GUIDELINES

The Indian Society of Critical Care Medicine Position Statement on the Management of Sepsis in Resource-limited Settings

Deven Juneja[1], Prashant Nasa[2], Gunjan Chanchalani[3], Anusha Cherian[4], Bharat G Jagiasi[5], Yash Javeri[6], Venkat R Kola[7], Amol T Kothekar[8], Prashant Kumar[9], Mohan Maharaj[10], Manish Munjal[11], Sivakumar M Nandakumar[12], Anand Nikalje[13], Rakesh Nongthombam[14], Sumit Ray[15], Mahesh K Sinha[16], Kanwalpreet Sodhi[17], Sheila N Myatra[18]

Received on: 19 February 2024; *Accepted on:* 25 March 2024; *Published on:* 10 August 2024

Abstract

Sepsis poses a significant global health challenge in low- and middle-income countries (LMICs). Several aspects of sepsis management recommended in international guidelines are often difficult or impossible to implement in resource-limited settings (RLS) due to issues related to cost, infrastructure, or lack of trained healthcare workers. The Indian Society of Critical Care Medicine (ISCCM) drafted a position statement for the management of sepsis in RLS focusing on India, facilitated by a task force of 18 intensivists using a Delphi process, to achieve consensus on various aspects of sepsis management which are challenging to implement in RLS. The process involved a comprehensive literature review, controlled feedback, and four iterative surveys conducted between 21 August 2023 and 21 September 2023. The domains addressed in the Delphi process included the need for a position statement, challenges in sepsis management, considerations for diagnosis, patient management while awaiting an intensive care unit (ICU) bed, and treatment of sepsis and septic shock in RLS. Consensus was achieved when 70% or more of the task force members voted either for or against statements using a Likert scale or a multiple-choice question (MCQ). The Delphi process with 100% participation of Task Force members in all rounds, generated consensus in 32 statements (91%) from which 20 clinical practice statements were drafted for the management of sepsis in RLS. The clinical practice statements will complement the existing international guidelines for the management of sepsis and provide valuable insights into tailoring sepsis interventions in the context of RLS, contributing to the global discourse on sepsis management. Future international guidelines should address the management of sepsis in RLS.

Keywords: Developing countries, Low- and middle-income countries, Low resource settings, Resource-limited settings, Sepsis, Septic shock.

Indian Journal of Critical Care Medicine (2024): 10.5005/jp-journals-10071-24682

Introduction

Sepsis remains a global health concern affecting millions of people and a leading cause of intensive care unit (ICU) admission. According to the recent Global Burden of Disease study, there were an estimated 48.9 million cases of sepsis worldwide in 2017.[1] Additionally, there were 11 million sepsis-related deaths, amounting to 19.7% of all global deaths. Low- and middle-income countries (LMICs) were reported to have the highest prevalence of sepsis which attributed to 85% of all deaths related to sepsis.[1] Although the highest prevalence of sepsis and sepsis-related deaths occurs in the LMICs, most of the sepsis-related epidemiological studies have been conducted in high-income countries (HICs).[2] In addition, the sepsis definitions and guidelines have been derived from studies conducted in high-income Western countries.[3] Therefore, the applicability of the data generated from these studies and the recommendations based on this data to LMICs, remain equivocal.

India though a rapidly emerging economy, still belongs to the LMIC category. According to the Global Burden of Disease study, India ranks 145th among 195 countries in the Healthcare Access and Quality Index.[4] India being a large and diverse country, has substantial disparity in access and quality of healthcare services among different regions and populations. This is further compounded by the fact, that despite having a large population, the doctor-to-patient ratio is low.[5] The majority of the public hospitals remain understaffed and poorly equipped. Most of the

[1]Department of Critical Care Medicine, Max Super Speciality Hospital, Saket, New Delhi, India

[2]Department of Critical Care Medicine, NMC Specialty Hospital, Dubai, United Arab Emirates

[3]Department of Critical Care Medicine, K.J. Somaiya Hospital & Research Center, Mumbai, Maharashtra, India

[4]Department of Anesthesiology and Critical Care, Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER), Puducherry, India

[5]Department of Critical Care, Kokilaben Dhirubhai Ambani Hospital, Navi Mumbai, Maharashtra, India

[6]Department of Critical Care and Emergency Medicine, Regency Super Speciality Hospital, Lucknow, Uttar Pradesh, India

[7]Department of Critical Care Medicine, Yashoda Hospitals, Hyderabad, Telangana, India

[8]Department of Anesthesiology, Critical Care and Pain, Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Tata Memorial Center, Homi Bhabha National Institute, Mumbai, Maharashtra, India

[9]Department of Critical Care Medicine, Yatharth Hospital, Noida, Uttar Pradesh, India

[10]Department of Critical Care, Medicover Hospitals, Visakhapatnam, Andhra Pradesh, India

[11]Department of Critical Care, ManglamPlus Medicity Hospital, Jaipur, Rajasthan, India

Indian population still relies on private hospitals and has to pay out of pocket for medical care.[6] Despite available antimicrobial stewardship programs, the prevalence of multidrug-resistant infections remains high in Indian hospitals. The mortality associated with sepsis in Indian ICUs is almost six times higher than mortality in patients without sepsis.[7]

Resource-limited regions similar to India, may find it challenging to apply all the diagnostic and management criteria recommended by the 2021 Surviving Sepsis Campaign (SSC) international guidelines for the management of sepsis and septic shock.[8] Healthcare settings lacking appropriate laboratory services may find it difficult to diagnose sepsis. Lack of equipment, infrastructure, and trained health professionals make it challenging to follow some of the recommendations. In addition, the type of infections in resource-limited settings (RLS) may require alternate management strategies, not prescribed in the guidelines. Therefore, there is a need for alternate guidance for specific interventions that are difficult or not possible to follow in the diagnosis and management of patients with sepsis in LMIC, such as in India, with limited resources and a high patient load.

Methods

Under the auspices of the Indian Society of Critical Care Medicine (ISCCM), a Task Force of Intensivists who were ISCCM members involved in the management of patients with sepsis was formed. The Task Force included 18 members representing different regions of India, working in both public and private institutions with clinical expertise in sepsis management and involved in education, advocacy, and/or research in sepsis management. Members were included in the task force after they accepted an e-mail invitation, to develop consensus in certain areas of sepsis management in RLS where the literature was inconclusive or absent. The context of RLS in this position statement applies only to India. A Delphi method was employed to develop the ISCCM Position Statement through consensus.

The task force members (DJ and PN) systematically searched PubMed, MEDLINE, and Science Direct for original articles on sepsis management in RLS between 1 January 2000 and 1 July 2023. The search string used for the literature search included "shock, septic" or "sepsis" and "resource-limited settings" or "developing countries." The search strategy generated 3,241 articles which were manually reviewed by PN and DJ for their relevance to the topic. The task force prepared a list of interventions in the absence of clear evidence. These interventions were presented as clinical statements under the following five broad domains after discussion in round-table and virtual meetings.

The clinical statements were divided into five domains:

1. Need for position statements for management of sepsis
2. Challenges from socioeconomic and population characteristics in managing adult sepsis
3. Considerations for diagnosis of sepsis
4. Patient management while awaiting an ICU bed
5. Treatment of sepsis and septic shock

Three task force members (DJ, PN, and SNM) formed a steering group to facilitate the Delphi process. The steering group drafted the clinical statements, developed the survey questionnaire for round one, analyzed the survey results, prepared survey reports, and facilitated the Delphi process. The clinical statements were presented to task force members through an online questionnaire using Google Forms. The steering group did not vote in the Delphi surveys.

The questions included in the Delphi rounds were either in a 7-point Likert scale or multiple-choice question (MCQ) format. The questions in the first round of the survey had open-ended text to receive feedback from the Task Force members. The members subsequently responded to several rounds of survey questionnaires anonymously and through an iterative and controlled feedback approach.

Consensus and Stability

The consensus was defined as "achieved" when more than 70% of members voted either agreement (scores 5–7) or disagreement (scores 1–3) in the Likert-scale statements or for a particular option in the MCQs.[9,10] Medians (IQR) were used to express the central tendency and dispersion of responses for the Likert-scale questions. The statements in two consecutive rounds were checked for stability of the responses using nonparametric Chi-squared (χ^2) tests or Kruskal–Wallis test from round two onwards. A *p*-value of less than 0·05 was considered a significant variation or unstable. The statements were continued in the Delphi process until the stability of the responses was achieved.

Clinical Practice Statements

Clinical practice statements were developed by the steering group from the statements that generated consensus. The final results of the Delphi process, clinical practice statements, and the manuscript were circulated among the task force members for approval before submission for publication.

