successfully underwent bilateral lung transplant on 33rd day of initiation of ECMO. The intraoperative ischemia time was 390 minutes. He was weaned off ECMO in operating room and shifted to ICU with inotropes and nitric oxide. He was started on triple immunosuppression regimen and prophylactic antibiotics. He was gradually weaned of supports and tolerated increasing duration of tracheostomy mask. He developed airway anastomotic stenosis needing regular bronchoscopy and balloon dilatation. Tracheostomy was decannulated on 26th day and he was discharged on oral medications on 35th postoperative day (POD). On regular follow-up, 5 months later he was at home and did not require oxygen **(Figs. 1A to D)**.

CASE #2

A 34-year-old male with no known comorbidities, had history of high-grade fever and was diagnosed COVID-19 positive. He was admitted with desaturation and started on

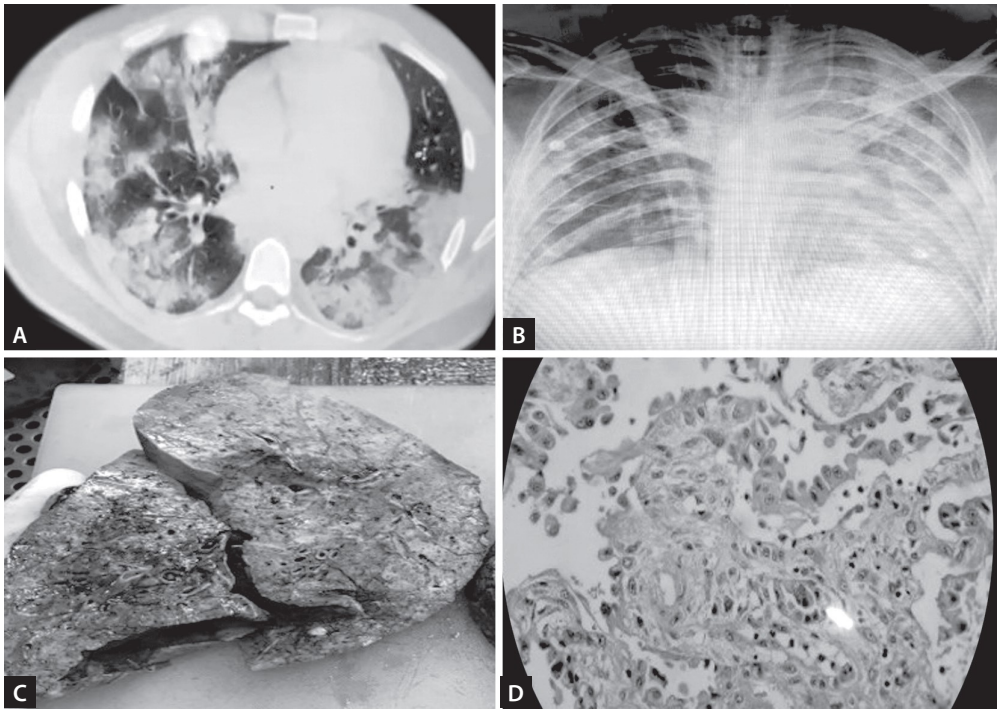


Figs. 1A to D: Case 1# (A) Preoperative computed tomography (CT); (B) Chest X-ray (CXR) on extracorporeal membrane oxygenation (ECMO); (C) Pneumonectomy specimen showing nodular consolidation; and (D) Histopathology showing vascular thickening and thrombus.

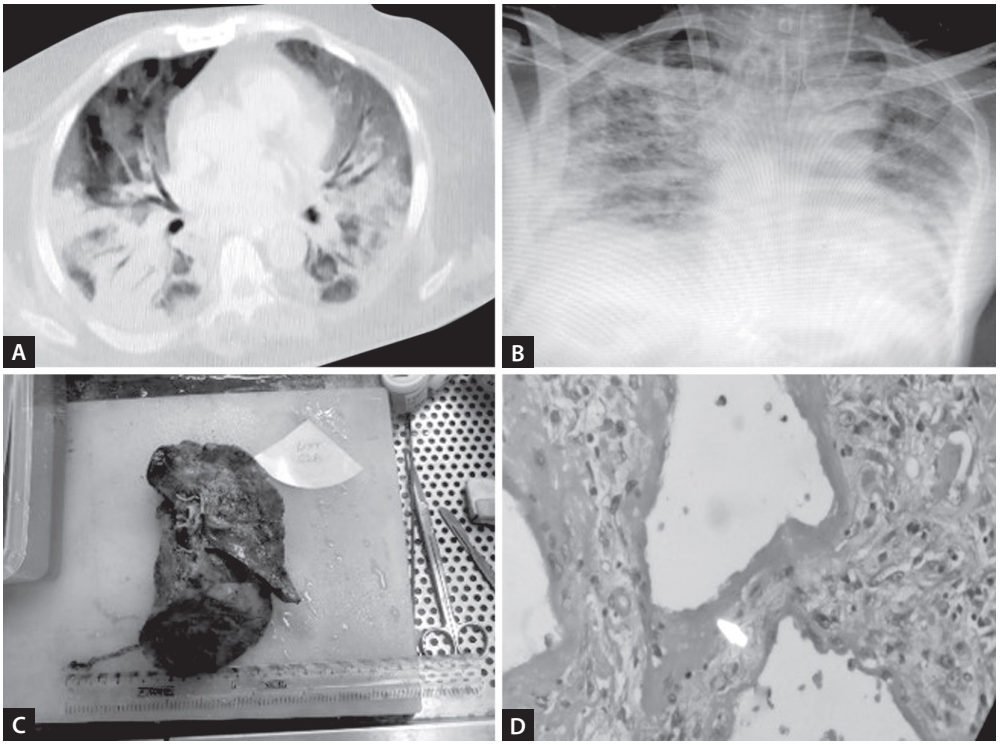
noninvasive ventilation. In view of worsening hypoxemia, he was intubated on 6th day of admission. Respiratory failure aggravated and VV-ECMO was initiated after 3 days. Repeat reverse transcription polymerase chain reaction (RT-PCR) was negative for COVID-19. He was airlifted to our center after a week of ECMO initiation. He was in sepsis and had femoral hematoma on admission which was managed conservatively. Elective tracheostomy was done in anticipation of prolonged wean from ventilatory support. After 6 weeks, he continued to be ECMO dependent with poor respiratory compliance and gas exchange. High-resolution computed tomography of the chest (HRCT) showed diffuse fibrotic changes and the decision was made to evaluate and list for lung transplantation. He underwent bilateral lung transplantation on 52nd day of initiation of ECMO. Ischemia time was 320 minutes. On table, VV-ECMO weaned and decannulation done. On POD-3, he was tolerating intermittent bilevel positive airway pressure (BiPAP) and T-piece trial. On POD-9, he was shifted to ward with intermittent BiPAP/T-piece. On POD-14, tracheostomy decannulation was done. Gradually O_2 was weaned off. In view of clinical improvement and hemodynamic stability, patient was discharged on 24th day after surgery. He recently completed 10 months of follow-up and not requiring oxygen **(Figs. 2A to D)**.

CASE #3

A 64-year-old male, known chronic obstructive pulmonary disease (COPD) was found COVID-19 positive and was admitted with desaturation. He was started on oxygen support along with other COVID-19 treatment. He was continued with 25 L of oxygen via HFNC (high flow nasal cannula). He had low saturation even on HFNC and was put on mechanical ventilatory support. He was started on antifibrotics, antibiotics, steroids, and other supportive measures. He progressed to type II respiratory failure regardless of fully ventilatory support and multiple sessions of proning. VV-ECMO was initiated on day 9 of mechanical ventilation. With continued poor lung compliance and HRCT of the chest showing feature of end-stage lung disease, need for transplantation was explained. He was registered for lung transplantation, under supra urgent category. On waitlist, he was extubated and was supported with intermittent noninvasive ventilation. He received a transplant call on day 34 of ECMO initiation and was taken up for bilateral lung transplantation. Following transplant, he was shifted to ICU with inotropes, nitric oxide, VV-ECMO, and ventilatory support. VV-ECMO was weaned off on postoperative day 2. He was slowly weaned off ventilator and supported with intermittent NIV. Triple regimen



Figs. 2A to D: Case 2# (A) Computed tomography (CT) of the chest; (B) Chest X-ray (CXR) on extracorporeal membrane oxygenation (ECMO); (C) Pneumonectomy specimen showing cystic changes; and (D) Histopathology showing pneumocyte hyperplasia.



Figs. 3A to D: Case #3 (A) Computed tomography (CT) of the chest; (B) Chest X-ray (CXR) on extracorporeal membrane oxygenation (ECMO); (C) pneumonectomy specimen showing fibrotic shrunken lung; and (D) histopathology showing interstitial fibrosis with honeycombing.

immunosuppressants were initiated. Bronchoscopy was done at periodic intervals to evaluate airway healing, anastomosis, and bronchial toileting. Patient was shifted to ward on postoperative day 14 with intermittent NIV support. Fungal culture grew *Paecilomyces* species and was treated appropriately. In view of clinical improvement and hemodynamic stability, patient was discharged on 28th postoperative day. On regular follow-up, 10 months later he was at home and did not require oxygen **(Figs. 3A to D)**.

DISCUSSION

Since the beginning of pandemic our center has managed 64 COVID patients on VV-ECMO. 45 were referred from other states, among which 42 ECMOs were instituted by our mobile team comprising of cardiac surgeon, anesthetist, perfusionist, and nursing staff and the patients were airlifted to our center. The ECMO configuration in these situations was femoral vein to internal jugular vein. Referring institutional resource limitation forced our hand to carry most of the equipment necessary for ECMO initiation. This coupled with individual state enforced travel restrictions and limited connecting flights, protracted the transfer of these sick patients.

Extracorporeal Membrane Oxygenation Management

On receiving at our institute, they were managed in separate ICU till the laboratory report of COVID-19 turned negative. They were managed as per recommendation of national and international bodies comprising of intensive therapies such as ARDS ventilation, ECMO management, invasive monitoring, nutrition, physiotherapy, and COVID-19-directed therapies such as steroid, antiviral, and immunomodulators.

We observed high need of sedation, antihypertensives and high ECMO flows to maintain acceptable oxygen saturation. In spite of adequate anticoagulation, some patients developed digital gangrene. 60% of our patients required ECMO oxygenator and/or circuit exchanges for oxygenator failure and thrombosis. All of our patients received multiple blood product transfusion during ECMO bridging. Confirmed heparin-induced thrombocytopenia was observed in three of our patients and were switched to bivalirudin with activated partial thromboplastin time target above 50 seconds. Postprocedural bleeding following tracheostomy or intercostal drain insertion was less observed in bivalirudin-treated group, when compared to heparin group. Intraoperatively we used heparin or continued with bivalirudin with additional citrate anticoagulant in the cell saver.

Critical illness neuropathy affecting both upper and lower limbs were often seen, demanding active physiotherapy and reconditioning. We observed high burden of sepsis with organisms such as *Pseudomonas*, *Klebsiella*, *Enterococcus*, *Enterobacter*, *Stenotrophomonas*, *Serratia*, *Elizabethkingia*, *Chryseobacterium*, and *Sphingomonas*. *Candida auris* was also seen in five cases, entailing change of invasive lines and ECMO circuit in addition to targeted antibiotics.

Patients were regularly evaluated with sedation breaks and spontaneous breathing trials. Their clinical status, ventilatory parameters, and ECMO requirements were routinely assessed and sequential radiologic evaluation was done to gauge the progression of disease or signs of recovery.

Listing and Evaluation for Lung Transplantation

Although lung transplantation is the definitive therapy in patients with post-COVID-19 ARDS-related end-stage lung disease, its effect is miniscule in the setting of a pandemic due to such a small number of patients successfully enduring it. The median survival postbilateral lung transplant in current era is approaching 7 years. This clearly illustrates that the spontaneous recovery is the best possible outcome. Many of the patients referred to our center were elderly, had uncontrolled comorbidities, were physically deconditioned, and had sepsis with multiple organisms. Some of them developed secondary organ dysfunction such as renal failure, severe right ventricular dysfunction, gastrointestinal bleed, and cerebrovascular accidents precluding them from the consideration of a probable transplant.

Preoperative Phase

After 4–6 weeks of ECMO run, the family of the patients demonstrating irreversible lung injury by clinical, ventilatory, and radiological parameters were communicated the need for evaluation for lung transplantation. After serial counseling sessions, the transplantation evaluation was started. History was carefully assessed for any pre-existing lung disease and comorbidities. Sensitization of the patients due to exposure to extracorporeal circuit and multiple product transfusions were checked with panel reactive antibody (PRA) levels. Subjects with PRA levels >30 (two in our cohort) were treated with five cycles of plasmapheresis (PLEX) and intravenous immunoglobulin and PRA levels were repeated a week later. Certain modifications in evaluation were prudent due to ECMO dependency of our cases. 6-minute walk test and right heart study were not performed and cardiac function was evaluated radiologically. We followed the standard principles for listing the patients and adhered to the guidelines laid out by our state and national cadaveric donation governing bodies. Cases were removed from active waiting list if new complications arose such as severe sepsis or organ dysfunction.

On waiting list, patients were and the family were regularly counseled for the need of transplantation in the face of nonrecovery. Any signs of clinical improvements were communicated and decision to delist from active organ waitlist was considered. Emergence of any new complication was timely and appropriately dealt with. Right ventricular dysfunction necessitated inhaled nitric oxide (iNO), inotrope, focused fluid management, and pulmonary dilators. Renal dysfunction usually resolved with a few sessions of renal replacement therapy. Gastrointestinal bleed was evaluated with endoscopies and coagulopathy management. Point-of-care coagulation testing with thromboelastography was routinely used in cases of active bleeding. Our transfusion triggers were restrictive and we used leukodepleted packed red cells and group-specific platelet transfusion if needed.