Results

Four Delphi rounds were conducted between 21 August and 21 September 2023. There was 100% participation of the task force

[12]Department of Critical Care Medicine, Royal Care Super Speciality Hospital, Coimbatore, Tamil Nadu, India
[13]Department of Medicine, Medical Centre and Research Institute (MCRI) ICU, MGM Medical College and Hospital, Aurangabad, Maharashtra, India
[14]Department of Anaesthesiology and Intensive Care, J.N. Institute of Medical Sciences, Imphal, Manipur, India
[15]Department of Critical Care Medicine, Holy Family Hospital, New Delhi, India
[16]Department of Critical Care Medicine, Ramkrishna CARE Hospitals, Raipur, Chhattisgarh, India
[17]Department of Critical Care, Deep Hospital, Ludhiana, Punjab, India
[18]Department of Anesthesiology, Critical Care and Pain, Division of Critical Care Medicine, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, Maharashtra, India
Corresponding Author: Sheila N Myatra, Department of Anesthesiology, Critical Care and Pain, Division of Critical Care Medicine, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, Maharashtra, India, Phone: +91 9820156070, e-mail: sheila150@hotmail.com
How to cite this article: Juneja D, Nasa P, Chanchalani G, Cherian A, Jagiasi BG, Javeri Y, *et al*. The Indian Society of Critical Care Medicine Position Statement on the Management of Sepsis in Resource-limited Settings. Indian J Crit Care Med 2024;28(S2):S4–S19.
Source of support: Nil
Conflict of interest: None

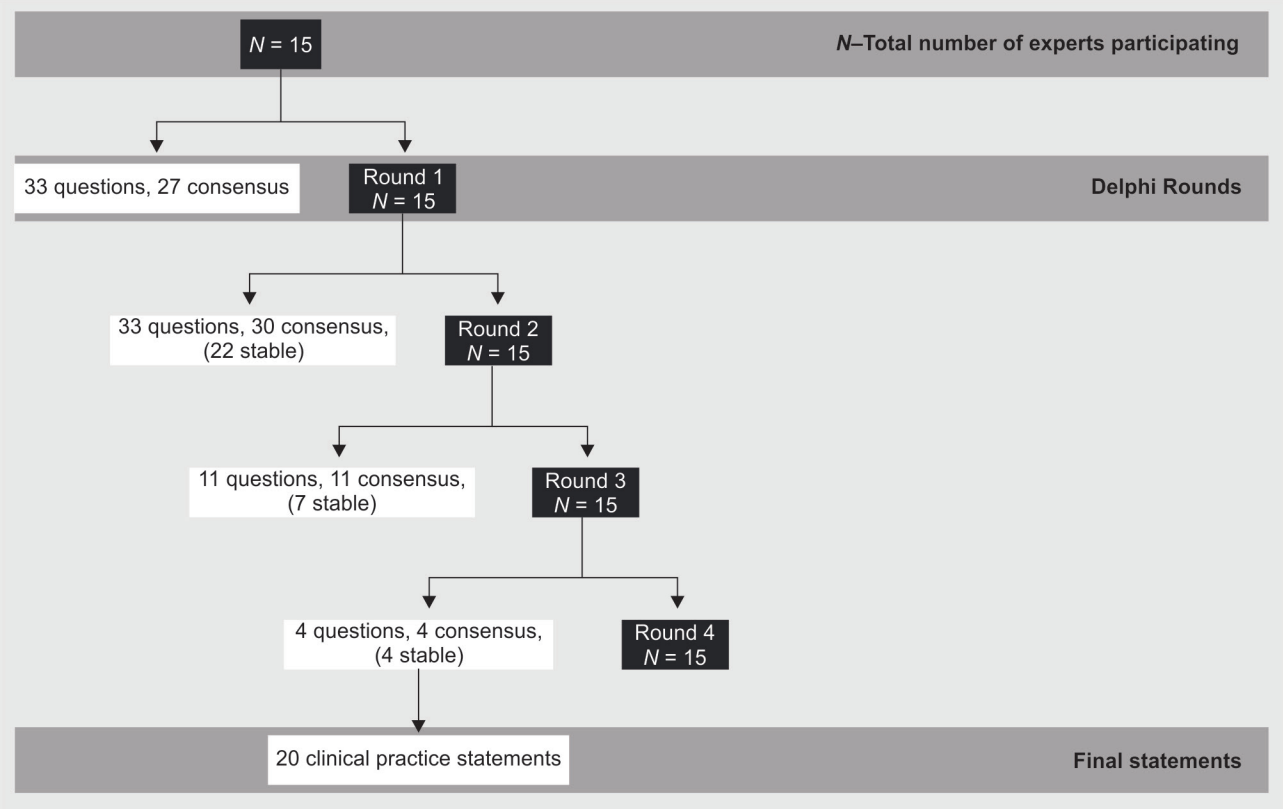

Fig. 1: Flow diagram depicting the steps of the Delphi process

in all four rounds (Fig. 1). The reports of the Delphi rounds and the consensus process are provided in the Supplementary Material. The results of the Delphi Process including the statements that achieved consensus are shown in Table 1. At the end of the Delphi process, 32 out of 35 (91%) statements reached consensus and stability, from which 20 clinical practice statements were drafted (Fig. 2).

Discussion

The Delphi process conducted among the Task force members generated 32 consensus statements from which 20 clinical practice statements were drafted to form the ISCCM position statement on the management of sepsis in RLS.

The consensus statements on the need for a position statement for the management of sepsis in RLS, the challenges from socioeconomic and population characteristics in managing adult sepsis, and the 20 clinical practice statements are enumerated below with the background and supporting literature.

Need for Position Statements for Management of Sepsis in RLS

- Lack of or limited availability of trained healthcare professionals, infrastructure, equipment for organ support, and microbiological diagnostics should be considered as a RLS in the context of clinical management of sepsis.
- Practice guidelines are required for the management of sepsis in RLS. There should be a separate section for the same in international guidelines.
- Factors limiting the application of the current SSC guidelines include lack of universal health cover or limited availability of health insurance, access to health care, financial constraints, delayed presentation, limited ICU resources, and lack of skilled workforce.
- Limitations related to the workforce include limited training, availability, and lack of multidisciplinary composition.

Sepsis and septic shock are medical emergencies. These patients need to be shifted to ICU as early as possible.[8] Delayed admissions of critically ill patients from the emergency department are associated with decreased sepsis bundle compliance and increased mortality, duration of mechanical ventilation, ICU, and hospital length of stay.[11]

Management of sepsis needs trained doctors who understand the physiological alterations and have skills including airway management, intravenous fluid management, arterial cannulation, and central venous catheter (CVC) insertion. Diagnosing sepsis using clinical evaluation, microbiological testing, and imaging technology helps clinicians manage sepsis more precisely. Therefore, lack of such facilities and trained workforce are usually considered as RLS.

In RLS, poverty, political corruption, health inequity, under-resourced and low-resilience public health, and lack of enough acute healthcare delivery systems are primary contributors to the burden of sepsis. Important differences in the populations at risk, infecting pathogens, and clinical capacity to manage sepsis in high and low-resource settings necessitate context-specific approaches to this significant problem.[12] While outcomes of septic patients in HIC have improved in recent decades, there is little evidence to support a similar trend in LMIC. Recent international guidelines from the SSC, include limited guidance for RLS but lack focus on its regional implications and population differences.[8,13] This justifies the need for a separate section within the international guidelines

Table 1: Consensus and stability analysis of the ISCCM position statements for the management of sepsis in RLS in India*

	Agree (%)	*Neutral (%)*	*Disagree (%)*	*Median (IQR)*	*χ^2 p-value*
Domain 1: Need for position statements for management of sepsis					
1. Lack/limited availability of which of the following should be considered as an RLS in the context of clinical management of sepsis?					0.99
• Trained healthcare professionals	100	–	–	–	
• Infrastructure (e.g., emergency room, ICU, monitored beds)	93.3	–	–	–	
• Invasive monitoring (e.g., CVCs and arterial lines)	66.7	–	–	–	
• Advanced monitoring (e.g., hemodynamic monitoring, bedside ultrasound)	60	–	–	–	
• Respiratory support (e.g., ventilators, noninvasive ventilators, and HFNO)	86.7	–	–	–	
• Other advanced organ support (e.g., ECMO and CRRT)	33.3	–	–	–	
• Drugs (e.g., antibiotics, antifungal, and IV fluids)	60	–	–	–	
• Radiological diagnostics	66.7	–	–	–	
• Microbiological diagnostics	86.7	–	–	–	
• Biochemical diagnostics (e.g., procalcitonin and lactate)	60	–	–	–	
• Bed capacity	66.7	–	–	–	
2. Practice guidelines are required for the management of sepsis in RLS.	93.3	6.7	0	7(0)	0.77
3. How should the practice guidelines for the management of sepsis in RLS be?					0.628
• Separate section for RLS in the present international guidelines	80	–	–	–	
• The management in RLS should be incorporated within each section of the guidelines	20	–	–	–	
• Other	0	–	–	–	
4. What are the factors limiting the application of SSC guidelines to RLS?					0.63
• Lack of awareness of SSC guidelines	60	–	–	–	
• Financial considerations (e.g., cost of drugs/consumables/service/hospitalization)	93.3	–	–	–	
• Limited availability of health insurance or lack of universal health cover	86.7	–	–	–	
• Disease-specific factors (e.g., zoonotic infections and tropical infections)	66.7	–	–	–	
• Demographic variations in the population (e.g., age, malnutrition, and genetic)	46.7	–	–	–	
• Inadequate access to health care	93.3	–	–	–	
• Delayed presentation (e.g., lack of disease awareness and social–cultural reasons)	80	–	–	–	
• Limited ICU beds	66.7	–	–	–	
• Limited ICU resources (e.g., monitors, ventilators, consumables, and ultrasound)	86.7	–	–	–	
• Skilled workforce (e.g., trained doctors/nurses/technicians)	93.3	–	–	–	
• Inadequate referral systems	73.3	–	–	–	
• Lack of advanced therapies (e.g., ECMO and CRRT)	13.3	–	–	–	
• Lack of adequate data on the epidemiology, microbiology, and outcomes of sepsis to inform policies	66.7	–	–	–	
5. What are the limitations from a workforce perspective while managing sepsis in RLS?					0.99
• Limited workforce	40	–	–	–	
• Limited trained workforce	100	–	–	–	
• Round-the-clock availability of workforce	80	–	–	–	
• Multidisciplinary composition of the workforce (including intensivists, other specialty doctors, nurses, physiotherapists, dieticians, pharmacists, etc.)	86.7	–	–	–	

(Contd...)

Table 1: *(Contd...)*

	Agree (%)	*Neutral (%)*	*Disagree (%)*	*Median (IQR)*	*χ^2 p-value*
Domain 2: Challenges from socioeconomic and population characteristics in managing adult sepsis					
1. Which of the following socioeconomic and cultural factor(s) can impact the management of sepsis in RLS?					0.99
• Poor public health services	100	–	–	–	
• Financial constraints	100	–	–	–	
• Lack of national health coverage/health insurance	100	–	–	–	
• Lack of public education and awareness	93.3	–	–	–	
• Political factors (e.g., lack of regulation, healthcare policies, commitment)	93.3	–	–	–	
• Large population	73.3	–	–	–	
• Overcrowding/poor living conditions	73.3	–	–	–	
• Cultural beliefs	66.7	–	–	–	
• Gender bias	53.3	–	–	–	
• Harsh environment (e.g., hilly terrains, desert, and tropical/subtropical climate)	40	–	–	–	
2. Which of the following patient characteristics can impact the management of sepsis in RLS?					0.99
• Uncontrolled or unrecognized chronic medical comorbidities (e.g., diabetes mellitus, hypertension, and obesity)	86.7	–	–	–	
• Malnutrition	93.3	–	–	–	
• Uncontrolled or unrecognized chronic infections (e.g., tuberculosis and HIV)	80	–	–	–	
• Unregulated and indiscriminate use of antimicrobials	100	–	–	–	
• Racial and genetic variation	46.7	–	–	–	
• Use of alternative medicines (e.g., heavy metals, herbal medications, or AYUSH therapies)	86.7	–	–	–	
Domain 3: Considerations for diagnosis of sepsis					
1. Which of the following clinical score(s) is feasible to use in the RLS?					0.39
• SIRS	66.7	–	–	–	
• qSOFA	80	–	–	–	
• SOFA	0	–	–	–	
• NEWS	46.7	–	–	–	
• MEWS	93.3	–	–	–	
2. Which of the following sepsis biomarkers are feasible to be used in RLS?					0.53
• CRP	93.3	–	–	–	
• Procalcitonin	6.7	–	–	–	
• Lactate	53.3	–	–	–	
• Other	20	–	–	–	
3. Appropriate cultures should be obtained in an RLS before starting antibiotics. However, antimicrobial administrations should not be delayed in patients with sepsis, or pending cultures (unavailability or delay).	100	0	0	7 (0)	0.74
4. The possibility of tropical infection (e.g., dengue, malaria, and leptospirosis) should be considered during the evaluation of sepsis in RLS.	100	0	0	7 (0)	1.0
Domain 4: Timing and location of patient during management of sepsis					
1. Patients with sepsis can be managed out of the ICU, awaiting a bed in an RLS	100	0	0	7 (1)	0.29
2. If an ICU bed is unavailable, the following alternative places of care may be considered for a patient with sepsis?					0.71
• Any monitored bed out of the ICU	100	–	–	–	
• Emergency room	100	–	–	–	
• Recovery room	93.3	–	–	–	
• Continued monitoring in operation theater (postsurgery)	73.3	–	–	–	
• Any hospital bed	13.3	–	–	–	

(Contd...)

Table 1: *(Contd...)*

	Agree (%)	*Neutral (%)*	*Disagree (%)*	*Median (IQR)*	*χ^2 p-value*
3. What is the minimum monitoring required for patients with sepsis monitored out of the ICU in an RLS?		–	–	–	0.99
		–	–	–	
• Blood pressure (continuous/intermittent)	100	–	–	–	
• Clinical monitoring (e.g., pulse rate, respiratory rate, breathing pattern, etc.)	100	–	–	–	
• Intermittent heart rate	33.3	–	–	–	
• Continuous heart rate	66.7	–	–	–	
• Intermittent respiratory rate	66.7	–	–	–	
• Continuous respiratory rate	33.3	–	–	–	
• Intermittent SpO_2	26.7	–	–	–	
• Continuous SpO_2	73.3	–	–	–	
• Capillary refill time	86.7	–	–	–	
• Intermittent urine output	46.7	–	–	–	
• Continuous urine output	53.3	–	–	–	
• Neurological status (AVPU, GCS, etc.)	93.3	–	–	–	
• End-tidal carbon dioxide	0	–	–	–	
• Ultrasound	26.7	–	–	–	
• Intermittent temperature monitoring	80	–	–	–	
• Continuous temperature monitoring	13.3	–	–	–	
4. What is the minimum monitoring required for patients with septic shock monitored out of the ICU in an RLS?					0.99
• Blood pressure (continuous/intermittent)	100	–	–	–	
• Clinical monitoring (e.g., pulse rate, respiratory rate, breathing pattern, etc.)	100	–	–	–	
• Intermittent heart rate	20	–	–	–	
• Continuous heart rate	86.7	–	–	–	
• Intermittent respiratory rate	46.7	–	–	–	
• Continuous respiratory rate	53.3	–	–	–	
• Intermittent SpO_2	20	–	–	–	
• Continuous SpO_2	80	–	–	–	
• Capillary refill time	86.7	–	–	–	
• Intermittent urine output	33.3	–	–	–	
• Continuous urine output	60	–	–	–	
• Neurological status (AVPU, GCS, etc.)	86.7	–	–	–	
• End-tidal carbon dioxide ($ETCO_2$)	6.7	–	–	–	
• Ultrasound	53.3	–	–	–	
• Intermittent temperature monitoring	80	–	–	–	
• Continuous temperature monitoring	13.3	–	–	–	
5. Which of the following are triggers (new onset) for transferring a patient to a higher level of care within the hospital, (e.g., ICU) when a patient with sepsis is managed out of ICU in an RLS?					0.99
• Any clinical deterioration	73.3	–	–	–	
• Hemodynamic instability	93.3	–	–	–	
• Increasing oxygen requirement	93.3	–	–	–	
• Respiratory instability requiring noninvasive mechanical ventilation	80	–	–	–	
• Respiratory instability requiring invasive mechanical ventilation	93.3	–	–	–	
• Altered mental status	93.3	–	–	–	
• Decrease in urine output	60	–	–	–	
• Failure of response to initial resuscitation	93.3				

(Contd...)

Table 1: *(Contd...)*

	Agree (%)	*Neutral (%)*	*Disagree (%)*	*Median (IQR)*	*χ^2 p-value*
6. What is the minimum monitoring required for transferring a patient with sepsis (interfacility transfer to hospital/ICU) in an RLS?					0.99
• Blood pressure (continuous/intermittent)	100	–	–	–	
• Clinical monitoring (pulse rate, respiratory rate, breathing pattern, etc.)	93.3	–	–	–	
• Intermittent heart rate	20	–	–	–	
• Continuous heart rate	80	–	–	–	
• Intermittent respiratory rate	53.3	–	–	–	
• Continuous respiratory rate	33.3	–	–	–	
• Intermittent SpO_2	20	–	–	–	
• Continuous SpO_2	80	–	–	–	
• Capillary refill time	73.3	–	–	–	
• Intermittent urine output	46.7	–	–	–	
• Continuous urine output	53.3	–	–	–	
• Neurological status (AVPU, GCS, etc.)	93.3	–	–	–	
• End-tidal carbon dioxide	13.3	–	–	–	
• Intermittent temperature monitoring	73.3	–	–	–	
• Continuous temperature monitoring	13.3	–	–	–	
7. What should be the minimum composition of the workforce accompanying a patient with sepsis (during interfacility transfer to another hospital) in an RLS?					NA
• Only a paramedic	66.7	–	–	–	
• Two persons (including at least one doctor)	13.3	–	–	–	
• Three persons (including at least one doctor)	13.3	–	–	–	
• Other	6.7	–	–	–	
8. What is the minimum qualification of the paramedic required for transferring a patient with sepsis (interfacility transfer to another hospital) in an RLS?					0.3
• Trained (ICU/ER/OR) paramedic	46.7	–	–	–	
• ACLS-trained paramedic	46.7	–	–	–	
• BLS-trained paramedic	6.6	–	–	–	
9. What is the minimum qualification of the doctor required for transferring a patient with sepsis (interfacility transfer to another hospital) in an RLS?					NA
• Trained ICU/ER physician	46.7	–	–	–	
• ACLS-trained physician	33.3	–	–	–	
• Other	20.0	–	–	–	
10. At least one medical doctor should accompany the patient with sepsis during interfacility hospital transfer	73.4	13.3	13.4	7 (3)	0.8
11. At least one person accompanying the patient with sepsis during interfacility hospital transfer should be trained in cardiopulmonary resuscitation	93.3	6.7	0	7 (0)	0.77
Domain 5: Treatment of sepsis and septic shock					
1. Clinical parameters (such as capillary refill time or neurological status, and urine output) should be used for the initial assessment of septic shock with or without lactate in RLS	100	0	0	7 (1)	0.83
2. In an RLS, decreasing lactate (if available) or capillary refill time can be used to guide resuscitation	100	0	0	7 (1)	0.48
3. For adults with sepsis or septic shock, when a BSS is indicated in RLS, a nonproprietary BSS (e.g., Ringer's lactate, Hartmann's solution etc.) may be used	100	0	0	7 (0)	0.17
4. Albumin may be considered only in a patient who needs resuscitation despite the use of the large volume of crystalloids, and if cost and availability permits	93.3	6.7	0	7 (1)	0.43
5. Careful and continuous clinical assessment of patients requiring fluid resuscitation should be performed to prevent fluid overload	100	0	0	7 (0)	0.75