Four patients who were awaiting lung transplant were delisted as three succumbed to sepsis and one developed intracranial hemorrhage. Our center performed 25 lung transplants (22 males, 3 female) for severe post-COVID ARDS between May 2020 and August 2021. The median age of the study population was 42 years [interquartile range (IQR) 31–66]. The median body mass index (BMI) was 26.7. Median pretransplant ventilatory days were 58 (IQR 22–87) and the mean duration of preoperative ECMO support was 50.9 days.

Intraoperative Phase

On receiving the group matched organ donor call, the size matching was done with predicted total lung capacity formula or CT of the chest based lung volume comparison if available. The donor history, laboratory parameters, radiography, and bronchoscopy were considered before accepting the lung for transplantation. As dictated by the logistics of organ arrival to our center, the recipient was prepared and shifted to operating room. The donor and the recipient blood were cross-matched to detect the presence of any donor-specific antibodies (DSAs).

After intravenous induction and relaxation, recipient lungs were isolated with double lumen tube. Bronchoscopy was utilized in cases of inadequate isolation of the lungs. The Clamshell incision was used to expose the native lungs to facilitate pneumonectomy. We observed dense adhesions, especially in patients with prior thoracic procedure such as intercostal drainage tube placement or presence of secretion or pus-filled cystic cavities. Due to this, the period of recipient pneumonectomy and hemostasis was lengthened.

Peripheral VV-ECMO was converted to central venoarterial ECMO with bicaval drainage to facilitate surgery and provide hemodynamic stability. Poor lung compliance necessitated provision of intravenous anesthetics throughout the surgery. Intraoperative cell saver was routinely used during the procedure. Induction immunosuppression with basiliximab 20 mg was used 1 hour prior to beginning of anastomosis, in most of our patients. Controlled reperfusion of lungs with gradual release of cross-clamp over 10 minutes was crucial. Transesophageal echocardiogram was used to determine the adequacy of de-airing. Methylprednisolone at the dose of 500 mg and 250 mg was administered before the reperfusion of first and second lung, respectively. One patient was positive for DSA and he received intraoperative PLEX and intravenous immunoglobulin before the release of cross clamp. The mean ischemic time in our cohort was 360 ± 155 minutes. ECMO was successfully weaned off on operating table in majority of the cases (n = 1765%). Bronchoscopy to assess the status of anastomotic sites, presence of primary graft dysfunction (PGD), and for clearing of clots was done on table prior to closure of chest. ECMO configuration was changed to peripheral venovenous for the patients with poor gas exchange or ventilatory parameters and shifted to ICU.

Postoperative Phase

In ICU, patients were sedated and ventilated with low tidal volume and iNO. The patients were gradually weaned off iNO, inotropes, and ventilatory support. Triple immunosuppression with tacrolimus, mycophenolate, and steroids were started on day 1. Tacrolimus trough levels were checked and the dose adjusted to the levels of 8–10. Antibiotics were based on donor and recipient cultures. Serial bronchoscopies were done to assess the anastomotic healing and clearance of secretions. Physiotherapy and early mobilization were started. The median length of ICU stay was 15.85 days (range 9–28).

Eight (34%) of patients had PGD presenting as low P/F ratio (PaO_2/FiO_2 ratio <150) with frothy PGD fluid in bronchoscopy. They were treated with continuation of ECMO support, low ventilatory support, iNO, and light diuresis. All our patients recovered from PGD and we were able to wean off ECMO. Renal dysfunction necessitating dialysis was seen in six (24%) of our cases. In our cohort, we observed high incidence of post-transplant airway complication such as anastomotic narrowing (3/25), distal airway narrowing (4/25) and coating, granulation, and polypi formation around bronchial anastomotic site. Overall incidence of airway complications in our study was 56%.[5] None of the patients had features of rejection observed in surveillance biopsies.

Mortality rate at the time of article submission was 32% (8/25). 17 patients are in regular follow-up with 3 patients on tracheostomy recovering in our hospital. Sepsis was the most common cause of mortality (6/8) with reactivation of cytomegalovirus and cerebrovascular accident afflicting the other two patients.

REVIEW OF LITERATURE

In an international cohort study of ECMO life support organization registry by Barbaro et al.,[4] the data of 1,035 COVID-19 ECMO supported patients were evaluated. The median age was 49 years. The median duration from endotracheal intubation to ECMO initiation was 4 days. Majority of patients received VV-ECMO (94%). The median duration of ECMO support was 13.9 days. Tracheostomy was performed in nearly half of patients. Renal replacement therapy usage was 44%. Incidence of in-hospital mortality 90 days after the initiation of ECMO was 38.0%. They concluded that, their results were consistent with previously reported survival rates in acute hypoxemic respiratory failure and recommended that centers experienced in ECMO must consider its use in refractory COVID-19-related respiratory failure.

In a narrative review by Huang et al.,[6] authors have reviewed vast literature regarding ECMO in COVID-19 ARDS. They recommended initiation of ECMO in patients with refractory COVID-19 ARDS despite optimal ventilatory strategies, in cases of prolonged mechanical ventilation, in patients with severe air leak or complicated by myocarditis and when the risk of death exceeded >50%. They advocated the usage of large multistage draining ECMO cannula in femorofemoral or femoro-internal jugular configuration. They concluded by saying that COVID-19 ARDS causes most COVID-19-related deaths and the appropriate use of ECMO in these situations improves the prognosis.

Yeung et al.,[7] in their case series described three patients who underwent bilateral lung transplant for COVID-19 ARDS-related end-stage fibrosis. All their patients were younger than 65 years, had radiological evidence of irreversible lung damage, negative for COVID-19 RT-PCR. They stressed that as the donor lungs are scarce, a balance between the needs of this very sick group of patients and others waiting on the list needed to be reached. All three cases in their series had good short-term outcomes showing the feasibility and considerations of lung transplantation in patients following severe acute COVID-19 in Toronto.

Bharat et al.,[8] in their multiinstitutional case series, chronicled 12 patients with COVID-19-associated ARDS who underwent bilateral lung transplantation at six transplantation centers between May 1 and September 30, 2020. The median age of recipients was 48 years. The CT scan of all their patients exhibited severe lung fibrosis that did not recover despite of long ECMO runs. The median duration of preoperative ECMO was 55 days. They reported that pleural adhesions and hilar lymphadenopathy made lung transplantation more technically demanding with increased intraoperative transfusions. ECMO was empirically continued postoperatively in 83% of cases. Pathology of the explanted lungs showed features of extensive, acute lung injury with fibrosis. At the time of publication, 11 patients were alive and had completed 80 days of follow-up. The authors concluded that lung transplantation was the only option for survival in some patients with severe, unresolving COVID-19-associated ARDS and could be done successfully in carefully selected patients.

Marcelo Cypeland and Shaf Keshavjee[9] in their paper laid out 10 factors to be scrutinized for, before listing these patients for lung transplantation. For the suitability of candidacy, they recommended that the patients were younger (<65 years), have single organ dysfunction, minimum of 6–8 weeks for the probability of recovery, and bear radiological features of irreversible lung damage such as severe bullous destruction or evidence of established fibrosis. They stressed that the patients must be awake and possess the ability to discuss transplantation. Patient should actively participate in physical rehabilitation and fulfill the remaining standard criteria for transplantation. The subject's latest infectivity assays using deep respiratory tract samples have to be negative. They emphasized that the transplantation center should have substantial experience with high-risk transplantation and have access to a broad donor pool and low waiting-list mortality.

CONCLUSION

Lung transplant is a viable option in severe COVID ARDS with irreversible damage to lung parenchyma. The probability of recovery and complications of continuing ECMO support should be weighed in individually. The ideal duration of ECMO bridge-to-recovery in COVID ARDS is currently unknown so the irrecoverable lung injury manifested in serial evaluation and communication with the patients and their family is of paramount importance. Careful selection with assiduous optimization and diligent perioperative care ensures positive outcome in these critical subjects.

REFERENCES

1. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed. 2020;91(1):157-60.
2. World Health Organization. WHO COVID-19 Dashboard. [online] Available from: https://covid19.who.int/. [Last accessed March 2022].
3. Grasselli G, Cattaneo E, Florio G, Ippolito M, Zanella A, Cortegiani A, et al. Mechanical ventilation parameters in critically ill COVID-19 patients: a scoping review. Crit Care. 2021;25:115.
4. Barbaro RP, MacLaren G, Boonstra PS, Combes A, Agerstrand C, Annich G, et al. Extracorporeal Life Support Organization. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life SupportOrganizationregistry.Lancet.2020;396(10257):1071-8.
5. Kumar S, Shah U, Ravipati S, Rahulan V, et al. Airway complications after lung transplant for post coronaviral disease (covid-19) acute respiratory distress syndrome (ARDS) related end stage lung disease: single centre experience. Abstract accepted for presentation at ISHLT annual meeting April 2022, Boston, USA.
6. Huang S, Zhao S, Luo H, Wu Z, Wu J, Xia H, et al. The role of extracorporeal membrane oxygenation in critically ill patients with COVID-19: a narrative review. BMC Pulm Med. 2021;21:116.
7. Yeung JC, Cypel M, Chaparro C, Keshavjee S. Lung transplantation for acute COVID-19: the Toronto Lung Transplant Program experience. CMAJ. 2021;193(38):E1494-7.
8. Bharat A, Machuca TN, Querrey M, Kurihara C, Garza-Castillon Jr R, Kim S, et al. Early outcomes after lung transplantation for severe COVID-19: a series of the first consecutive cases from four countries. Lancet Respir Med. 2021;9(5):487-97.
9. Cypel M, Keshavjee S. When to consider lung transplantation for COVID-19. Lancet Respir Med. 2020;8(10):944-6.

CHAPTER 149

Cytomegalovirus Reactivation in COVID Patients

Nikhilesh Jain, Vishwesh Mehta

INTRODUCTION

While a predominant majority of individuals getting SARS-COV-2 are symptomatic/develop mild-to-moderate symptoms, 15% of the entire cohort is documented to require hospitalization/oxygen support and 5% go on to develop acute respiratory distress syndrome (ARDS), septic shock, and multiple organ dysfunction syndrome (MODS) leading to mortality of affected individuals. The major risk factors implicated in a severe disease include old age, diabetes mellitus, hypertension, obesity, and male sex along with pre-existing cardiovascular issues.[1,2] Historically Wikby et al. documented cytomegalovirus (CMV) as a key component of increased 5-year mortality in elderly individuals.[3] The influence of virus appeared to be worse for male sex with corroboratory finding documenting a worse outcome in men infected with SARS-COV-2.[4]

Cytomegalovirus is a herpes virus which has a community spread by close contact and sexual transmission along with documented viral carriage by 60–100% of adults. Epidemiologically CMV seroprevalence has been reported to approach 100% in low- to middle-income countries; however, severe COVID-related mortality is low in these subsets.[5,6] CMV primary infection is known to give rise to an asymptomatic/mild infection in majority which gives rise to a lifelong latent/persistent infection from which reactivation can happen throughout lifetime of a patient.[5]

With increasing age there is an accumulation of CMV-specific T cells (both helper and effector) which may lead to an inflated T cell response owing to persistent CMV antigenemia. This leads to further depletion of T cell lines and an interplay of NK cells, T cells, and B cells rendering elderly individuals relatively incapable of mounting a severe immune response against other viral infections including COVID.[7,8] To add to above CMV has reported associations with thrombotic episodes, deep venous thrombosis (DVT), myocardial infarction (MI), diabetes mellitus (DM), hypertension (HTN), stroke, and atypical Kawasaki disease-like manifestations in pediatric subgroups and multisystem inflammatory syndrome in children with COVID infections.[9-13]

SALIENT POINTS TO REMEMBER ON CYTOMEGALOVIRUS INFECTIONS

Inflammatory and immune stimulation components remain an opening gambit for CMV reactivation and specifically lungs are a huge reservoir organ for a latent CMV virus.[14] Moss et al. have envisaged a facilitatory role for CMV in metabolic and cardiac complications documented in COVID-19 subgroups.[15] Reactivation of CMV has been reported in severe sepsis cohorts from a duration at a median of 4 days after onset and a similar mechanism is proposed for CMV reactivation especially in bowels and lungs as a likely corollary of immune activation.[16] Reactivation of CMV has been well described in 30–35% of patients getting shifted to ICU and it is associated with higher mortality with a higher CMV viral load in patients shifted to ICU and improved outcomes were documented in patients on antiviral therapy.[17]

Interplay of Cytomegalovirus with COVID Infection

Both CMV and SARS-COV-2 infections act through similar immune pathways and ironically CMV infection may play a contributory role in cytokine storm induced by SARS-COV-2 infections. In addition, it also contributes to a weakened interferon response leading to a greater severity of infection for COVID-19 cohorts.[9,18,19] The incidence of coinfection with CMV and SARS-COV-2 is reported as high as 30% and CMV reactivation is associated with greater likelihood of mortality.

There is documentation of gastrointestinal infections mainly in cases of coinfection along with a few reports of pneumonia as well. Lymphopenia and prolonged duration of mechanical ventilation are identified as risk factors for acquiring secondary infections in cohorts with COVID-19 and as far as CMV reactivation is concerned both above coupled with administration of steroids as per recommendations

of RECOVERY trial contribute to reactivation of CMV. The focus ought to be detecting remnant inflammation in cases of COVID-19 as it is difficult to differentiate COVID pneumonia from a CMV reactivation-related pneumonia purely on clinical and imaging studies. There is a published communication which has attempted the same using a combination of lymphocyte counts and immunoglobulin G (IgG) antibody levels against spike and receptor binding domain. It does make for a case of suspecting a CMV coinfection when an unexplained worsening in terms of imaging/respiratory failure is observed in COVID-19 cohorts.

Since the time Wikby et al.[3] documented CMV as an immune risk phenotype particularly for geriatric subgroups, there were other papers in literature which have concurred with above findings along with conflicting studies for the same. CMV seropositivity is capable of enhancing maturation of Th1 immune responses following a CMV infection in pediatric age groups; hence, there is an opinion which favors better immune responses in younger age groups vis-à-vis older ones wherein the immune responses are diminished paradoxically. This is often referred to as memory inflation corresponding to higher stores of memory and effector cells peculiar to CMV as an individual ages along with losses of natural unexposed T cells.

To illustrate the same, the differences between CMV seropositive and seronegative are as mentioned below.

Cytomegalovirus Seropositive

There is a vascular damage which is aggravated by increased sugar levels along with decrease in number of innocent/ignorant T cells and a heightened senescent response. Simultaneously there is an increase in Th1 and NK cells specific for CMV all of which gets accelerated in geriatric age groups. This is also postulated to increase replication of CMV in cohorts with SARS-COV-2 infections.

Cytomegalovirus Seronegative

There is an intact CD4:CD8 ratio along with a lower quantum of Th1 and NK cells leading to an increased number of innocent/unexposed T cells. This also leads to a better adaptive immunity response in patients as they have a larger number of T cells which leads to a better immune response against COVID 19.

Cytomegalovirus Prophylaxis for Solid Organ Transplants in COVID Era

Universal prophylaxis with valganciclovir remains a gold standard for a duration of 3–6 months based on risk factors for transplant recipients. In COVID era, this assumes further significance as leukopenia being a major risk factor for use of ganciclovir derivatives precludes use in leukopenic subsets which is an adverse prognostic variable for COVID subgroups. To avoid the same, an appropriate monitoring of valganciclovir dosing, monitoring of treatment failures, and resistance remain an area of concern. Persistent leukopenia in the aforementioned subsets may require modification of immunosuppressive therapies namely decreasing the doses of antimetabolites such as mycophenolate mofetil and azathioprine/addition of prednisone or increasing the dose of the same and augmenting the regimen with granulocyte-colony-stimulating-factor can be considered as rescue strategies. If leukopenia remains persistent, a shift of approach to preemptive monitoring (administering and targeting antiviral therapy only for patients whose CMV replication levels exceed a predefined threshold) may be required; however, the documentary evidence for this strategy is not yet defined clearly. Certain other strategies which can be attempted include administration of large doses of acyclovir/dose reduction for valganciclovir/administration of letermovir but validation in large data sets is lacking for the above and there are chances of increasing drug resistance.

AREAS OF FUTURE RESEARCH

Scientific research on COVID-19 and various aspects involving the same remains unexplored and though a definitive impact documenting effect of CMV reactivation on COVID 19 would be worthwhile in terms of designing outcome studies.

This could involve following areas:

- Assessment of matched COVID-19 cohorts along with their CMV seropositivity status.
- Documenting CMV-specific antibody titers with reference to immunopathological effects and exploring a cause–effect relationship in cohorts with range of comorbidities.
- If an association between above is indeed proven, it would be worthwhile to investigate impact of viral loads in cohorts with COVID-19 with a coexistent CMV infection and the quantum of immunological response against COVID-19 in CMV seropositive individuals.
- It would also mean that reactivation of CMV per se in COVID-19 patients can be quantified as an epidemiological exercise to document reactivation of above in COVID 19 patients.
- To continue from above if an association between both COVID-19 and CMV is established, whether using antivirals to modify the course and outcomes in a coinfection would be another area for research and possibly design a vaccine for future with a view to modify the course of the aforementioned infections.

CONCLUSION

COVID-19 infections are associated with a higher mortality in geriatric subgroups and patients with significant comorbidities. In that context, CMV infections are very

common in community and the quantum of infected individuals increases with progression of age and geriatric patients with a CMV infection are known to have an altered T cell and NK cell response leading to higher replication of CMV in cohorts with COVID-19 infections. Whether therapeutic strategies targeting CMV including antiviral drugs and vaccines be able to modify the course of infections in subgroups with CMV reactivation remains to be seen.

REFERENCES

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
3. Wikby A, Johansson B, Olsson J, Löfgren S, Nilsson BO, Ferguson F. Expansions of peripheral blood CD8 T-lymphocyte subpopulations and an association with cytomegalovirus seropositivity in the elderly: the Swedish NONA immune study. Exp Gerontol. 2002;37(2-3):445-53.
4. Roberts ET, Haan MN, Dowd JB, Aiello AE. Cytomegalovirus antibody levels, inflammation, and mortality among elderly Latinos over 9 years of follow-up. Am J Epidemiol. 2010;172(4):363-71.
5. Griffiths P, Baraniak I, Reeves M. The pathogenesis of human cytomegalovirus. J Pathol. 2015;235(2):288–97.
6. Zuhair M, Smit GSA, Wallis G, Jabbar F, Smith C, Devleesschauwer B, et al. Estimation of the worldwide seroprevalence of cytomegalovirus: A systematic review and meta-analysis. Rev Med Virol. 2019;29(3):e2034.
7. Chidrawar S, Khan N, Wei W, McLarnon A, Smith N, Nayak L, et al. Cytomegalovirus-seropositivity has a profound influence on the magnitude of major lymphoid subsets within healthy individuals. Clin Exp Immunol. 2009;155(3):423-32.
8. Powers C, DeFilippis V, Malouli D, Früh K. Cytomegalovirus immune evasion. Curr Top Microbiol Immunol. 2008; 325:333-59.
9. Soderberg-Naucler C. Does cytomegalovirus play a causative role in the development of various inflammatory diseases and cancer? J Intern Med. 2006;259(3):219-46.
10. Belga S, MacDonald C, Chiang D, Kabbani D, Shojai S, Abraldes JG, et al. Donor graft CMV-serostatus and the risk of arterial and venous thrombotic events in seronegative recipients after non-thoracic solid organ transplantation. Clin Infect Dis. 2021;72(5):845-52.
11. Simanek AM, Dowd JB, Pawelec G, Melzer D, Dutta A, Aiello AE. Seropositivity to cytomegalovirus, inflammation, all-cause and cardiovascular disease-related mortality in the United States. PLoS One. 2011;6(2):e16103.
12. Catalano-Pons C, Quartier P, Leruez-Ville M, Kaguelidou F, Gendrel D, Lenoir G, et al. Primary cytomegalovirus infection, atypical Kawasaki disease, and coronary aneurysms in 2 infants. Clin Infect Dis. 2005;41(5):e53-6.
13. Consiglio CR, Cotugno N, Sardh F, Pou C, Henckel E, Arzoomand A, et al. The immunology of multisystem inflammatory syndrome in children with COVID-19. Cell. 2020;183(968):981.
14. Poole E, Juss JK, Krishna B, Herre J, Chilvers ER, Sinclair J. Alveolar macrophages isolated directly from human cytomegalovirus (HCMV)-seropositive individuals are sites of HCMV reactivation in vivo. J Infect Dis. 2015;211(12):1936-42.
15. Moss P. "The ancient and the new": is there an interaction between cytomegalovirus and SARS-CoV-2 infection? Immun Ageing. 2020;17:14.
16. Kutza AS, Muhl E, Hackstein H, Kirchner H, Bein G. High incidence of active cytomegalovirus infection among septic patients. Clin Infect Dis. 1998;26(5):1076-82.
17. Cowley NJ, Owen A, Shiels SC, Millar J, Woolley R, Ives N, et al. Safety and efficacy of antiviral therapy for prevention of cytomegalovirus reactivation in immunocompetent critically ill patients: A randomized clinical trial. JAMA Intern Med. 2017;177(6):774-83.
18. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020;130(5):2620-9.
19. McSharry BP, Avdic S, Slobedman B. Human cytomegalovirus encoded homologs of cytokines, chemokines and their receptors: roles in immunomodulation. Viruses. 2012;4(11):2448-70.

CHAPTER 150

Inflammatory Markers in COVID

YP Singh, Akhil Taneja, Gaurav Pratap Singh

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) in March 2020 and the virus was officially named as SARS-CoV-2.[1]

Although the most common clinical presentation is pneumonia and acute respiratory distress syndrome (ARDS), COVID-19 presents clinically with a wide variety of symptoms and now it is being recognized as a multisystem inflammatory syndrome (MIS).

With the repeated and overwhelming surges in the number of cases, healthcare systems around the world have been struggling to meet the increasing demand created by the sheer number of the infected population. Rapid and accurate diagnosis has widespread implications on patients, healthcare personnel, and administrative bodies. Effective utilization of available resources is of paramount importance to keep a check on healthcare burden and maximize the number of lives saved.[2]

Diagnosis of COVID-19 is based mainly on detection of SARS-CoV-2 nucleic acid by polymerase chain reaction (PCR) and detection of the outer proteins of the viral envelope (antigen test).

COVID-19 has two distinct phases in the evolution of disease, viremic phase (8–10 days), which in most cases is followed by resolution. The remaining patients progress to inflammatory phase—featuring multisystem involvement, linked cytokine storm. While clinical assessment is most important, inflammatory biomarkers can provide important information which is helpful in decision-making regarding various aspects of patient care including but not limited to triage, diagnosis, severity assessment, treatment protocol, and prognosis.[2]

IMMUNO-THROMBO-INFLAMMATORY RESPONSE IN COVID

Hyperinflammation and *cytokine storm* are the key factors in pathogenesis of severe COVID-19, a complex interplay of the inflammatory, immunological, and coagulation cascades altered by genetic differences in immune system of host result in diffuse systemic inflammation and multiorgan involvement.[3]

Activation of inflammatory, immunological, and coagulation cascades and subsequent organ damage can be assessed by presence and levels of various markers **(Table 1)**.[2] Viral infections induce both innate and adaptive immune

TABLE 1: Potential inflammatory markers.

Hematological	• Leukocytosis/leukopenia • Lymphopenia • Neutrophilia • Depletion of CD4+ and CD8+ cells • Elevated neutrophil-to-lymphocyte ratio (NLR) • Thrombocytopenia/thrombocytosis
Inflammation	• Cytokines • Chemokines • Growth factors • C-reactive protein • Procalcitonin • Lactate dehydrogenase
Coagulation	• D-dimer levels • Fibrinogen • Fibrin degradation products (FDPs) • Prothrombin time (PT) • Activated partial thromboplastin time (aPTT)
Cardiac	• Cardiac troponin (ctn) • Brain natriuretic peptide (BNP)/NT-proB
Hepatic	• Aspartate aminotransferase (AST) • Alanine aminotransferase (ALT) • Bilirubin • Albumin
Muscles	• Creatine-kinase (CK) • Myoglobin
Renal	Serum creatinine
Electrolytes	• Hyponatremia • Hypokalemia • Hypocalcemia

(*Adapted from*: Samprathi M, Jayashree M. Biomarkers in COVID-19: An up-to-date review. Front Pediatr. 2021;8:607647.)

responses leading to induction of T cells and the release of various antigen specific antibodies by the B cells which is followed by release of various proinflammatory cytokines and chemokines promoting increased concentration of macrophages and neutrophils at the affected site. This phenomenon generally results in clearing of infection but sometimes an intense, exaggerated response can lead to destruction of host tissue.[4]

The coagulation cascade involves endothelial cells, platelets, neutrophils, monocytes, and macrophages. Disruption of vascular endothelium which is both antithrombotic and anti-inflammatory by SARS-CoV-2 leads to thrombosis and inflammation primarily driven by thrombin.

This disproportionate *immuno-thrombo-inflammatory response* is central to pathogenesis of multiorgan failure in COVID-19. COVID-19 patients admitted to intensive care unit (ICU) have higher levels of inflammatory cytokines such as interleukin (IL)-2, IL-7, IL-10, interferon (IFN)-γ-induced protein (IP)-10, tumor necrosis factor (TNF), and granulocyte-colony stimulating factor (G-CSF) as compared to the plasma of patients not admitted in the ICU. COVID-19 patients have higher levels of IL-6 as compared to healthy individuals.

BIOMARKERS STUDIED IN COVID-19

Hematological Parameters

Hemoglobin

Anemia and altered iron homeostasis are common in hospitalized COVID-19 patients. Anemia on presentation is associated with increased risk of mortality and a higher ferritin/transferrin ratio predicts need for ICU admission and mechanical ventilation.[5]

Lymphocyte

Lymphocytopenia is a hallmark of COVID-19 and directly correlate with disease severity and death. It is multifactorial in origin including direct viral invasion, lymphocyte apoptosis-induced by ILs, reduced lymphocyte turnover due to the "cytokine storm"-induced atrophy of lymphoid organs and reduced lymphocyte proliferation due to lactic acidosis.[6]

Lymphopenia on admission (defined as lymphocyte count ≤1,100 cells/μL) is associated with increased risk of mortality, ARDS, and need for ICU admission. Appearance of significant lymphopenia at 7–14 days coincides with worsening clinical status, increase in inflammatory mediators, and "cytokine storm."[7]

Patients with <20% and <5% lymphocytes at days 10–12 and 17–19 from the onset of symptoms, respectively, had the worst prognosis. Patients requiring admission to the ICU had higher percentage and absolute number of neutrophils.[8]

Other Hematological Markers

Patients requiring admission to the ICU had higher percentage and absolute number of neutrophils. Monocytes and basophils are also decreased, both thrombocytopenia and thrombocytosis have been observed, and bleeding is uncommon.

"NLP score" devised by Zheng et al. based on neutrophil, lymphocyte, and platelet counts predicts progression to severe disease when value is >6.[9]

Neutrophil–lymphocyte ratio (NLR) at admission is a good surrogate marker for diagnosis of COVID-19 in appropriate clinical setting, also a rising NLR has prognostic value.[10,11]

Inflammatory Parameters

C-reactive Protein

C-reactive protein is a pentameric protein synthesized by the liver under the action of cytokine IL-6. Raised levels of CRP are seen in various inflammatory conditions vis–a-vis bacterial infection, trauma, and acute cardiovascular disease. Elevated CRP levels suggest a proinflammatory state and can also be used as a prognostic marker for the underlying disease processes.