(Contd...)

Table 1: *(Contd...)*

	Agree (%)	*Neutral (%)*	*Disagree (%)*	*Median (IQR)*	*χ^2 p-value*
6. Which of the following dynamic measures of fluid responsiveness can be considered to guide fluid resuscitation in the presence of a CVC and invasive arterial line (but absence of cardiac output monitoring)?					0.8
• Change in CVP	46.7	–	–	–	
• Pulse-pressure variation/tidal-volume challenge	80	–	–	–	
• PLR test	60	–	–	–	
• End-expiratory occlusion test	33.3	–	–	–	
• Fluid challenge	93.3	–	–	–	
• Variation in IVC diameter using ultrasound (if available)	73.3	–	–	–	
7. Which of the following indices (if available) can be used to guide fluid therapy (to give or not to give) in the absence of an arterial line?					0.72
• CVP	46.7	–	–	–	
• Delta-pulse pressure with fluid challenge	46.7	–	–	–	
• Delta CVP with fluid challenge	60	–	–	–	
• Clinical assessment (e.g., heart rate, BP, SpO_2 drop, CRT, urine output, etc.)	93.3	–	–	–	
• Biochemical parameters (e.g., hematocrit and urea)	33.3	–	–	–	
• Imaging (e.g., B-lines with ultrasound or chest X-ray)	66.7	–	–	–	
8. Norepinephrine is the vasopressor of first choice in patients with septic shock. Epinephrine may be used alternatively in case norepinephrine is unavailable	100	0	0	7 (1)	0.8
9. Vasopressin is the second-line vasopressor to norepinephrine in patients with septic shock. Epinephrine may be used alternatively in case vasopressin is unavailable	100	0	0	7 (1)	0.77
10. Vasopressors may be continued through a dedicated large bore peripheral venous access (e.g., external jugular vein), in the absence of a CVC (due to unavailability, cost, or lack of expertise for insertion).	100	0	0	7 (0)	0.66
11. Empirical antiparasitic agents (e.g., antimalarial, doxycycline, etc.) should be administered as early as possible to patients with suspected sepsis of parasitic origin	100	0	0	7 (0)	0.21
12. Noninvasive ventilation can be considered for the management of AHRF with sepsis, in case of HFNO is unavailable	100	0	0	7 (1)	1.0
13. When available, telecommunication should be used for the management of patients with sepsis in areas where medical expertise is lacking	100	0	0	7 (0)	0.98

*The statements which did not achieve consensus are highlighted in gray. ABG, arterial blood gas; ACLS, advanced cardiac life support; AVPU, alert, voice, pain, unresponsive; AYUSH, Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homoeopathy; ABG, arterial blood gas; CRRT, continuous renal replacement therapy; CRP, C-reactive protein; CVP, central venous pressure; ECMO, extracorporeal membrane oxygenation; ER, emergency room; GCS, Glasgow coma scale; HFNO, high-flow nasal oxygen; HIV, human immunodeficiency virus; ICU, intensive care unit; IV, intravenous; IVC, inferior vena cava; IQR, interquartile range; MEWS, modified early warning score; NA, not available; NEWS, national early warning score; OR, operation room; qSOFA, quick sequential organ failure assessment; RLS, resource-limited settings; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment; SpO_2, peripheral oxygen saturation; SSC, surviving sepsis campaign; χ^2, Chi-square

for the management of sepsis in RLS, that achieved consensus by the task force.

The prevalent ICU-based sepsis management guidelines usually originate from HICs that have the necessary equipment, laboratory and imaging services, and physician and nurse staffing, with the workforce following specific uniform protocols.[14,15] A direct adoption of the same guidelines may be challenging, lack individualization, or may cause harm in certain population settings.[13] Hence, it is crucial to develop guidelines specifically targeted to RLSs such as ours.

More than 80% of patients admitted to ICUs in India are self-paying.[16] This is associated with a lack of preventive health, inadequate or delayed treatment, and premature discharge from the ICU, thus adversely influencing patient outcomes.[17] The underlying reasons for this may be disparity in incomes, education status, and lack of adequate coverage/unawareness of government insurance schemes for most patients.[14,17,18] The wide disparity and lack of uniform policies across ICUs and the variations in case mix contribute to a lack of consistency in ICU services at the national level.

The principal challenges in applying existing guidelines in India are mainly 4-fold: inadequate resources and poor resilience of public health and acute care delivery services;[12] gross healthcare inequalities exacerbated by disparate funding of health systems; absence of a systematic approach to triage and emergency care; and a rudimentary prehospital emergency care transfer and referral system that contributes to delay in initiating timely intensive care.[17,19] The lack of trained staff leads to a lack of familiarity and

Considerations for diagnosis of sepsis

- Among the various clinical scores, qSOFA and MEWS are most feasible to be performed.
- Among the various sepsis biomarkers, CRP is most feasible to measure.
- Appropriate cultures should be obtained before starting antibiotics. However, antimicrobial administration should not be delayed in patients with sepsis, due to unavailability or delay in performing cultures.
- The possibility of tropical infection should be considered during evaluation of sepsis.

Patient management while awaiting an ICU bed

- While awaiting a bed in ICU, a patient may be managed in any monitored area such as an emergency room or recovery room.
- At a minimum, the monitoring of a patient with sepsis managed out of ICU includes neurological status, peripheral perfusion (with capillary refill time), clinical assessment of temperature, pulse, respiration, and intermittent blood pressure.
- At a minimum, the monitoring of a patient with septic shock managed out of ICU includes neurological status, peripheral perfusion (with capillary refill time), clinical assessment of temperature, pulse, respiration, and intermittent blood pressure, continuous heart rate, and SpO_2.
- The triggers for escalation of care for a patient awaiting an ICU bed are respiratory instability such as increasing oxygen requirement, need for invasive mechanical ventilation, hemodynamic instability, and failure to respond to initial resuscitation.
- At a minimum, the medical team accompanying the patient transferred to another facility should include a doctor trained in cardiopulmonary resuscitation. The patient should be monitored for neurological status, clinical assessment of temperature, pulse, respiration, and intermittent blood pressure, continuous heart rate, and SpO_2.

Management of sepsis and septic shock

- Clinical parameters such as neurological status, capillary refill time, urine output and lactate (if available) should be used for initial assessment of a patient with sepsis.
- When a balanced salt solution is indicated for resuscitation of patients with sepsis or septic shock, a non-proprietary balanced salt solution (e.g., Ringer's lactate, Hartmann's solution) may be used.
- Albumin (if available) may be considered in patients who need resuscitation despite the use of large volume of crystalloids.
- Frequent clinical assessment using heart rate, blood pressure, capillary refill time, drop in SpO_2, urine output or a trend of decreasing lactate (if available) may be used to guide fluid resuscitation.
- The dynamic measures of fluid responsiveness such as pulse-pressure variation, tidal-volume challenge, or fluid challenge should be considered to guide fluid resuscitation, when a central venous catheter and arterial line are present.
- Careful and continuous clinical assessment of patients requiring fluid resuscitation should be performed to prevent fluid overload.
- Epinephrine may be used as an alternative for the management of septic shock in case norepinephrine or vasopressin are unavailable.
- Vasopressors may be continued through a dedicated large bore peripheral venous catheter in the absence of a central venous catheter.
- Empirical antiparasitic agents should be administered as early as possible to patients with suspected sepsis of parasitic origin.
- Noninvasive ventilation should be considered for the management of acute hypoxemic respiratory failure in patients with sepsis in case of high-flow nasal oxygen is unavailable.
- Telecommunication (if available) should be used for the management of patients with sepsis in areas where medical expertise is lacking.