Raised levels of CRP on admission and a rising trend over duration of illness strongly correlate with risk of venous thromboembolism (VTE), acute kidney injury (AKI), critical illness, and in-hospital mortality in patients with COVID-19. A cut-off value of 26 mg/L can be considered to predict risk of progression to severe disease and as a guide to rationalize therapy.[12]

Cytokines

Interleukin-6 is consistently elevated in COVID-19 patients. As per existing evidence, IL-6 is superior to CRP and other markers of inflammation in predicting respiratory failure and ARDS in COVID-19.

Higher IL-6 value (>24 pg/mL) on admission correlates with severity, risk of progression to severe respiratory disease, and mortality with excellent sensitivity and good specificity. IL-6 levels can also be used to monitor therapeutic response.[13,14]

Other proinflammatory cytokines [IL-1β, IL-2, IL-8, IL-17, G-CSF, granulocyte-macrophage colony-stimulating factor (GMCSF), IP-10, monocyte chemoattractant protein (MCP)-1, (C-C motif chemokine ligand 3) CCL3, and TNF-α] are significantly increased in patients with severe disease.

Ferritin

Ferritin levels >500 μg/L (normal range: females 10–200 μg/L; males 30–300 μg/L) have been associated with severity of disease. Existing evidence is not enough to make a clear case in favor or against the use of ferritin level for prognostic purpose.[2]

Coagulation Parameters

Coagulopathy in COVID-19 differs from the usual disseminated intravascular coagulation (DIC), in having a high fibrinogen, normal or mildly prolonged prothrombin time and activated partial thromboplastin time, mild thrombocytopenia (platelet count >100 × 103/mL), and no evidence of microangiopathy.

Elevated D-dimer levels are a common finding in patients with COVID-19. There is enough evidence to show that D-dimer levels have prognostic value and correlate with disease severity and in-hospital mortality. A level of >1.5–2 µg/mL on admission predicts increased mortality.

D-dimer levels also help to decide regarding anticoagulation.[15,16]

Other Biomarkers

Creatine kinase-MB (CK-MB), cardiac troponin I (cTnI), Myoglobin (Mb), and N-terminal-proB-type natriuretic peptide (NT-proBNP) are myocardial injury specific and increased to varying degrees, in severe and critical illness. Higher levels were associated with higher mortality; their routine use can be misleading and cannot be recommended.

About half of patients presented with increased lactate dehydrogenase (LDH) levels which is associated with a higher risk of respiratory failure need for ICU admission and mortality.

TEMPORAL TRENDS IN BIOMARKERS

Temporal variation of biomarkers provides early and important clue along the course of the illness regarding disease progression and therapeutic response. **Table 2** summarizes the temporal course of various biomarkers.

ROLE OF BIOMARKERS IN VARIOUS AREAS OF PATIENT MANAGEMENT

Biomarkers in COVID-19 can be useful in the following areas:[2]

- Early suspicion and diagnosis of disease (leukopenia, lymphopenia, high NLR ratio, and LDH)
- Confirmation and classification of disease severity [lymphopenia, IL-6, CRP, ferritin, LDH, D-dimers, cardiac biomarkers—CK-MB, cardiac troponin T (CTnT), Mb, and NT-proBNP]
- Response to therapy (CRP and IL-6)
- Prognosis [IL-6, ferritin, LDH, CRP, procalcitonin (PCT), lymphocyte count, NLR, platelet count, cardiac biomarkers—CK-MB, CTnT, Myoglobin (Mb), and NT-proBNP]

TABLE 2: Temporal trends: Biomarkers in COVID-19.

<8 days	• Total leukocyte count and lymphocyte count normal or slightly low • CRP, ferritin, cardiac enzymes, LDH, D-dimer—may be early markers of severe disease and mortality
8–16 days	• Total leukocyte count and lymphocyte count progressively fall to reach nadir at 8–9 days • Increasing IL-6, D-dimer, and CRP
>16 days	Increasing total leukocyte count, lymphocyte, and platelet count predict recovery while reducing counts predict mortality

(CRP: C-reactive protein; LDH: lactate dehydrogenase; IL: interleukin)

CONCLUSION

An understanding of *immuno-thrombo-inflammatory response* in host body as a response to viral antigen is essential for the initial identification of potential biomarkers. To put in simple words, an understanding of what the virus does to the body and how the body reacts to it, is central to concept of using biomarker for initial assessment, risk stratification, therapy rationalization, and prognostication.

A thorough knowledge regarding temporal trends of biomarkers add meaningful insight to clinical and bedside decision-making.

REFERENCES

1. World Health Organization. Naming the Coronavirus Disease (COVID-19 and the Virus That Causes it. (2020). [online] Available from: https://www.who.int/ emergencies/diseases/novel-coronavirus-2019/technical-guidance/namingthe coronavirus-disease-(covid-2019)-and-the-virus-that-causes it. [Last accessed March 2022].
2. Samprathi M, Jayashree M. Biomarkers in COVID-19: an up-to-date review. Front Pediatr. 2021;8:607647.
3. Upadhyay J, Tiwari N, Ansari MN. Role of inflammatory markers in corona virus disease (COVID-19) patients: a review. Exp Biol Med. 2020;245(15):1368-75.
4. Catanzaro M, Fagiani F, Racchi M, Corsini E, Govoni S, Lanni C. Immune response in COVID-19: addressing a pharmacological challenge by targeting pathways triggered by SARS-CoV-2. Signal Transduct Target Ther. 2020;5(1):84.
5. Bellmann-Weiler R, Lanser L, Barket R, Langer L, MacMillan TE, Cavalcanti R, et al. Prevalence and predictive value of anemia and dysregulated iron homeostasis in patients with COVID-19 infection. J Clin Med. 2020;9:E2429.
6. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, et al. Hematological findings and complications of COVID-19. Amer J Hematol. 2020;95(7):834-47.
7. Huang I, Pranata R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis. J Intensive Care. 2020;8:36.
8. Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang YQ, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther. 2020;5:33.
9. Zheng Y, Zhang Y, Chi H, Chen S, Peng M, Luo L, et al. The hemocyte counts as a potential biomarker for predicting disease progression in COVID-19: a retrospective study. Clin Chem Lab Med. 2020;58(7):1106-15.

10. Yan X, Li F, Wang X, Yan J, Zhu F, Tang S, et al. Neutrophil to lymphocyte ratio as prognostic and predictive factor in patients with coronavirus disease 2019: a retrospective cross-sectional study. J Med Virol. 2019;92(11):2573-81.
11. Ma A, Cheng J, Yang J, Dong M, Liao X, Kang Y. Neutrophil-to-lymphocyte ratio as a predictive biomarker for moderate-severe ARDS in severe COVID- 19 patients. Crit Care. 2020;24:288.
12. Wang G, Wu C, Zhang Q, Wu F, Yu B, Lv J, et al. C-reactive protein level may predict the risk of COVID-19 aggravation. Open Forum Infect Dis. 2020;7:ofaa153.
13. Chen R, Sang L, Jiang M, Yang Z, Jia N, Fu W, et al. Medical treatment expert group for COVID-19. Longitudinal hematologic and immunologic variations associated with the progression of COVID-19 patients in China. J Allergy Clin Immmunol. 2020;146(1):89-100.
14. Liu T, Zhang J, Yang Y, Ma H, Li Z, Zhang J, et al. The role of interleukin-6 in monitoring severe case of coronavirus disease 2019. EMBO Mol Med. 2020;12(7):e12421.
15. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost. 2020;18(6):1324-9.
16. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. J Intensive Care. 2020;8:49.

CHAPTER 151

Hyperferritinemia in COVID-19 Patients

Vajrapu Rajendra, K Subba Reddy, Sambit Sahu

INTRODUCTION

Iron is essential for cellular respiration and oxygen transport, but free form of iron can also be potentially lethal due to its ability to catalyze redox reactions in tissues to generate highly toxic free radicals.[1] Hence, iron is bound to proteins and ferritin is the major intracellular iron storage protein. The primary role of ferritin in health is iron storage, but in inflammation, it acts as an immune modulator.[2]

Ferritin is considered as a molecule essential for iron metabolism in the body also as acute inflammatory biomarker. There is a feedback regulation of ferritin as per proinflammatory and anti-inflammatory processes. A serum ferritin >300 μg/L for men and >200 μg/L for women is considered as hyperferritinemia.[3]

In COVID-19 infection, ferritin is an early elevated biomarker along with lymphopenia and is associated with "cytokine storm syndrome" (CSS).[4] It appears that there is a significant association of hyperferritinemia and the severity of COVID-19 disease. Many retrospective studies from Wuhan demonstrated that admission ferritin levels were between three and four times higher in nonsurvivors compared to survivors and 5.3 and 1.5 times higher in patients in severe than in milder forms of the disease, respectively. Several studies found that mild and moderate disease [surviving and without acute respiratory distress syndrome (ARDS)] serum ferritin levels were <1,000 μg/L, while in severe (nonsurvivors and with ARDS) were >1,000 μg /L.[5] Thus, high serum ferritin can identify a more severe COVID-19, which helps in early and aggressive inpatient management and utilizing the limited resources more judiciously.[6] It is also observed that hyperferritinemia can continue for few months after the onset of COVID-19 and it may suggest a long COVID syndrome.[7] Serum ferritin and CRP (C-reactive protein) seems to be better screening tools for the early diagnosis of a severe form of COVID-19 (CSS) with lesser cost and wider availability than interleukin (IL)-6.[8]

BASIC PATHOPHYSIOLOGY OF FERRITIN

Toxic levels of iron injure cells by release of free radicals and cause fibrosis. Ferritin is an intracellular, nonglycosylated protein of the reticuloendothelial system and liver. Each molecule of ferritin stores iron up to 4,500 ions in Fe^{3+} form. It acts as a dynamic buffer of iron in maintaining constant reserve of iron. Intracellular concentrations of ferritin about 1,000 times higher than those in the serum, serum ferritin is the result of cell lysis.[9] There is regulation of ferritin by cytokines in macrophages, which causes increase in ferritin values in inflammatory conditions. There is increased levels of hepcidin (a major iron regulator) causing increased ferritin. It is also found that there is a similarity in spike protein of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) virus and hepcidin, causing a *hepcidin-like effect.*[10]

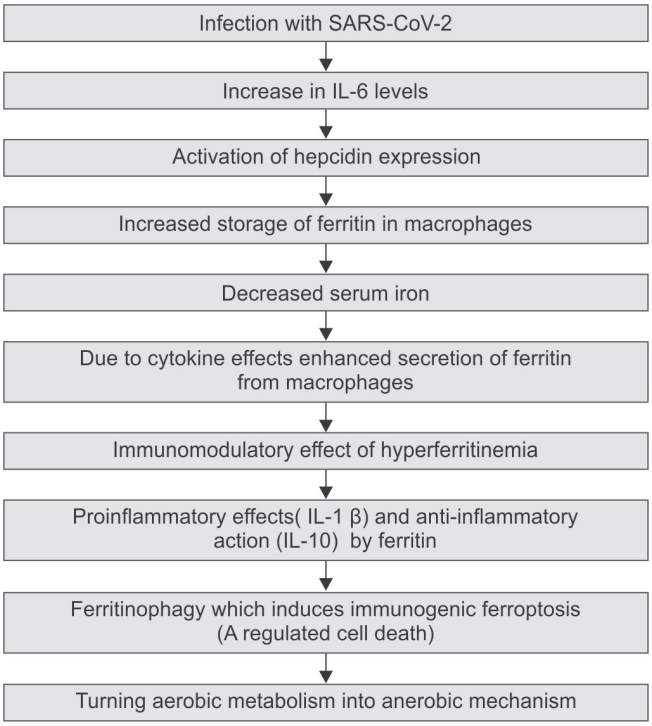
Disbalance in iron metabolism and regulation leads to following effects:[11]

- Low hemoglobin levels due to low serum iron and erythropoiesis
- Toxic-free circulating heme causing lipid peroxidation and free radical release
- Hyperferritinemia
- Limits the availability of essential iron to microbes
- Reduced nitric oxide synthesis
- Coagulation activation
- Mitochondrial degeneration and ferroptosis
- Enhanced inflammatory activity [IL-1β, inhaled nitric oxide (iNO)]
- Immunosuppression [by inhibiting T-cell proliferation, or immunoglobulin G (IgG) production]
- Hemochromatosis type hepatic injury
- Hyperferritinemia syndromes.

As per Shoenfeld et al., the heavy chain of ferritin may have a role in macrophage activation by increased secretion of inflammatory cytokines.[12] Hyperferritinemic syndromes include catastrophic antiphospholipid

syndrome (CAPS), adult-onset Stills disease (AOSD), macrophage activation syndrome (MAS), secondary hemophagocytic lymphohistiocytosis (HLH), septic shock, and COVID-19 CSS. It is still under research whether ferritin is a marker of disease severity, or a modulator in disease pathogenesis.[13]

COVID-19 AND HYPERFERRITINEMIA[14]



There are many hypotheses that reducing the ferritin levels may result in a better outcome in this set of patients. Several iron-chelating agents such as deferoxamine, deferasirox, and deferiprone are under scrutiny. Some anecdotal evidence also suggests recombinant human erythropoietin (rhEPO) may have also a role to play.[15]

Hyperferritinemia is seen in COVID-19, Ebola, and dengue fever but not in other coronavirus epidemics such as MERS (Middle East respiratory syndrome), SARS, and influenza B infection. This knowledge could be useful during flu season to differentiate among different pathologies.[16]

CONCLUSION

Many disease processes cause hyperferritinemia, hence a systematic diagnostic protocol is needed to differentiate the pathogenesis. In COVID-19, ferritin appears to be both the cause and the result of the disease evolution. Early identification of hyperferritinemia can help to give intensive therapies to reduce mortality and morbidity.

REFERENCES

1. Su LJ, Zhang JH, Gomez H, Murugan R, Hong X, Xu D, et al. Reactive oxygen species-induced lipid peroxidation in apoptosis, autophagy, and ferroptosis. Oxid Med Cell Longev. 2019;2019(30):1-13.
2. Kuhn LC. Iron regulatory proteins and their role in controlling iron metabolism. Metallomics. 2015;7(2):232-43.
3. Cullis JO, Fitzsimons EJ, Griffiths WJ, Tsochatzis E, Thomas DW; British Society for Haematology. Investigation and management of a raised serum ferritin. Br J Haematol. 2018;181(3):331-40.
4. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.
5. Kappert K, Jahić A, Tauber R. Assessment of serum ferritin as a biomarker in COVID-19: bystander or participant? Insights by comparison with other infectious and non-infectious diseases. Biomarkers. 2020;25(8):616-25.
6. Ruscitti P, Berardicurti O, Di Benedetto P, Cipriani P, Iagnocco A, Shoenfeld Y, et al. Severe COVID-19, another piece in the puzzle of the hyperferritinemic syndrome. An immunomodulatory perspective to alleviate the storm. Front Immunol. 2020;11:1130.
7. Sonnweber T, Boehm A, Sahanic S, Pizzini A, Aichner M, Sonnweber B, et al. Persisting alterations of iron homeostasis in COVID-19 are associated with non-resolving lung pathologies and poor patients' performance: a prospective observational cohort study. Respir Res. 2020;21:276.
8. Melo AKG, Milby KM, Caparroz ALMA, Pinto ACPN, Santos RRP, Rocha AP, et al. Biomarkers of cytokine storm as red flags for severe and fatal COVID-19 cases: A living systematic review and meta-analysis. PLoS One. 2021;16(6):e0253894.
9. Kell B, Pretorius E. Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. Metallomics. 2014;6:748-73.
10. Čepelak I, Dodig S, Vučenik I. Hyperferritinemia and COVID-19? RAD CASA - Medical Sciences. [online] Available from: file:///C:/Users/91966/Downloads/1100524.2020_hyperferritinemia_and_COVID.pdf. [Last accessed March, 2022].
11. Nairz M, Weiss G. Iron in infection and immunity. Mol Aspects Med. 2020;75:100864.
12. Rosario C, Zandman-Goddard G, Shoenfeld Y, Meyron-Holtz EG, D'Cruz DP, et al. The hyperferritinemic syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. BMC Med. 2013;11:185.
13. Colafrancesco S, Alessandri C, Conti F, Priori R. COVID-19 gone bad: A new character in the spectrum of the hyperferritinemic syndrome? Autoimm Rev. 2020;19(7):102573.
14. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immuno. 2020;215:108427.
15. Vlahakos VD, Marathias KP, Arkadopoulos N, Vlahakos DV. Hyperferritinemia in patients with COVID-19: An opportunity for iron chelation? Artif Organs. 2021;45(2):163-7.
16. Jusufovic V, Umihanic S, Stratton R, Alibegovic E, Piljic D, Mujkanovic A, et al. Ferritin and LDH as predictors of mortality in COVID-19 infection, bosnia and herzegovina single center study. DOI: https://doi.org/10.21203/rs.3.rs-143696/v1.

CHAPTER 152

Extracorporeal Membrane Oxygenation in COVID-19: Is it Different?

Dipanjan Chatterjee, Arpan Chakraborty

INTRODUCTION

Since the end of 2019, global pandemic caused by novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) has resulted in death of millions of people. India has witnesses >5.15 lac deaths due to coronavirus disease 2019 (COVID-19). Severe COVID-19 is a multisystemic disease, with lungs being the most common organ affected, leading to acute respiratory failure and acute respiratory distress syndrome (ARDS). These patients have high risk of mortality in spite of best critical care practices.

Clinicopathophysiological features of COVID-19-associated ARDS (CARDS) are different from the ARDS due to other infective etiologies. Two phenotypes have been described. Type L (atypical ARDS) has low elastance, high compliance and low recruitability. Type H (typical ARDS) has high elastance, low compliance and high recruitability.[1] CARDS may not conform to the Berlin criteria in truest sense, since the time of onset is usually 8–12 days, and the type L has high compliance as well as lack the typical picture of dependent lung consolidation of ARDS. The severe hypoxia disproportionate to the extent of radiological extent of lung consolidation has been postulated due to pulmonary vascular endothelial dysfunction with loss of hypoxic pulmonary vasoconstriction (HPV) function, cytokine storm-induced pulmonary vasodilatation, formation of microthrombi due to loss of endothelial barrier, and renin-angiotensin system dysregulation all leading to severe V/Q mismatch.[2] In addition, severe COVID-19 also may result in acute myocarditis and acute coronary syndrome, acute right heart dysfunction due to severe ARDS, acute kidney injury (AKI), acute hepatic dysfunction, ischemic stroke, coagulation abnormalities with pulmonary embolism, and dysregulated immune response (cytokine storm). Due to the above features the natural course of disease in CARDS differs from typical ARDS due to other etiologies.

Extracorporeal membrane oxygenation (ECMO) has been used to support patients with severe ARDS due to COVID-19. ECMO during global pandemic is fraught with various issues regarding logistics and ethics. ELSO has issued guidelines for proper utilization of this modality for optimum patient care.[3] Prior to ECMO, the patient should have received and exhausted conventional care for severe ARDS including lung protective ventilation, neuromuscular blockade, recruitment strategies, systemic corticosteroids, anticoagulation, prone positioning, and pulmonary vasodilators. Initiation of ECMO provides adequate oxygenation and allows lung protective ventilation.

Patients may be considered for ECMO if they have at least any one of the following:[3]

- $PaO_2/FiO_2 < 50$ mm Hg for at least 3 hours.
- $PaO_2/FiO_2 < 80$ mm Hg for at least 6 hours.
- Arterial blood pH < 7.25 and $PaCO_2 \geq 60$ mm Hg for 6 hours.

Contraindications to ECMO are few and include:

- Age > 70 years (relative contraindication).
- Severe comorbidities incompatible with recovery such as metastatic malignancy, unmanageable organ failure, and unreversible neurological impairment.
- Invasive ventilation duration longer than 10 days with high driving pressure.

TIMING OF EXTRACORPOREAL MEMBRANE OXYGENATION INITIATION

During the pandemic, ECMO was seen as a modality of last resort, hence referral for ECMO is frequently delayed. Often patients are on prolonged noninvasive ventilation (NIV) support, with delayed intubation and acute hypoxia/hypercarbia long after onset of initial symptom. Hence, the duration on NIV should be accounted for while considering eligibility of ECMO initiation since delayed initiation of ECMO has poorer outcome.[4]

Cannulation

Femoro-jugular cannulation with a large drainage cannula is the most common configuration followed by femoro-femoral cannulation. Dual lumen cannulation has also been used as these patients can be better mobilized leading

to early recovery and rehabilitation in prolonged ECMO. Almost all these patients are on anticoagulants, hence care should be taken during cannulation to prevent bleeding at cannulation site.

Bleeding and Thrombosis—Anticoagulation Management

There has been reports of frequent thrombotic events on ECMO including circuit clotting and massive pulmonary embolism. Hence, adequate anticoagulation is to be maintained with unfractionated heparin, and monitored with activated partial thromboplastin time (aPTT) (60–75 seconds) or anti-Xa activity 0.3–0.5 IU/mL. Some centers prefer to use direct thrombin inhibitors.

These patients also are at high risk of major bleeding including intracranial hemorrhage. Hence, a balanced anticoagulation regime needs to be followed with regular monitoring of coagulation factors and platelets. COVID-19 patients have higher need of circuit changes, oxygenator failures, pump failures, and cannula conditions compared to non-COVID-19 patients.[5] Hence, careful monitoring of circuit and oxygenator is needed.

Cardiovascular Dysfunction

Some patients of COVID-19 present with acute myocarditis and acute coronary syndrome, leading to cardiogenic shock. Despite initial treatment with inotropes and vasopressors, some are in severe low cardiac output state needing ECMO support in the form of veno-arterial (V-A) or veno-arterial-venous (V-AV) (hybrid) configuration. Some patients may develop low cardiac output state later, after initiation of veno-venous extracorporeal membrane oxygenation (VV-ECMO). Change of circuit configuration to V-AV is needed to support the circulation in this patient population. ECMO for circulatory support is associated with higher risk of mortality (hazard ratio 1.89, 95% confidence interval (CI) 1.20–2.97). In contrast, children needing VA-ECMO for multisystem inflammatory syndrome in children (MIS-C)-related circulatory impairment have very high survival rates.[6]

Some patients with severe right ventricular dysfunction, most likely secondary to high right ventricular afterload, have worse outcome. Some centers have adopted altered cannulation using ProtekDuo TandemHeart cannula (CardiacAssist Inc., Pittsburgh, Pennsylvania) to provide right atrium-pulmonary artery (RA-PA) right-ventricular assist device (RVAD)/ECMO with good outcome.[7,8]

Patients with severe COVID-19 needing ECMO support also have high incidence of AKI, hepatic dysfunction, and ischemic stroke, all associated with adverse outcome.[9]

Barotrauma

Patients with severe COVID-19-related ARDS on invasive mechanical ventilation, have higher incidence of barotrauma-related events (14.7%) [pooled estimates, 16.1% (95% CI, 11.8–20.4%)], compared to ARDS due to other causes (6.3%; pooled estimates, 5.7%; 95% CI, 2.1–13.5%).[10]

Barotrauma can manifest as pneumothorax, pneumomediastinum or subcutaneous emphysema even with lung protective ventilation and VV-ECMO support. These patients have prolonged duration of ECMO and worse outcomes. Mortality in COVID-19 patients who developed barotrauma is 56.1% (pooled estimates, 61.6%; 95% CI, 50.2–73.0%) compared to 10% in non-COVID-19 ARDS.[10] Management includes chest tube drainage for significantly large pneumothorax, mechanical ventilation with lower positive end-expiratory pressure (PEEP) and lower driving pressure, and awake ECMO with spontaneous respiration may be attempted.

Adjuvant Therapy—Proning

Beneficial effects of proning in COVID-19 have been demonstrated in spontaneously breathing patients as well as in patients on invasive mechanical ventilation. The use of prone position ventilation (PPV) has been attempted in patients on VV-ECMO support. Mobilization of patients on ECMO from supine to prone is dependent on trained manpower support. These patients have ECMO cannulae, either femoro-femoral or femoro-jugular. The patient needs to be monitored continuously during the process to note cannulae displacement or kinking, alteration in flow or hemodynamic instability. PPV is indicated in patients with poor oxygenation in spite of ECMO support. PPV optimizes lung recruitment and perfusion, mitigates VILI, preventing ongoing native lung damage, improves right ventricular function, and overall hemodynamics.[11] PPV also eases clearance of secretions.

Adjuvant Therapy—Awake Extracorporeal Membrane Oxygenation

To avoid the deleterious effects of invasive mechanical ventilation [ventilator-induced lung injury, ventilator-associated pneumonia (VAP)], awake ECMO has been advocated, where patient is not on mechanical ventilation.[12] Other postulated benefits of awake ECMO being patient are able to actively participate in physiotherapy and interact with family. The inability to monitor and effectively control the transpulmonary pressure, which is the major determinant of patient self-induced lung injury (P-SILI), is the major drawback. Increased breathing efforts and coughing can cause large swings in intrapleural pressure, resulting in reduced blood flow in drainage cannula and subsequent hypoxemia. This can be attempted in patients with air leak syndromes such as surgical emphysema and spontaneous pneumothorax.

Prolonged Extracorporeal Membrane Oxygenation

It is seen that time on ECMO is longer in COVID-19 than in other causes of ARDS, and a large number of patients need prolonged (≥28 days) ECMO support.[13] These patients are most likely to need circuit changes. Prolonged ECMO patients stretch human and financial resources as well as logistic support, all of which are scarce during a pandemic. Severe endothelial injury could play a crucial role in the need for prolonged ECMO support as it might take more time to recover.

The use of neuromuscular blocking drugs needs to be restricted and early mobilization and rehabilitation should be targeted.

Interestingly, greater duration of ECMO support is not associated with death. Prolonged ECMO allows time for lung parenchymal recovery and survival without lung transplantation. Hence, lack of improvement of lung function in the first weeks of ECMO or even temporarily worsening should not be seen as an indication to stop treatment, since favorable outcomes can be expected even after prolonged ECMO support.

NEW ONSET INFECTION

COVID-19 patients on ECMO exhibit higher incidence of secondary bacterial and fungal infections during the course of treatment. 85–89% incidence of antibiotic treated VAP has been reported. 44–51% patients had ≥1 treated bacteremia episodes.[14] Gram-negative pathogens maintained an overall predominance as causative agents of initial and subsequent infections. High incidence of fungal infections has also been reported. These patients have poor clinical progression and higher mortality. It is postulated that these patients have higher susceptibility due to treatment with broad-spectrum antibiotics and immunosuppressive therapies.[15] Septic shock due to secondary infection can lead to multiorgan dysfunction with poor prognosis.

OUTCOME

Though initial reports of ECMO in COVID-19 from China reported dismal outcome with mortality of 83%.[16] Later studies from large volume centers have reported better outcomes. Barbaro et al. in their initial study of 1,035 patients on ECMO reported mortality of 39%.[5] In another meta-analysis of 1,896 patients by Ramanathan et al. mortality rate was 37.1%.[17] These data show mortality rate is comparable to that of ECMO for non-COVID-19 ARDS.

Shaefi et al. found significantly lower 60-day mortality in patients receiving ECMO 35.3% (95% CI 27.2–43.5%) versus invasive mechanical ventilation 47.9% (95% CI 44.9–50.8%) in acutely hypoxic respiratory failure (PaO_2/FiO_2 ratio < 100).[18]

Recent studies comparing data from first and second waves suggest poorer outcomes in the later phase of the pandemic, with higher mortality rate (51.9–60.1% vs. 36.9–41.1%), and higher rate of coinfections (bacterial and fungal).[19,20] This data needs to be considered while assessing a COVID-19 patient for ECMO and possible outcomes discussed prior to initiation.