Fig. 2: Clinical practice statements for the management of sepsis and septic shock in RLS

awareness of existing guidelines, a failure to recognize sepsis, and a lack of motivation to follow guidelines.[20]

Challenges from Socioeconomic and Population Character in Managing Adult Sepsis

- Poor public health services, financial constraints, lack of universal health cover or limited availability of health insurance, lack of public education and awareness, political factors, and access to health care are the socioeconomic and cultural factors that can impact the management of sepsis.
- Uncontrolled or unrecognized chronic medical comorbidities, malnutrition, uncontrolled or unrecognized chronic infections, unregulated and indiscriminate use of antimicrobials, and use of alternative medicines are the population characteristics that can impact the management of sepsis.

There are many challenges to the delivery of healthcare services in India. Overall lack of awareness among the public regarding their own health. Lack of universal availability of healthcare facilities within a 5-km radius of residence or work. Lack of adequate human resources is common, and so is the lack of accountability. Hence, public sector health care is generally perceived to be of poor quality and unreliable and is usually preferred when one cannot afford private care.[6]

India is known to have poor health insurance coverage. In a survey conducted in 2014 by the Ministry of Statistics and Programme Implementation, Government of India, the total

insurance cover, including that funded by the government, private sector, or household purchased, was as low as 15.2%. The insurance coverage was slightly higher in urban areas than in rural areas (18% vs 14%)[21] While the majority of patients are paying from their pockets for health care, the cost of hospital admission and treatment, especially in tertiary care centers, remains beyond the reach of the common man.[22]

India has a considerable proportion of the adult population having cardiovascular and other comorbidities such as diabetes, with an alarmingly low incidence of awareness and treatment especially in the rural areas.[23] India also has a large population of diabetic individuals, along with a significant number of individuals with undiagnosed diabetes.[24]

A significant proportion of our population is at risk for health-related issues due to poor housing infrastructure, and lack of universal availability of safe drinking water and sanitation. In addition, the population is exposed to environmental pollution secondary to the use of biomass fuels, and vehicular, industrial, and construction activities. Therefore, it is not surprising that there is a very high prevalence of infective conditions like cough, fever, and diarrhea (124 per 1,000 individuals) among the Indian population.[25,26]

Indiscriminate use of antibiotics, especially for acute upper respiratory infections in outpatient departments is well known.[27] Widespread access to over-the-counter antibiotics, lack of access to safe-pure drinking water, and inadequate sanitation fuel the spread of antibiotic-resistant "superbugs." Another challenge is the paradoxically high prevalence of underweight and obese population.[28] These conditions further compound the challenges in managing sepsis in India.

Clinical Practice Statements

- Considerations for the diagnosis of sepsis
  - Among the various clinical scores, quick Sequential Organ Failure Assessment (qSOFA) and modified early warning system (MEWS) are the most feasible to be performed.
  - Among the various sepsis biomarkers, C-reactive protein (CRP) is the most feasible to measure.
  - Appropriate cultures should be obtained before starting antibiotics. However, antimicrobial administrations should not be delayed in patients with sepsis due to unavailability or delay in performing cultures.
  - The possibility of tropical infection should be considered during the evaluation of sepsis.

No single score can identify, with accuracy, patients with suspected infections or sepsis at high risk of death or clinical deterioration. Among the scores, systemic inflammatory response syndrome (SIRS) and MEWS could be applied as initial screening tools to identify those patients requiring high-level care, followed by qSOFA to prognosticate for mortality prediction. For qSOFA, the sensitivity and specificity in predicting clinical deterioration are better in LMIC than in HIC.[29]

Procalcitonin and CRP levels are widely used as adjunctive tests in sepsis, with limitations. CRP is an acute-phase reactant and is elevated in inflammatory conditions, including infection. C-reactive protein has often been used as a comparator for newer biomarkers including, procalcitonin.[30] However, high CRP levels have limitations with poor specificity like other biomarkers.

Diagnostic simplicity, availability, and low cost make CRP the most feasible biomarker in the Indian context. Elevated CRP levels in sepsis have been correlated with an increased risk of death and organ failure.[31] Sepsis is not only associated with bacterial or fungal infections but also other infections such as viral, protozoal (e.g., malaria), or tropical infections, which are common in India. C-reactive protein has been studied as a prognostic marker in a few of these infections.[32] While acknowledging the limitations of these scores and biomarkers, the task force agreed that CRP testing is most feasible to perform in RLS.

Obtaining cultures is an essential component of sepsis management and may aid in the diagnosis, source identification, and antimicrobial stewardship. However, taking cultures is time consuming, and may delay the administration of antibiotics if adequate resources are not immediately available. In addition, the yield of cultures may be low even after a single dose of antibiotics.[33] In RLS, it may take time to obtain cultures, leading to delays in administering appropriate antimicrobial therapy. As early administration of appropriate antibiotics has shown to be instrumental in reducing mortality in patients with sepsis,[34,35] the SSC guidelines recommend to initiate empiric antibiotic therapy within the first hour of presentation in patients with septic shock.[8] Therefore, due to the challenges often encountered in performing culture the task force agreed that initial empiric antibiotic therapy should not be delayed because of a lack of resources to obtain cultures.

The SSC guidelines primarily cater to bacterial and fungal infections responsible for most of cases of sepsis in HICs.[8] However, in tropical countries like India, tropical infections contribute significantly to the burden of sepsis. Even though the incidence of malaria is constantly reducing in North America and Europe (which has been free of Malaria since 2015), its incidence has been increasing in the LMICs of Africa and Southeast Asia. India contributed to 79% of all malaria cases and 83% of all malaria-related deaths in the Southeast Asia region in 2022.[36] Even for dengue, more than 63,000 cases were reported from India in the year 2022.[37] The diagnosis of these tropical infections may be challenging because of significant overlap of symptoms. Therefore, the consensus among the Task Force to consider or rule out the possibility of tropical infections during the evaluation of patients with suspected sepsis, especially in the endemic zones and during the season when they peak, is justified.

- Patient management prior to ICU admission
  - While awaiting a bed in the ICU, a patient may be managed in a monitored area such as an emergency room or recovery room.
  - At a minimum, the monitoring of a patient with sepsis managed outside the ICU includes neurological status, peripheral perfusion (with capillary refill time), clinical assessment of temperature, pulse, respiration, and intermittent blood pressure (BP).
  - At a minimum, the monitoring of a patient with septic shock managed outside the ICU includes neurological status, peripheral perfusion (with capillary refill time), clinical assessment of temperature, pulse, respiration, intermittent BP, continuous heart rate, and SpO_2.
  - The triggers for escalation of care for a patient awaiting an ICU bed are respiratory instability characterized by increasing oxygen requirement, need for invasive mechanical ventilation, hemodynamic instability, and failure to respond to initial resuscitation.

- At a minimum, the medical team accompanying the patient transferred to another facility should include a doctor trained in cardiopulmonary resuscitation. The patient should be monitored for neurological status, clinical assessment including temperature, pulse, respiration, intermittent BP, continuous heart rate, and SpO_2.

Most patients with sepsis are critically ill and need urgent ICU admission. However, if the situation arises when such patients have to be treated outside the ICU due to the unavailability of an ICU bed, for logistic or cost issues (quite common in RLS), they need to be adequately monitored in these areas, with predetermined triggers for escalation of care and safe transfer to an ICU when available.[38] The emergency department or recovery room is well equipped for monitoring and interventions, if the situation demands.[39] Critically ill patients with sepsis managed out of ICU can be monitored physically as well as remotely. The critical care physician should be involved in clinical management and set triggers should be defined for escalation of care. The hospital triage committee should be involved in providing policies and guidance for ensuring proper triaging and resource allocation.[40]

In patients with sepsis, the necessity for monitoring is to ensure early recognition of signs of an inflammatory response and tissue hypoperfusion. Early interventions based on monitoring may improve outcomes significantly, even in RLS.[41,42] A diagnosis of shock or hypoperfusion is based on clinical, hemodynamic, and biochemical signs. There can be systemic arterial hypotension, but the magnitude of hypotension may only be moderate, especially in patients with chronic hypertension. Typically, in adults, a systolic blood pressure (SBP) below 90 mm Hg or mean arterial pressure (MAP) of below 65 mm Hg, with associated tachycardia is considered hypotension. Shock index (HR/SBP) can be a simple surrogate of hemodynamic compromise.[43]

Further, there can be clinical signs of tissue hypoperfusion, which are apparent through the three clinical "windows": Cutaneous (cold and clammy skin, with vasoconstriction and cyanosis—most evident in low-flow states), renal (urine output of <0.5 mL/kg/hour), and neurologic (altered mental state, which includes obtundation, disorientation, and confusion).[44] Thus, it is essential to monitor neurological status regarding alertness and responsiveness. The ANDROMEDA-SHOCK trial showed that a nail bed cardiac resynchronization therapy (CRT) of ≥4 seconds was a good indicator of hypoperfusion in septic shock and resuscitation based on improving the CRT, which improved outcomes in terms of shock reversal.[45]

Continuous pulse oximetry helps not only in monitoring the oxygen levels but can also be an early indication of reduced perfusion, based on the waveform analysis. A decrease in SpO_2 while fluid resuscitating a patient of shock, along with crepitations on auscultation, can indicate increasing extravascular lung water. Monitoring respiration in terms of rate, depth, effort, and pattern can give a broad indication of the severity of illness. Both tachypnea and bradypnea in a patient of shock can indicate the severity of the illness.[44] Temperature monitoring in sepsis not only indicates the severity of the SIRS response, but a temperature difference between core and periphery (skin or toe) of above 7°C may be an indicator of hypoperfusion and shock.[46]

While urine output is another important component to monitor response to fluid therapy in patients with septic shock, the experts felt that it may not always be feasible to monitor outside the ICU in an RLS, probably the reason why it did not reach the required consensus.