LOGISTIC CONSTRAINTS AND ETHICAL CONCERNS

During the first and second wave, the huge number of patients have overwhelmed the hospital infrastructure and facilities manifold. Demand for trained staff to critical care beds and equipment, all resources were inadequate despite hospitals surging their capacity. ECMO is a resource intensive program. During the pandemic, due consideration should be given for judicious utilization of ECMO in patients most likely to recover is warranted (younger age, single organ affected, no comorbidities, etc.). In a pandemic, treatment modalities such as ECMO should be reserved in specialized high volume centers with adequate equipment and manpower resources. Mobile ECMO units are utilized to initiate ECMO and transport patients from remote locations.

COVID-19 patients are admitted in isolation wards. All members of the ECMO team need to comply with standard personal protective equipment (PPE) as safety of all team members is of prime importance. Monitoring and nursing of these patients by limited number of nursing staff in these isolation wards is tedious. Hence, additional support by remote monitoring helps to supplement the care of these patients. Additional time needed to comply with PPE application should be taken into account while mobilization of appropriate manpower to tackle emergency situations.

Interhospital transfer of such patients should also be handled carefully, as there is chance of members of medical team getting exposed.

Aerosol-generating procedures (AGPs) such as tracheostomy and bronchoscopy need to be performed carefully. In authors's institute, the protocol is to stop mechanical ventilation for short duration and increasing VV-ECMO flow and sweep gas rates.

LUNG TRANSPLANTATION AND FUTILITY

In patients who survive prolonged ECMO, some patients develop permanent fibrotic changes and continue to remain dependent on ECMO. These patients can be considered for lung transplantation, if they fulfill the criteria.[21] It should be noted that lung transplantation is an option of last resort and sufficient time should be given for lungs to recover, as several cases of successful weaning from ECMO after >60 days of ECMO runs.[22] Similarly before declaring futility in those who do not fulfill the criteria for transplant, sufficient time on ECMO should be given and all factors discussed with the patient's attendants.

COMMUNICATION

Since COVID-19 patients are cohorted in isolation wards, where the relatives usually do not have access. The ECMO team members should develop efficient communication with the relatives and the patient, discussing all the relevant aspects of patient's condition, allaying anxiety, and providing reassurance, formulating appropriate expectations about outcome, since many of the patients have prolonged ECMO support, and some have significant adverse events and outcomes.

CONCLUSION

Extracorporeal membrane oxygenation has been used to support patients with severe COVID-19 ARDS with satisfactory outcome. Since the pathophysiology of the disease and its manifestations differ, the management of ECMO and other treatment in these patients need to be carefully monitored and altered as dictated by changes in clinical condition of the patient. Data analysis and research in this field would help us understand the disease process better and formulate and refine ECMO management in these patients. With reducing burden on ECMO units, patient care shall improve, with likely improvement in clinical outcomes.

REFERENCES

1. Gattinoni L, Chiumello DC, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. 2020;46:1099-102.
2. Habashi NM, Camporota L, Gatto LA, Nieman G. Functional pathophysiology of SARS-CoV-2-induced acute lung injury and clinical implications. J Appl Physiol (1985). 2021;130(3):877-91.
3. Badulak J, Antonini MV, Stead CM, Shekerdemian L, Raman L, Paden ML, et al. Extracorporeal Membrane Oxygenation for COVID-19: Updated 2021 Guidelines from the Extracorporeal Life Support Organization. ASAIO J. 2021;67(5):485-95.
4. Li X, Hu M, Zheng R, Wang Y, Kang H, et al. Delayed Initiation of ECMO Is Associated With Poor Outcomes in Patients With Severe COVID-19: A Multicenter Retrospective Cohort Study. Front Med (Lausanne). 2021;8:716086.
5. Barbaro RP, MacLaren G, Boonstra PS, Iwashyna TJ, Slutsky AS, Fan E, et al. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. Lancet. 2020;396(10257):1071-8.
6. Belhadjer Z, Meot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute Heart Failure in Multisystem Inflammatory Syndrome in Children in the Context of Global SARS-CoV-2 Pandemic. Circulation. 2020;142(5):429-36.
7. Mustafa AK, Alexander PJ, Joshi DJ, Tabachnick DR, Cross CA, Pappas PS, et al. Extracorporeal Membrane Oxygenation for Patients With COVID-19 in Severe Respiratory Failure. JAMA Surg. 2020;155(10):990-2.
8. Cain MT, Smith NJ, Barash M, Simpson P, Durham LA 3rd, Makker H, et al. Extracorporeal Membrane Oxygenation with Right Ventricular Assist Device for COVID-19 ARDS. J Surg Res. 2021;264:81-9.
9. Huang S, Zhao S, Luo H, Wu Z, Wu J, Xia H, et al. The role of extracorporeal membrane oxygenation in critically ill patients with COVID-19: a narrative review. BMC Pulm Med. 2021;21(1):116.
10. Belletti A, Todaro G, Valsecchi G, Losiggio R, Palumbo D, Landoni G, et al. Barotrauma in Coronavirus Disease 2019 Patients Undergoing Invasive Mechanical Ventilation: A Systematic Literature Review. Crit Care Med. 2021. doi: 10.1097/CCM.0000000000005283. Online ahead of print.
11. Garcia B, Cousin N, Bourel C, Jourdain M, Poissy J, Duburcq T, et al. Prone positioning under VV-ECMO in SARS-CoV-2-induced acute respiratory distress syndrome. Crit Care. 2020;24(1):428.
12. Azzam MH, Mufti HN, Bahaudden H, Ragab AZ, Othman MM, Tashkandi WA. Awake Extracorporeal Membrane Oxygenation in Coronavirus Disease 2019 Patients Without Invasive Mechanical Ventilation. Crit Care Explor. 2021;3(6):e0454.
13. Dreier E, Malfertheiner MV, Dienemann T, Fisser C, Foltan M, Geismann F, et al. ECMO in COVID-19-prolonged therapy needed? A retrospective analysis of outcome and prognostic factors. Perfusion. 2021;36(6):582-91.
14. Schmidt M, Langouet E, Hajage D, James SA, Chommeloux J, Bréchot N, et al. Evolving outcomes of extracorporeal membrane oxygenation support for severe COVID-19 ARDS in Sorbonne hospitals, Paris. Crit Care. 2021;25(1):355.
15. Marcus JE, Sams VG, Barsoumian AE. Elevated secondary infection rates in patients with coronavirus disease 2019 (COVID-19) requiring extracorporeal membrane oxygenation. Infect Control Hosp Epidemiol. 2021;42(6):770-2.
16. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-81.
17. Ramanathan K, Shekar K, Ling RR, Barbaro RP, Wong SN, Tan CS, et al. Extracorporeal membrane oxygenation for COVID-19: a systematic review and meta-analysis. Crit Care. 2021;25(1):211.
18. Shaefi S, Brenner SK, Gupta S, O'Gara BP, Krajewski ML, Charytan DM, et al. Extracorporeal membrane oxygenation in patients with severe respiratory failure from COVID-19. Intensive Care Med. 2021;47(2):208-21.
19. Barbaro RP, MacLaren G, Boonstra PS, Combes A, Agerstrand C, Annich G, et al. Extracorporeal membrane oxygenation for COVID-19: evolving outcomes from the international Extracorporeal Life Support Organization Registry. Lancet. 2021;398(10307):1230-8.
20. Riera J, Roncon-Albuquerque R Jr, Fuset MP, Alcántara S, Blanco-Schweizer P; ECMOVIBER Study Group. Increased mortality in patients with COVID-19 receiving extracorporeal respiratory support during the second wave of the pandemic. Intensive Care Med. 2021;47(12):1490-3.
21. Cypel M, Keshavjee S. When to consider lung transplantation for COVID-19. Lancet Respir Med. 2020;8(10):944-6.
22. Walter K. Lung Transplants for COVID-19—The Option of Last Resort. JAMA. 2021;326(1):14-6.

153

CHAPTER

Approach to Shock in COVID Patients

Manasi Shahane, Sameer Jog, Srinath Marreddy

INTRODUCTION

Shock is a state of circulatory insufficiency characterized by impaired cellular oxygen utilization or delivery.[1] Of the 5–10% patients infected with SARS-CoV-2 that land up into the intensive care unit (ICU), almost up to 67% patients develop shock.[2] Shock is diagnosed on the basis of clinical, hemodynamic, and biochemical signs broadly grouped into three components. First, there usually is systemic arterial hypotension with systolic blood pressure (BP) being <90 mm Hg or mean arterial pressure of <65 mm Hg associated with tachycardia. Second, clinical signs of tissue hypoperfusion occur, such as cold clammy extremities, oliguria, and altered mental status. Third, a rise in blood lactate level of >1.5 mmol/L is observed which indicates impaired cellular oxygen metabolism.[1]

The general initial approach to the management until the etiology is established is fairly common to all types of shock. The initial step of clinical assessment must include examination of skin color and temperature, core to surface temperature gap, nailbed circulation, peripheral edema, jugular venous distention, presence of rales, mental status, and urine output. A quick bedside two-dimensional (2D) echocardiography assessing the left and right ventricular function, pericardial effusion, aortic velocity time integral, and variations in the dimensions of inferior vena cava with respiration aids in the etiologic diagnosis. Irrespective of the cause of shock, an initial fluid challenge of 250 mL of crystalloids is generally useful and can guide about the fluid responsiveness. In case of no response to fluid resuscitation, early vasopressor support needs to be instituted. If there is no rapid reversal of shock, then insertion of arterial line for blood gas measurement and central line for rapid infusion of fluids and vasopressors is advisable. Determination of trend of lactate levels, central venous oxygen saturation ($ScvO_2$) (target $ScvO_2$ above 70%), venoarterial PCO_2 ($V\text{-}APCO_2$) gap helps streamline the resuscitation. Lastly, prompt administration of oxygen therapy and mechanical ventilation if indicated is an essential early intervention to improve the oxygen delivery and correct tissue hypoxia.[1]

The shock in COVID-19 patients tends to follow a timeline as regards its etiology, as illustrated in **Figure 1**.

Table 1 illustrates the common etiologies of shock in COVID and their distinguishing features.

CASE VIGNETTE 1

A 45-year-old healthy male, admitted to the ward within first week of COVID-19 pneumonitis, requiring 4 L/min of oxygen via nasal prongs, was shifted to the ICU with shortness of breath, confusion, and severe asthenia. His heart rate was 120/min, BP was 75/50 mm Hg, and SpO_2 on 4 L, oxygen was 85%. He was tachypneic and chest auscultation revealed bilateral crackles. Axillary temperature was 37.8°C. ECG showed sinus tachycardia. Chest X-ray showed vascular congestion and mild bilateral interstitial infiltrates. Transthoracic echocardiography revealed severely impaired biventricular function with a left ventricular ejection fraction (LVEF) of 25%, tricuspid annular plane systolic excursion (TAPSE) 12 mm, global hypokinesia, and mild biventricular dilatation. Laboratory analysis showed mild leukocytosis and serially rising troponin T. N-terminal pro-brain natriuretic peptide (NT-proBNP) and C-reactive protein (CRP) were grossly elevated. Serum procalcitonin was negative. Contrast-enhanced computed tomography (CT) of thorax was done which showed bilateral peripheral ground glass opacities with CT severity score of 12/25 and ruled out pulmonary embolism (PE).

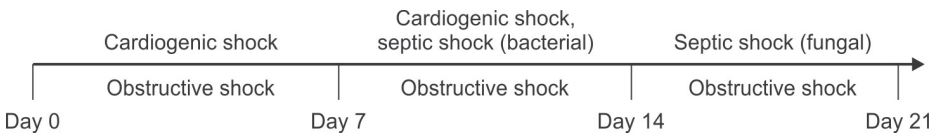


Fig. 1: Type of shock common with the duration of illness of COVID-19.

TABLE 1: Common etiologies of shock in COVID and their distinguishing features.[2]

Type of shock	*Etiologies*	*Extremities*	*Cardiac Output*	*$ScvO_2$*	*LV systolic function*	*RV size/function*
Cardiogenic	• Pre-existing heart disease • Acute myocardial ischemia • Cardiomyopathy • Acute myocarditis	Cold	Low	Low	Reduced	Normal or dilated/reduced function
	• Right ventricular failure	Cold	Low	Low	Normal or hyperdynamic	Dilated/reduced function
Distributive	• Sepsis • Cytokine storm • Medication-related vasoplegia	Warm (sometimes cold)	Normal or high	Normal or high	Normal or hyperdynamic	Normal
Obstructive	• Pulmonary embolism	Cold	Low	Low	Normal or hyperdynamic	Dilated/reduced function
	• Pneumothorax • Dynamic hyperinflation • Abdominal compartment syndrome • Pericardial tamponade	Cold	Low	Low	Normal/hyperdynamic	Normal
Hypovolemic	Rare in COVID					

(LV: left ventricular; RV: right ventricular)

Cardiogenic Shock

Acute cardiac injury occurs in around 20–30% patients of COVID-19 and is associated with increased mortality.[3] Severe left ventricular systolic failure in COVID-19 may occur due to myocarditis,[4] ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), worsening of underlying cardiovascular disease, and arrhythmias.[5] Right ventricular dysfunction may occur due to PE, pulmonary hypertension due to hypoxia, hypercapnia, and due to high mean airway pressures. Secondary cardiac involvement may occur as a part of a systemic inflammatory syndrome and may manifest as acute cardiac injury with biomarker elevation or even frank cardiac failure.[6]

The clinical and echocardiographic features of cardiogenic shock have been summarized in **Table 1**. Laboratory work-up should include NT-proBNP, cardiac troponin levels, and interval focused cardiac ultrasound. Treatment of the underlying cause must be carried out. NSTEMI needs to be treated with dual antiplatelet agents and statins, while thrombolysis or mechanical revascularization needs to be undertaken for STEMI. Myocarditis or sepsis-related cardiomyopathy has no specific treatment and supportive care must be rendered in such cases. Although with a limited evidence, norepinephrine is the first-line vasopressor in hypotensive patients with cardiogenic shock.[7] If despite using norepinephrine, the shock is persistent then inotropes such as dobutamine, levosimendan, or milrinone need to be considered.[8]

Acute respiratory distress syndrome (ARDS) is commonly associated with right ventricular (RV) failure with incidence rates ranging from 25 to 50%.[9,10] RV failure from ARDS or deleterious ventilatory settings needs to be managed with right ventricle protective ventilation, guided by change in pulmonary artery (PA) pressure on 2D echocardiography, which primarily involves minimizing airway pressures by optimizing positive end-expiratory pressure (PEEP), driving pressure, and prone position ventilation.[11,12] Inhaled pulmonary vasodilators may be used to reduce pulmonary vascular resistance, improve right ventricular performance, and reduce the pulmonary ventilation perfusion (V/Q) mismatch.[13]

Mechanical circulatory assist devices or venoarterial extracorporeal life support may be considered in refractory cardiogenic shock patients.

CASE VIGNETTE 2

A 63-year-old male, known case of type 2 diabetes mellitus and hypertension, presented with history of fever and cough for the past 5 days and breathlessness for the past 1 day. On evaluation in emergency room, he was found to have hypoxemic respiratory failure and was started on noninvasive ventilation. Subsequently he was tested positive for COVID-19. Initial laboratory values: Hemoglobin (Hb)—11.5 g/L, total leukocyte count (TLC)—4,600/mm^3, and platelet count (PLT)—170,000/mm^3. Serum creatinine and NT-proBNP were within normal range. Inflammatory markers are elevated (CRP 104 mg/L, ferritin 424 ng/mL, and D-dimer 323 ng/mL). 2D echo was normal. Serum procalcitonin and serum galactomannan were negative. He was shifted to ICU with worsening hypoxia for invasive

ventilation and received three cycles of prone ventilation with poor response. On day 6 of ICU admission, patient developed purulent endotracheal tube (ET) secretions, fever spikes with progressive increase in oxygen requirements. He developed hypotension and was started on vasopressors after adequate fluid resuscitation. Chest X-ray showed new zone of consolidation. Complete blood count (CBC) showed neutrophilic leukocytosis.

Distributive Shock

The predominant cause of distributive shock in COVID-19 patients is septic shock, which may be secondary to the virus or from secondary bacterial infections. Septic shock generally occurs post second week of illness. COVID-19 patients are specifically susceptible to secondary infections owing to the exposure to immunomodulatory agents such as steroids or interleukin 6 (IL)-6 inhibitors such as tocilizumab. Risk of sepsis and septic shock is particularly higher in patients receiving tocilizumab. It must be noted that bacterial sepsis with negative serum procalcitonin is possible in COVID-19 patients, hence clinicians need to be vigilant and not depend on procalcitonin values alone for the diagnosis or management of sepsis.

Critically ill patients with COVID-19 are at high-risk of hospital-acquired infections, especially ventilator-associated pneumonias, bloodstream infections which are frequently caused by multidrug-resistant organisms, especially in Indian ICUs. The clinical course of such patients when complicated by septic shock leads to a significant rise in mortality risk.[14]

Second week of COVID-19 illness may be complicated by a hyperinflammatory immune response secondary to cytokine release which may lead to loss of vasomotor tone, vasodilatation, and shock, which despite being nonbacterial or nonfungal is distributive in nature. The treatment for the same remains largely supportive. The use of immunomodulatory agents such as tocilizumab or itolizumab has been proposed in such a scenario; however, concrete evidence is lacking. Transfusion of plasma as a therapeutic measure in COVID-19 patients may also incite an inflammatory response and lead to distributive shock.

Empiric antimicrobial regimen is largely guided by patient's clinical history and local antibiogram. A 5-day course of remdesivir is recommended by current IDSA (Infectious Diseases Society of America) guidelines in COVID-19 patients who require supplemental oxygen.[15] A conservative approach for fluid resuscitation is preferred over liberal approach.[16] A fluid resuscitation strategy based on preload responsiveness, better indicated by dynamic measures such as pulse pressure variation (PPV), stroke volume variation (SVV), passive leg raise, and end expiratory occlusion tests, has shown improved outcomes with reduced need for renal replacement therapy and mechanical ventilation.[17-20]

Norepinephrine is the preferred vasopressor in septic shock. Vasopressin or epinephrine may be added as second-line agents if the shock is unresponsive to norepinephrine and fluid resuscitation. The Surviving Sepsis Campaign Guidelines for the management of critically ill adults with COVID-19 recommend titrating vasopressors to a target mean arterial pressure (MAP) of above 65 mm Hg.[17] A higher MAP of 75 mm Hg may be targeted for hypertensive individuals. A majority of COVID-19 patients are already on some form of steroids such as dexamethasone or methylprednisolone, hence switching over to hydrocortisone in refractory septic shock may not be deemed necessary.

CASE VIGNETTE 3

A 42-year-old man with a body mass index of 34 and a history of asthma presented to the hospital with hypoxemic respiratory failure and was admitted to the ICU for invasive mechanical ventilation. Testing to detect SARS-CoV-2 infection was positive along with TLC—12,000/mm^3, PLT—134,000/mm^3, ProBNP—196 pg/mL, negative trop T, normal creatinine, CRP—174, and D-dimer 304 ng/mL. The patient did not have a personal or family history of hypercoagulability and had received enoxaparin for prophylaxis against venous thromboembolism. Previous outpatient echocardiographic findings showed a normal biventricular size and function. On ICU day 8, the patient became acutely hypotensive and had rapid progression to cardiac arrest with pulseless electrical activity. He received cardiopulmonary resuscitation with administration of epinephrine and intravenous thrombolytics (injection alteplase 100 mg) and spontaneous circulation returned. Echocardiography showed acute right ventricular dilatation with impaired systolic function and subsequent CT confirmed the presence of thromboembolism obstructing the left PA.

Obstructive Shock

COVID-19 is associated with increased thrombotic risk and coagulopathy. The incidence ranges from 25 to 50%, with some thrombotic events occurring despite adequate prophylactic or therapeutic anticoagulation.[21,22] Acute PE must be considered in patients with sudden hemodynamic and/or respiratory compromise. The presence of acute PE as a cause of shock, whether it is massive PE or submassive PE with signs of RV failure and shock, is an indication of systemic thrombolysis with alteplase or streptokinase.[23] Full therapeutic anticoagulation needs to be administered in case of any acute venous thromboembolism. There is no evidence for the use of empiric therapeutic anticoagulation or half dose thrombolysis in unproven cases.

The occurrence of pneumothorax is not uncommon in COVID-19 patients with ARDS. It is an important differential to be considered in patients with acute decompensation.

Needle decompression or tube thoracostomy is urgently needed to relieve the obstructive shock in such a scenario.

Acute respiratory distress syndrome patients who are ventilated with high respiratory rates tend to have inadequate expiratory time. In presence of high airway resistance, it may lead to dynamic hyperinflation with increased intrinsic PEEP. This may lead to hypercarbia, hypoxia, and acute rise in pulmonary pressures causing shock. High airway resistance may be due to mucous plugging in the airways and smaller endotracheal tubes. Regular assessment to detect intrinsic PEEP and high airway resistance must be carried out. The use of bronchodilators, hypertonic saline, neuromuscular blockade, airway clearance, use of largest possible endotracheal tubes, and heated humidified ventilatory circuits will help reduce such events, although there is no conclusive evidence.

Hypovolemic Shock

Hypovolemic shock is quite uncommon in COVID patients. It may rarely occur in the initial phase of illness due to inadequate oral compensation for the insensible losses occurring in high-grade fever. Replenishing the losses with intravenous fluids guided by tests of preload responsiveness to avoid pulmonary edema is the mainstay of treatment. Hemorrhagic shock may develop when the patient bleeds due to the commonly used anticoagulants and antiplatelet agents in COVID-19 cases. No specific recommendation for the blood transfusion threshold exists in these patients. However, the usual threshold of transfusing packed cells of 7 g% can be considered appropriate based on prior data. The transfusion of other blood products may be considered when coagulopathy ensues and in need of massive transfusion.

Finally, advanced hemodynamic monitoring may be employed to decipher complex shock scenarios such as shock of mixed etiologies and that complicating ARDS. Fluid responsiveness may be assessed by measuring PPV and SVV. With the help of devices such as EV 1000/PiCCO (pulse index continuous cardiac output), which use transpulmonary thermodilution technique, volumetric parameters such as extravascular lung water (EVLW), global end-diastolic volume (GEDV), and pulmonary vascular permeability index (PVPI) can be determined, which are useful for prediction of pulmonary edema, cardiac output, and fluid responsiveness more accurately. Although employing advanced hemodynamic monitoring helps in timely therapeutic decisions, scientific evidence for improved patient outcomes is lacking.

CONCLUSION

Critically ill patients with COVID-19 may present with shock of a variety of etiologies. Early recognition and aggressive correction of hypoperfusion and treatment of the underlying process are the fundamental aspects of management. Clinical examination, bedside echocardiography, simple hemodynamic monitoring with arterial line for accurate BP measurement, $ScvO_2$, and V-A PCO_2 gap are important aspects of shock assessment. The timeline for various etiologies of shock in COVID-19 needs to be considered while managing the patients with some degree of overlap between each etiology. With the lack of a definitive treatment for COVID-19, supportive care and vigilance for shock and prompt treatment go a long way in mitigating the issue.

REFERENCES

1. Vincent J-L, De Backer D. Circulatory shock. N Engl J Med. 2013;369(18):1726-34.
2. Fox S, Vashisht R, Siuba M, Dugar S. Evaluation and management of shock in patients with COVID-19. Cleve Clin J Med. 2020;17.
3. Akhmerov A, Marbán E. COVID-19 and the heart. Circ Res. 2020;126(10):1443-55.
4. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5(7):819-24.
5. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: A review. JAMA Cardiol. 2020;5(7):831-40.
6. Ranard LS, Fried JA, Abdalla M, Anstey DE, Givens RC, Kumaraiah D, et al. Approach to acute cardiovascular complications in COVID-19 infection. Circ Heart Fail. 2020;13(7):e007220.
7. van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, et al. Contemporary management of cardiogenic shock: A scientific statement from the American Heart Association. Circulation. 2017;136(16):e232-68.
8. Vieillard-Baron A. Is right ventricular function the one that matters in ARDS patients? Definitely yes. Intensive Care Med. 2009;35(1):4-6.
9. Mekontso Dessap A, Boissier F, Charron C, Bégot E, Repessé X, Legras A, et al. Acute cor pulmonale during protective ventilation for acute respiratory distress syndrome: Prevalence, predictors, and clinical impact. Intensive Care Med. 2016;42(5):862-70.
10. Vieillard-Baron A, Charron C, Caille V, Belliard G, Page B, Jardin F. Prone positioning unloads the right ventricle in severe ARDS. Chest. 2007;132(5):1440-6.
11. Zochios V, Parhar K, Vieillard-Baron A. Protecting the right ventricle in ARDS: The role of prone ventilation. J Cardiothorac Vasc Anesth. 2018;32(5):2248-51.
12. Searcy RJ, Morales JR, Ferreira JA, Johnson DW. The role of inhaled prostacyclin in treating acute respiratory distress syndrome. Ther Adv Respir Dis. 2015;9(6):302-12.
13. Grasselli G, Scaravilli V, Mangioni D, Scudeller L, Alagna L, Bartoletti M, et al. Hospital-acquired infections in critically ill patients with COVID-19. Chest. 2021;160(2):454-65.
14. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, et al. Infectious Diseases Society of America Guidelines on the treatment and management of patients with COVID-19. Clin Infect Dis. 2020;ciaa478.
15. Silversides JA, Major E, Ferguson AJ, Mann EE, McAuley DF, Marshall JC, et al. Conservative fluid management or

deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: A systematic review and meta-analysis. Intensive Care Med. 2017;43(2):155-70.
16. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving sepsis campaign: Guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Crit Care Med. 2020;48(6):e440-69.
17. Bednarczyk JM, Fridfinnson JA, Kumar A, Blanchard L, Rabbani R, Bell D, et al. Incorporating dynamic assessment of fluid responsiveness into goal-directed therapy: A systematic review and meta-analysis. Crit Care Med. 2017;45(9):1538-45.
18. Monnet X, Marik P, Teboul J-L. Passive leg raising for predicting fluid responsiveness: A systematic review and meta-analysis. Intensive Care Med. 2016;42(12):1935-47.
19. Cherpanath TG, Hirsch A, Geerts BF, Lagrand WK, Leeflang MM, Schultz MJ, et al. Predicting fluid responsiveness by passive leg raising: A systematic review and meta-analysis of 23 clinical trials. Crit Care Med. 2016;44(5):981-91.
20. Douglas IS, Alapat PM, Corl KA, Exline MC, Forni LG, Holder AL, et al. Fluid response evaluation in sepsis hypotension and shock: A randomized clinical trial. Chest. 2020;158(4):1431-45.
21. Llitjos JF, Leclerc M, Chochois C, Monsallier JM, Ramakers M, Auvray M, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost. 2020;18(7):1743-6.
22. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: A multicenter prospective cohort study. Intensive Care Med. 2020;46(6):1089-98.
23. Chatterjee S, Chakraborty A, Weinberg I, Kadakia M, Wilensky RL, Sardar P, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: A meta-analysis. JAMA. 2014;311(23):2414-21.

CHAPTER 154

Full-term Pregnancy with COVID-19: An Intensivist's Perspective

Arti Singh, Shikha Sachan

INTRODUCTION

Pregnant women can get COVID-19 infection as any other healthy adult, but they are at a slightly higher risk of becoming severely affected, particularly in the third trimester. They are more likely to have pregnancy-associated complications such as pre-term labor, preterm prelabor rupture of membrane, intrauterine device (IUD), stillbirth, and preeclampsia. Roughly, 70% of pregnant females with COVID-19 are asymptomatic or minimal symptoms and some of pregnant females have clinically significant symptoms, in form of acute upper respiratory tract infection and fever. However, pregnancy is included in high-risk group because of COVID-19-associated complication (clinically vulnerable).