Patients requiring invasive mechanical ventilation and vasopressors need ICU admission, while those without shock or respiratory distress may be judiciously managed out of the ICU. For those in between these extremes, close observation, and a low threshold for admission to the ICU is prudent.[47] The triggers call for an urgent critical care physician review and a shift to ICU. These triggers help activate the critical care team for a deteriorating patient with sepsis and help in triaging such patients.[48] Implementing sepsis triggers improves compliance with SSC recommendations and optimizes the utilization of limited critical care resources.[49]

Sepsis patients tend to become unstable during transfer. Thus, transportation should be done only when it is absolutely required. Through careful planning, and presence of appropriately qualified personnel, and adequately functioning transport equipment, after proper patient evaluation stabilization and communication, the risks can be minimized.[8]

At least two personnel should accompany the patient; one of which should be a medical practitioner with competency in cardiopulmonary resuscitation, airway care, ventilation, and other organ support.[50] The monitoring during transport should be appropriate to identify the clinical deterioration at the earliest. The minimum standards include continuous clinical monitoring, electrocardiography, noninvasive BP, arterial oxygen saturation (SaO_2), Glasgow coma score (GCS), and temperature.[51]

- Management of sepsis and septic shock
  - Clinical parameters such as neurological status, capillary refill time, urine output, and lactate (if available) should be used for the initial assessment of a patient with sepsis.
  - When a balanced salt solution (BSS) is indicated for resuscitation of patients with sepsis or septic shock, a nonproprietary BSS (e.g., Ringer's lactate and Hartmann's solution) may be used.
  - Albumin (if available) may be considered in patients who need fluid resuscitation despite the use of the large volume of crystalloids.
  - Frequent clinical assessment using heart rate, BP, capillary refill time, drop in SpO_2, urine output, or a trend of decreasing lactate (if available) may be used to guide fluid resuscitation.
  - The dynamic measures of fluid responsiveness such as pulse pressure variation, tidal volume (*V*t) challenge, or fluid challenge should be considered to guide fluid resuscitation when a CVC and arterial line are present.
  - Careful and continuous clinical assessment of patients requiring fluid resuscitation should be performed to prevent fluid overload.
  - Epinephrine may be used as an alternative for the management of septic shock when norepinephrine or vasopressin are unavailable.
  - Vasopressors may be continued through a dedicated large bore peripheral venous catheter in the absence of a CVC.
  - Empirical antiparasitic agents should be administered as early as possible to patients with suspected sepsis of parasitic origin.
  - Noninvasive ventilation (NIV) should be considered for the management of acute hypoxemic respiratory failure (AHRF) with sepsis, in case high-flow nasal oxygen therapy is unavailable.

– Telecommunication (if available) should be used for the management of patients with sepsis in areas where medical expertise is lacking.

In critically ill patients with septic shock and multiorgan dysfunction, clinical assessment plays a crucial role. Neurological assessment can be done to look for any signs of neurologic impairment due to hypoperfusion. Patients with sepsis may present with varied signs like anxiety, lethargy, delirium, confusion, or coma.[52] The SOFA score, which has better predictability than qSOFA and SIRS criteria to predict sepsis, incorporates the comprehensive Glasgow coma scale.[53] Furthermore, CRT is a marker of peripheral perfusion that worsens during circulatory failure. Poor prognosis has been linked to prolonged CRT in patients with septic shock following resuscitation in the ICU.

Following initial fluid resuscitation, patients with sepsis who have prolonged CRT have worse clinical outcomes and a greater mortality rate than those with normal CRT.[54] Urine output is critical in evaluating kidney function and is a marker for renal perfusion. It is an independent prognostic marker for septic shock. The SOFA score and urine output have similar predictive values; however, the combined predictive value of the two is higher than the SOFA score alone.[55] If available, measuring lactate levels can provide valuable information. Elevated lactate levels often indicate tissue hypoperfusion and can serve as a marker of the severity of septic shock.[56] In RLS these assessments, in combination with other vital signs and laboratory data, help healthcare providers gauge the patient's condition, guide treatment decisions, and allocate resources effectively.

The SSC guidelines suggest using balanced crystalloids instead of normal saline for resuscitation. Commercially available BSSs have more physiological composition than Ringer's lactate and Hartmann's solution with alternative buffers, such as acetate and gluconate, that are rapidly metabolized or excreted. However, the high cost limits the routine acceptability and usage in the RLS. A randomized controlled trial comparing ringer lactate with BSS in adult critically ill patients showed that commercially available BSS did not confer any advantage in time to or extent of correction of metabolic acidosis but incurred a higher cost.[57] Another retrospective study on 53,448 septic patients from 360 US hospitals showed decreased rates of in-hospital mortality with the use of BSS such as Ringer's lactate compared to 0.9% saline.[58] These results justify the use of Ringer's lactate in RLS when a BSS is indicated as suggested in the Clinical Practice Statements by the task force.[58]

Although with promising anti-inflammatory, antioxidant, and plasma volume expansion properties, the role of albumin in fluid therapy is still debated. The postulated benefits include longer intravascular confinement due to the interaction between its surface negative charges and the endovascular glycocalyx, thereby improving hemodynamics; but clinical data supporting albumin has been conflicting.[59] In patients with sepsis, albumin may be given for the following two indications: To restore or expand intravascular volume and to supplement serum albumin in septic patients with hypoalbuminemia. The albumin Italian outcome sepsis (ALBIOS) study showed improved hemodynamic indices with albumin, without any mortality benefit, but its *post hoc* subgroup analysis did detect a statistically significant lower risk of mortality in patients with septic shock who received albumin.[60] In a meta-analysis of five studies including 3,658 severe sepsis and 2,180 septic shock patients, the use of albumin for resuscitation significantly decreased 90-day mortality in septic shock patients [odds ratio (OR): 0.81; 95% CI: 0.67–0.97; $p = 0.03$).[61] A network meta-analysis of 14 studies including 18,916 patients with 15 direct comparisons at the 4-node level, showed lower mortality with albumin than with crystalloids or starches, and at the 6-node level, showed lower mortality with albumin than with saline.[62] Another retrospective data analysis showed an increased survival at 28 days, in septic patients receiving albumin combined within the first 24 hours after crystalloid administration.[63] The current data suggests that albumin may reduce morbidity and improve survival in patients with septic shock. Therefore, considering the high cost of albumin in RLS, the task force suggested that if acute hypovolemia is not responsive to crystalloids alone, the use of human albumin may be considered, if available.[64]

Titration of initial fluid resuscitation with frequent monitoring in patients with septic shock is recommended.[8] Progressive improvement in various physiological parameters such as heart rate (HR), BP, CRT, urine output, changes in SpO_2, and objective measurement of a trend of dropping lactate can be used to assess a patient's response to fluid administration. Tachycardia is a sensitive but nonspecific marker of shock. A decrease in HR in response to a fluid bolus may be used as a surrogate for improvement in intravascular volume status. In addition, a rise in BP may be used as a surrogate marker for change in cardiac output after a fluid bolus, though it is not very reliable.[65] Change in pulse pressure and systolic arterial pressure through a brachial cuff may be used to assess fluid-induced increase in cardiac output in RLS.[66,67] However, excess fluid administration can lead to pulmonary fluid leakage, appearance of B-lines, and drop in SpO_2. Though a delayed marker and often unreliable in patients with multiorgan involvement, this drop in SpO_2 can be used as an indicator to stop fluid administration.

Repeated bedside assessment of these parameters can be used as a general guide to fluid resuscitation. However, no goals of HR or BP can serve as a guide to organ perfusion and should not be used in isolation. Frequent bedside assessment of CRT, urine output, and clearance of lactate levels can indicate if fluid resuscitation is improving organ perfusion. Urine output is a valuable surrogate of organ perfusion; however, it takes time to assess the same. The skin is an accessible organ and allows bedside assessment of peripheral tissue perfusion by the CRT.[45] Lactate is a common but nonspecific surrogate for tissue perfusion and a failure to reduce lactate levels should lead to a re-evaluation of hemodynamic/perfusion status.[68]

There is a growing concern about increasing mortality and worse outcomes with aggressive fluid resuscitation, especially after the initial resucitation.[69–71] Hence, to improve the accuracy of assessment, certain dynamic measures may be used to assess fluid responsiveness in patients having only a CVC and arterial line in situ. The use of pulse pressure variation (PPV) in mechanically ventilated patients is reliable and can easily assess fluid responsiveness in patients with arterial pressure monitoring. In certain conditions like spontaneous breathing, arrhythmias, low *V*t ventilation, increased intra-abdominal pressure, and low lung compliance, it is often unreliable.[72] The tidal volume challenge (TVC) test can be used in patients ventilated using low *V*t ventilation to reliably predict fluid responsiveness using PPV. This test does not require cardiac output monitoring, making it useful in RLS.[73] Passive leg raising (PLR) combined with BP change above 15% may be used, though less reliable than the use of an increase in cardiac output. Performing PLR may be a challenge in RLS as adjustable beds to raise the foot end of the bed may

be unavailable.[74] A fluid challenge by rapid administration of a relatively low fluid volume to test if a patient has a cardiac preload reserve, has a lower risk of volume overload, and may be used to assess fluid responsiveness at the bedside.[75]

Fluid overload is a common occurrence in critically ill patients, and it is independently associated with increased morbidity and mortality. During fluid resuscitation in critically ill, three steps will help in restricting fluid overload: Avoid excessive fluid administration during resuscitation; careful and continuous clinical monitoring; and early active de-resuscitation. Fluid overload recognition and assessment require accurate documentation of intake and output, calculation of daily fluid balance, cumulative fluid balance, features of pulmonary edema or peripheral edema, etc. Fluid overload is usually first clinically diagnosed upon recognition of the development of pulmonary edema and sometimes the development of effusion. However, the measurement of change in body weight is considered a good surrogate for clinical monitoring of fluid balance in critically ill patients.[76,77]

Norepinephrine and vasopressin are the preferred vasopressor agents, if available, in the management of septic shock.[8] Epinephrine is the second-line vasopressor agent in septic shock after norepinephrine and vasopressin. However, if the first-line vasopressor agent, is not available, epinephrine may be used as an alternative agent. It acts on α-1, β-1, and β-2 receptors and causes increased contractility of the left ventricle, increases venous and arterial tone, and increases HR. Its major side effects are tachyarrhythmias, peripheral ischemia, splanchnic ischemia, increased myocardial oxygen consumption, and lactic acidosis. The SSC experts suggested adding epinephrine to norepinephrine and vasopressin, aiming to maintain target MAP while reducing norepinephrine requirements. For adults with septic shock, cardiac dysfunction, and persistent hypoperfusion despite adequate volume status, guidelines suggest either adding dobutamine to norepinephrine or using epinephrine alone.[8] Annane et al. comparing two vasopressor strategies (norepinephrine with dobutamine *vs* epinephrine) in patients with septic shock reported no differences in both efficacy and safety.[78] Therefore, the use of epinephrine, which is both cheap and readily available, may be a suitable alternative to norepinephrine in RLS.

Timely vasopressor therapy is fundamental in managing septic shock by correcting the vascular tone depression, recruiting microvessels, and improving microcirculation which subsequently increases organ perfusion pressure.[8,79] While CVC access is recommended for vasopressor administration, peripheral vasopressor administration may be considered in RLS when central access is not immediately available or feasible to avoid delay in therapy.[80,81] Nevertheless, it should be emphasized that peripheral vasopressor administration is a temporary solution until central venous access is established.

Considering the high prevalence of tropical infection in RLS, when there is strong clinical suspicion of sepsis of parasitic origin, empirical antiparasitic agents should be considered, while awaiting confirmatory diagnostic test results. The choice of empirical treatment will depend on factors such as the patient's travel history, exposure to endemic regions, and clinical symptoms. Therapeutic intervention may include empirical treatment with antimalarial drugs such as chloroquine, artemisinin-based combination therapies (ACTs), antihelminthic drugs (albendazole or praziquantel) for suspected protozoal infections like amoebiasis or giardiasis.[82] Empirical treatment should be temporary until the specific parasitic infection can be confirmed and appropriately treated.

Face masks and high-flow nasal oxygen (HFNO) are the preferred modes of oxygenation, in the management of AHRF, if available.[8] The HFNO device is expensive and needs pressurized oxygen and air supply, disposables, and training for use. Further, HFNO has a relatively higher oxygen consumption, which may be a limiting factor in RLS. Noninvasive ventilation on the other hand, uses regular oxygen supply and is available more widely. In a systematic review and meta-analysis,[83] there was a decrease in intubation, all-cause mortality, hospital-acquired pneumonia, and patient discomfort with HFNO vs NIV. Noninvasive ventilation with helmet and oronasal interfaces has been reported to be superior to conventional oxygen therapy in AHRF.[84] The heterogeneity in NIV interfaces, modes, and levels of pressure support contribute to the apparent inferiority in studies. Therefore, the use of NIV as an alternative, in case of nonavailability of HFNO in septic patients with AHRF is justified.

Tertiary hospitals may be connected through video or voice calls for real-time consultation and decision support in remote areas. This allows increased access to intensivists, helps in early recognition of sepsis and its severity, initiation of evidence-based care, and appropriate triage and transfer to higher centers.[85,86] Additionally, large data capture and analysis can aid in developing future goals and benchmarks. Literature is nascent, and despite design flaws, reduction in mortality and better sepsis bundle adherence have been reported.[87,88] While implementing these programs, legal and regulatory aspects such as informed consent, licensing, data protection, conflict of interest, and clinical privileges should be considered in addition to internet connectivity and infrastructure requirements which may be a challenge in RLS.

Conclusion

The Delphi process conducted among the task force members generated 32 consensus statements from which 20 clinical practice statements were drafted to form the ISCCM position statement on the management of sepsis in RLS. This position statement should provide Indian clinicians and those in other RLSs, guidance for the management of sepsis in RLS. These statements will complement the existing international guidelines for the management of sepsis and provide valuable insights into tailoring sepsis interventions in the context of RLS, contributing to the global discourse on sepsis management. Future international guidelines should address the management of sepsis in RLS.

Supplementary Materials

All the supplementary materials are available online on the website of https://www.ijccm.org/journalDetails/IJCCM.

Orcid

Deven Juneja https://orcid.org/0000-0002-8841-5678
Prashant Nasa https://orcid.org/0000-0003-1948-4060
Gunjan Chanchalani https://orcid.org/0000-0001-8429-8526
Anusha Cherian https://orcid.org/0000-0001-9017-5311
Bharat G Jagiasi https://orcid.org/0000-0002-3068-1201
Yash Javeri https://orcid.org/0000-0002-7384-3637
Venkat R Kola https://orcid.org/0000-0002-6971-1236
Amol T Kothekar https://orcid.org/0000-0002-7751-1314

Prashant Kumar https://orcid.org/0000-0002-5046-7421
Mohan Maharaj https://orcid.org/0009-0008-4971-4545
Manish Munjal https://orcid.org/0000-0003-1435-753X
Sivakumar M Nandakumar https://orcid.org/0000-0002-2036-7390
Anand Nikalje https://orcid.org/0000-0003-1694-800X
Rakesh Nongthombam https://orcid.org/0009-0001-1376-7978
Sumit Ray https://orcid.org/0000-0001-5192-4711
Mahesh K Sinha https://orcid.org/0009-0007-4623-6675
Kanwalpreet Sodhi https://orcid.org/0000-0002-7377-9225
Sheila N Myatra https://orcid.org/0000-0001-6761-163X