Studies have shown that there are higher rates of admission to hospital and intensive care unit (ICU) in case of pregnant women with COVID-19, as compared to nonpregnant females. This may be because clinicians are more likely to take a more cautious approach when deciding whether to admit to ICU when a female is pregnant.

WHY ARE PREGNANT FEMALES DIFFERENT?

- In pregnancy, maternal and fetal oxygen consumption is increased by 40% over nonpregnant. To provide increased oxygen requirement (by 20%), there is physiological dyspnea with decreased $PaCO_2$ and HCO_3^-. There is decreased functional residual capacity (FRC), because of which there is decreased intolerance for apnea and hypoventilation.
- While treating pregnant females with COVID-19, anatomical and physiological changes of pregnancy have to be kept in mind and target of treatment should be to achieve levels equivalent to non-COVID pregnant females.

IMPACT OF OXYGEN SATURATION AND HYPOXIA IN PREGNANCY

- In nonpregnant patient, the recommendation for SpO_2 is 92% but in case of pregnancy, these recommendations are modified to keep SpO_2 >95% at room air.[1] Treating team of intensivist and obstetrician must assure that patient is maintaining oxygen saturation at what method of oxygen supplementation whether facemask, nasal cannula, or high flow nasal cannula (HFNC).
- In this group of patients, oxygen saturation should be monitored very strictly. Every patient should be asked to monitor her oxygen saturation specially during walking. If this is decreasing up to 95% or less than that, she should be advised hospitalization for further management and monitoring because these patients can deteriorate very fast.
- Treating team should follow every patient for any clinical signs of deterioration such as use of accessory respiratory muscles, gradually increasing respiratory rate, unable to talk full sentence, or any signs of hypoxia such as cyanosis. These patients should be placed on oxygen therapy and advised to get admitted in higher center.
- Once these patients improve and clinician is planning to discharge from the hospital, the level of oxygen must be reassessed at rest and during walking. All preventing measures should be taken at discharge including patient education regarding warning signs.

IN-HOSPITAL MANAGEMENT

All patients' vitals should be strictly monitored by nursing staff, frequency and level of monitoring depends upon severity and criticality of that particular patient. Noninvasive monitoring should be preferred but invasive cardiovascular monitoring can be considered if indicated in hemodynamically unstable patients. All vital signs, including respiratory rate, heart rate, and level of respiratory support should be recorded every 1 hour. Along with patient, monitoring of fetus is of paramount importance that includes cardiotocography monitoring. Option of delivery would be considered based on gestational age, and severity of maternal disease status.

Methods for Oxygen Delivery

- Nasal cannula
- *Face mask*: "Nonrebreather"

- Venturi face mask
- HFNC
- *Use noninvasive ventilation (NIV)*: Bilevel positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP).

Selection of mode of oxygen delivery should be based on the degree of hypoxia and other clinical parameters of the patient.

IN-HOSPITAL TREATMENT OF SEVERE DISEASE

Treating team must train the nursing staff and patient including attendants regarding the early warning signs of disease deterioration and progression. These include the following:

- An increased severity of breathlessness
- Poor oxygen saturation (SpO_2 <95%) at room air
- Persistent or increasing pyrexia
- Increasing muscle pain.

Scoring Systems of Monitoring

Some protocol-based scoring systems must be utilized for assessment of severe disease, like Sequential Organ Failure Assessment (SOFA) score,[2] the "quick" qSOFA, and the modified Early Warning Signs score.[3] However, data are limited or inconclusive on clinical utility of early warning signs in pregnancy, and these proposed scoring systems may not consistently reflect who will become the most critically ill pregnant patient with COVID-19.

ADMISSION TO INTENSIVE CARE

If the patient is having any of these criteria, she should be admitted to critical care unit.

- Inability to maintain SpO_2 > 95% with O_2 supplementation
- Hypotension mean arterial pressure (MAP) <65 mm Hg
- Development of new organ dysfunction.

WHEN TO INTUBATE AND VENTILATE THE PATIENT?

In all patients, the timing of intubation should be individualized. Clinician must observe and look for maternal status, any evidence of multiorgan failure, associated pre-existing co-morbidities, and unable to maintain SpO_2 > 95% in spite of oxygen therapy. The inability to maintain and protect upper airway due to altered mental status or Glasgow Coma Scale of < 9 should also be considered for intubation as well.

INDICATIONS OF PRONE POSITION

- To improve oxygenation, prone positioning can be performed in pregnant and postpartum patients, including the recently delivered.
- "Awake prone positioning" can be practiced in patient without intubation. Patient herself can change her positions, either the lateral decubitus or fully prone position, this may improve patient comfort and can also avoid intubation in some patients of less severity. Change in position should be done typically for about 2 hours in each position.

NEUROMUSCULAR BLOCKADE (PARALYTICS)

All ventilated patients, neuromuscular blockade is one pharmacological intervention that decreases oxygen demand in moderate and severe acute respiratory distress syndrome (ARDS), especially if instituted early. Therefore, paralysis and deep sedation can be considered in COVID-19 with refractory hypoxemia in pregnant patients.

USE OF EXTRACORPOREAL MEMBRANE OXYGENATION

Extracorporeal membrane oxygenation (ECMO) is one of the advanced ventilatory method of management for these patients, especially who are having refractory hypoxia. A pregnant patient with severe hypoxia is not a contraindication to the use of ECMO. However, there may be many logistical challenges related to procedure. Despite these challenges, this modality should not be withheld from a pregnant patient for whom it may potentially benefit if the patient is otherwise a candidate. In general, ECMO for a pregnant patient should occur in a center with significant experience with its use.[4]

INDICATIONS OF ANTICOAGULATION IN CRITICALLY ILL COVID-19 PREGNANT PATIENTS

COVID-19 patients who are suffering with critical illnesses are at increased risk of thromboembolic-related complications. Patients who are admitted in ICU and on mechanical ventilation should receive prophylactic unfractionated heparin or low-molecular weight heparin, except when there are some contraindications to its use. However, clinical data is nonconclusive that early anticoagulation is beneficial in this group of patients.[5]

Three different dosing strategies can be practiced such as prophylactic, intermediate-dose, and full anticoagulation. There are no significant differences in primary outcome when we compare prophylactic verses intermediate dosing schedule.

INDICATIONS AND USE OF PHARMACOLOGICAL AGENTS FOR COVID-19

Various therapeutic agents have been investigated for the treatment of COVID-19 disease. While some have shown benefit in decreasing hospital stay or improving other outcomes, there is no cure or optimal and agreed-upon comprehensive approach. Pregnant patients with clinical

findings of COVID-19 should be admitted in a hospital and need monitoring during pharmacotherapy treatment.

Remdesivir

The Adaptive COVID-19 Treatment Trial investigated the use of antiviral agent, remdesivir, among patients requiring oxygen therapy due to COVID-19 infection and demonstrated a decreased duration of disease in treated patients. National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel recommends remdesivir for treatment of COVID-19 in hospitalized patients with $SpO_2 \leq 94\%$ at room air or those who needed oxygen therapy. The Panel also recommends remdesivir for patients of COVID-19-associated pneumonia and respiratory failure and are on invasive mechanical ventilation or ECMO.[6] There is no known fetal toxicity associated with remdesivir. With result of various trials, Society for Maternal-Fetal Medicine (SMFM) recommends that remdesivir should be given to pregnant patients with COVID-19.

Dexamethasone

RECOVERY trial demonstrated that dexamethasone was associated with a decreased risk of mortality among people requiring mechanical ventilation and also demonstrated a small but statistically significant decrease in mortality risk among those requiring oxygen for COVID-19.

The Panel recommends against using dexamethasone in patients with mild disease of COVID-19 who are not hypoxic and do not require oxygen therapy.[7] These recommendations are not specific to pregnant patients. Since the benefit of mortality reduction outweighs the risk of fetal steroid exposure for this short course of treatment, SMFM recommends that this treatment can also be instituted in pregnant patients with COVID-19 requiring respiratory support in form of oxygen supplementation or mechanical ventilation:

- If systemic steroids are indicated for fetal lung maturity, dexamethasone 6 mg twice a day for 2 days, followed by up 10 days of 6 mg dexamethasone daily.
- If steroids are not indicated for fetal lung maturity, 6 mg dexamethasone daily for up to 10 days as in nonpregnant patients.

Use of Antibiotics

Use of antibiotics in pregnancy needs extra physiological and pharmacological consideration in respect to mother and fetus. If antibiotics are indicated, it should be started as early as possible preferably within 1 hour. A procalcitonin level is an indicator of bacterial infection and is not required in the assessment of COVID-19; it can be helpful in diagnosis of superimposed bacterial pneumonia. It should be noted that a high procalcitonin level does not rule out COVID-19 infection.[8,9]

Monoclonal Antibodies

These drugs such as casirivimab, imdevimab, and bamlanivimab are not routinely recommended by NIH COVID guidelines. However, there is no absolute contraindication to their use in pregnant patients.

TIMING OF DELIVERY IN CRITICALLY ILL PREGNANT PATIENTS

Timing of delivery in critically ill patient is very important and has to be individualized depending on maternal status, associated comorbidities, and gestational age. In pregnant patient at term who is suffering with severe disease and having refractory hypoxemia, delivery must be considered because it will allow for further optimization of care. The severity of illness may dictate earlier delivery. Major neonatal morbidity occurs infrequently at these gestational ages as well: 8.7% at 32 weeks, 4.2% at 33, 4.4% at 34, 2.8% at 35, and 1.8% at 36 weeks of gestation.[10]

In the third trimester, the pressure of the uterus can decrease expiratory reserve volume, inspiratory reserve volume, and FRC, which can increase the risk of severe hypoxemia in pregnant patients, especially those who are critically ill.[11] Although available data in literature about optimal delivery timing and acute respiratory distress syndrome are limited, it is reasonably good to conduct delivery in the setting of worsening disease.

In case of disease progression in COVID-19, teams should discuss individualized delivery criteria in the setting of deteriorating maternal status, worsening fetal status, or no improvement in maternal disease status. In these patients, mechanical ventilation alone is not an indication for delivery.

If delivery is considered based on degree of hypoxemia, other treatment options should also be discussed among the team such as prone positioning, ECMO, and use of other advanced ventilator methods, especially in patient of gestational age is <30–32 weeks.

IMMEDIATE POSTPARTUM CARE CONSIDERATIONS

Anesthesia Concerns

These patients are very prone for fluid overload so strict input and output monitoring must be done for 48 hours at least. All vitals should be observed in respect to organ dysfunction. Mode of anesthesia should be chosen according to demand of oxygen, hemodynamically stability, and state of coagulopathy. Patient who may need invasive ventilation or high respiratory support should be operated under general anesthesia. Anticoagulation if started earlier should be continued.

Breastfeeding

Breastfeeding should be encouraged because this is an important source of antibody which protects the infant from various infections.

Fetal Concerns in Pregnant Patients with COVID-19

There are limited data for reassuring regarding fetal risks in the setting of maternal COVID-19 infection. There is no definitive evidence of fetal transmission till date.

Preeclampsia

Clinical and laboratory findings for COVID-19 can overlap with those found in HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome and preeclampsia with severe features. The diagnostic criteria proposed for preeclampsia remains the same in COVID pandemic, and management should be according to available guidelines. However, it is recommended to consider reverse transcription polymerase chain reaction (RT-PCR) for COVID-19, if a patient having transaminitis and thrombocytopenia is having additional risk factors for COVID-19.[12]

CONCLUSION

COVID-19 is an unprecedented pandemic affecting the whole world. The management of pregnancy with COVID-19 poses another challenge to the clinician as well as the family members because we are dealing with two lives, and there are significant physiological changes which make treatment difficult. Clinical presentation and management options are same, except that we have to take extra precautions in respect to hypoxia management and timings of the delivery. Every patient should be analyzed according to the clinical situation and available facilities. Potentially effective diagnostic modalities and treatment should not be withheld because of theoretical concerns related to safety, whereas investigational drugs should only be used after shared decision-making between the patient's family and clinical team, and considering the severity of maternal disease (NIH consensus).

REFERENCES

1. Alhazzani W, Moller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: Guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Crit Care Med. 2020;49(3):e219-34.
2. Grissom CK, Brown SM, Kuttler KG, Boltax JP, Jones J, Jephson AR, et al. A modified sequential organ failure assessment score for critical care triage. Disaster Med Public Health Prep. 2010;4(4):277-84.
3. Van der Woude SW, van Doormaal FF, Hutten BA, Nellen FJ, Holleman F. Classifying sepsis patients in the emergency department using SIRS, qSOFA or MEWS. Neth J Med. 2018;76(4):158-66.
4. Pacheco LD, Saade GR, Hankins GDV. Extracorporeal membrane oxygenation (ECMO) during pregnancy and postpartum. Semin Perinatol. 2018;42(1):21-5.
5. Barrett CD, Moore HB, Yaffe MB, Moore EE. ISTH interim guidance on recognition and management of coagulopathy in COVID-19: A comment. J Thromb Haemost. 2020;18(8): 2060-3.
6. National Institutes of Health. (2020). COVID-19 Treatment Guidelines Panel. Remdesivir. [online] Available from: https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/remdesivir/. [Last accessed March, 2022].
7. National Institutes of Health. (2020). COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines: Corticosteroids. [online] Available from: https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/corticosteroids/. [Last accessed March, 2022].
8. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
9. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395(10223):507-13.
10. Manuck TA, Rice MM, Bailit JL, Grobman WA, Reddy UM, Wapner RJ, et al. Preterm neonatal morbidity and mortality by gestational age: a contemporary cohort. Am J Obstet Gynecol. 2016;215(1):103.e1-14.
11. Oxford CM, Ludmir J. Trauma in pregnancy. Clin Obstet Gynecol. 2009;52(4):611-29.
12. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical characteristics of Covid-19 in New York City. N Engl J Med. 2020;382(24):2372- 4.

Index

Page numbers followed by *b* refer to box, *f* refer to figure, *fc* refer to flowchart, and *t* refer to table.

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

Z