References

1. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: Analysis for the Global Burden of Disease Study. Lancet 2020;395(10219):200–211. DOI: 10.1016/S0140-6736(19)32989-7.
2. Prest J, Sathananthan M, Jeganathan N. Current trends in sepsis related mortality in the United States. Crit Care Med 2021;49(8):1276–1284. DOI: 10.1097/CCM.0000000000005017.
3. Singer M, Deutschman CS, Seymour CW, Shankar–Hari M, Annane D, Bauer M, Bellomo R, et al. The Third International Consensus Definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315(8):801–810. DOI: 10.1001/jama.2016.0287.
4. GBD 2016 Healthcard Access and Quality Collaborators. Measuring performance on the Healthcare Access and Quality Index for 195 countries and territories and selected subnational locations: A systematic analysis from the Global Burden of Disease Study 2016. Lancet 2018;391(10136):2236–2271. DOI: 10.1016/S0140-6736(18)30994-2.
5. Bagcchi S. India has low doctor to patient ratio, study finds. BMJ 2015;351:h5195. DOI: 10.1136/bmj.h5195.
6. Kasthuri A. Challenges to healthcare in India: the five A's. Indian J Community Med. 2018;43(3):141–143. DOI: 10.4103/ijcm.IJCM_194_18.
7. Hammond NE, Kumar A, Parmeet K. Estimates of sepsis prevalence and outcomes in adult patients in the ICU in India: A cross-sectional study. Chest 2022;161(6):1543–1554. DOI: 10.1016/j.chest.2021.12.673.
8. Nasa P, Jain R, Juneja D. Delphi methodology in healthcare research: How to decide its appropriateness. World J Methodol 2021;11(4):116–129. DOI: 10.5662/wjm.v11.i4.116.
9. Nasa P, Azoulay E, Chakrabarti A, Divatia JV, Jain R, Rodrigues C, et al. Infection control in the intensive care unit: Expert consensus statements for SARS-CoV-2 using a Delphi method. Lancet Infect Dis 2022;22(3):e74–e87. DOI: 10.1016/S1473-3099(21)00626-5.
10. 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):1974–1982. DOI: 10.1097/CCM.0000000000005357.
11. Mohr NM, Wessman BT, Bassin B, Elie–Turenne MC, Ellender T, Emlet LL, et al. Boarding of critically ill patients in the emergency department. Crit Care Med 2020;48(8):1180–1187. DOI: 10.1097/CCM.0000000000004385.
12. Rudd KE, Kissoon N, Limmathurotsakul D, Bory S, Mutahunga B, Seymour CW, et al. The global burden of sepsis: barriers and potential solutions. Crit Care 2018;22(1):232. DOI: 10.1186/s13054-018-2157-z.
13. Morton B, Stolbrink M, Kagima W, Rylance J, Mortimer K. The early recognition and management of sepsis in sub-Saharan African adults: A systematic review and meta-analysis. Int J Environ Res Public Health 2018;15(9): E2017. DOI: 10.3390/ijerph15092017.
14. Dondorp AM, Iyer SS, Schultz MJ. Critical care in resource-restricted settings. JAMA 2016;315(8):753–754. DOI: 10.1001/jama.2016.0976.
15. Riviello ED, Letchford S, Achieng L, Newton MW. Critical care in resource-poor settings: Lessons learned and future directions. Crit Care Med 2011;39(4):860–867. DOI:10.1097/ccm.0b013e318206d6d5.
16. Kissoon N. Healthcare costs to poor families: An agonising burden. Indian J Pediatr 2016;83(10):1063–1064. DOI: 10.1007/s12098-016-2170-7.
17. Divatia JV, Amin PR, Ramakrishnan N, Kapadia FN, Todi S, Sahu S, et al. Intensive care in India: The Indian intensive care case mix and practice patterns study. Indian J Crit Care Med 2016;20(4):216–225. DOI: 10.4103/0972-5229.180042.
18. Phua J, Joynt GM, Nishimura M, Deng Y, Myatra SN, Chan YH, et al. Withholding and withdrawal of life-sustaining treatments in low-middle-income versus high-income Asian countries and regions. Intensive Care Med 2016;42(7):1118–1127. DOI: 10.1007/s00134-016-4347-y.
19. Schultz MJ, Dünser MW, Dondorp AM, Adhikari NKJ, Iyer S, Kwizera A, et al. Current challenges in the management of sepsis in ICUs in resource-poor settings and suggestions for the future. In: Dondorp A, Dünser M, Schultz M, editors. Sepsis Management in Resource-limited Settings. Springer, Cham; 2019. DOI: 10.1007/978-3-030-03143-5_1.
20. Kissoon N. Sepsis guideline implementation: Benefits, pitfalls and possible solutions. Crit Care 2014;18(2):207. DOI: 10.1186/cc13774.
21. William Joe. Population Research Centre Institute of Economic Growth, New Delhi, India. Health insurance coverage in India: Insights for national health. Available at: https://prc.mohfw.gov.in/fileDownload?fileName=Health%20Insurance%20Coverage%20in%20India%20Insights%20for%20National%20Health%20Protection%20Scheme.pdf. Accessed on: 12 November 2023.
22. Chauhan AS, Guinness L, Bahuguna P, Singh MP, Aggarwal V, Rajsekhar K, et al. Cost of hospital services in India: a multi-site study to inform provider payment rates and Health Technology Assessment. BMC Health Serv Res 2022;22(1):1343. DOI: 10.1186/s12913-022-08707-7.
23. Anchala R, Kannuri NK, Pant H, Khan H, Franco OH, Di Angelantonio E, et al. Hypertension in India: A systematic review and meta-analysis of prevalence, awareness, and control of hypertension. J Hypertens 2014;32(6):1170–1177. DOI: 10.1097/HJH.0000000000000146.
24. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract 2022;183:109119.
25. Desai S, Dubey A, Joshi BL, Sen M, Shariff A, Vanneman R, editors. Human development in India: Challenges for a society in transition. Oxford; New York: Oxford University Press; 2010.
26. Ministry of Health and Family Welfare, Government of India. Accessibility Standards for Healthcare. Available from: https://main.mohfw.gov.in/sites/default/files/Accessibility%20Standard%20for%20Healthcare%20%281%29_0.pdf. Accessed on: 12 November 2023.
27. Farooqui HH, Mehta A, Selvaraj S. Outpatient antibiotic prescription rate and pattern in the private sector in India: Evidence from medical audit data. PLoS One 2019;14(11):e0224848. DOI: 10.1371/journal.pone.0224848
28. Dutta M, Selvamani Y, Singh P, Prashad L. The double burden of malnutrition among adults in India: Evidence from the National Family Health Survey-4 (2015–16). Epidemiol Health 2019;41:e2019050. DOI: 10.4178/epih.e2019050.
29. Adegbite BR, Edoa JR, Ndoumba WFN, Mbadinga LBD, Mombo–Ngoma G, Jacob ST, et al. A comparison of different scores for diagnosis and mortality prediction of adults with sepsis in low- and-middle-income countries: A systematic review and meta-analysis. EClinicalMedicine 2021;42:101184. DOI: 10.1016/j.eclinm.2021.101184.
30. Sugitharini V, Prema A, Thangam EB. Inflammatory mediators of systemic inflammation in neonatal sepsis. Inflamm Res 2013;62(12):1025–1034. DOI: 10.1007/s00011-013-0661-9.
31. Lobo SM, Lobo FR, Bota DP, Lopes–Ferreira F, Soliman HM, Mélot C, et al. C-reactive protein levels correlate with mortality and organ failure in critically ill patients. Chest 2003;123(6):2043–2049. DOI: 10.1378/chest.123.6.2043.
32. Paul R, Sinha PK, Bhattacharya R, Banerjee AK, Raychaudhuri P, Mondal J. Study of C reactive protein as a prognostic marker in malaria from Eastern India. Adv Biomed Res 2012;1:41. DOI: 10.4103/2277-9175.100140.

33. Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. Intensive Care Med 2018;44(6):925–928. DOI: 10.1007/s00134-018-5085-0.
34. Kalil AC, Johnson DW, Lisco SJ, Sun J. Early goal-directed therapy for sepsis: A novel solution for discordant survival outcomes in clinical trials. Crit Care Med 2017;45(4):607–614. DOI: 10.1097/CCM.0000000000002235.
35. Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, et al: Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med 2017;376(23):2235–2244. DOI: 10.1056/NEJMoa1703058.
36. World Health Organisation, World Malaria Report 2022. Available at: https://www.mmv.org/sites/default/files/content/document/WorldMalariaReport_2022.pdf. Assessed on: 20th November 2023.
37. Singh N, Singh AK, Kumar A. Dengue outbreak update in India: 2022. Indian J Public Health 2023;67(1):181–183. DOI: 10.4103/ijph.ijph_1517_22.
38. Ahmad D, Moeller K, Chowdhury J, Patel V, Yoo EJ. Impact of outlier status on critical care patient outcomes: Does boarding medical intensive care unit patients make a difference? J Crit Care 2018;44:13–17. DOI: 10.1016/j.jcrc.2017.10.004.
39. Jayaprakash N, Pflaum–Carlson J, Gardner–Gray J, Hurst G, Coba V, Kinni H, et al. Critical care delivery solutions in the emergency department: Evolving models in caring for ICU boarders. Ann Emerg Med 2020;76(6):709–716. DOI: 10.1016/j.annemergmed.2020.05.007.
40. Supady A, Curtis JR, Abrams D, Lorusso R, Bein T, Boldt J, et al. Allocating scarce intensive care resources during the COVID-19 pandemic: Practical challenges to theoretical frameworks. Lancet Respir Med 2021;9(4):430–434. DOI: 10.1016/S2213-2600(20)30580-4.
41. Permpikul C, Tongyoo S, Viarasilpa T, Trainarongsakul T, Chakorn T, Udompanturak S. Early use of norepinephrine in septic shock resuscitation (CENSER). A randomized trial. Am J Respir Crit Care Med 2019;199(9):1097–1105. DOI: 10.1164/rccm.201806-1034OC.
42. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345(19):1368–1377. DOI: 10.1056/NEJMoa010307.
43. Middleton DJ, Smith TO, Bedford R, Neilly M, Myint PK. Shock index predicts outcome in patients with suspected sepsis or community-acquired pneumonia: A systematic review. J Clin Med 2019;8(8):1144. DOI: 10.3390/jcm8081144.
44. Vincent JL, De Backer D. Circulatory shock. N Engl J Med 2013;369(18):1726–1734. DOI: 10.1056/NEJMra1208943.
45. 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):654–664. DOI: 10.1001/jama.2019.0071.
46. Bourcier S, Pichereau C, Boelle PY, Nemlaghi S, Dubée V, Lejour G, et al. Toe-to-room temperature gradient correlates with tissue perfusion and predicts outcome in selected critically ill patients with severe infections. Ann Intensive Care 2016;6(1):63. DOI: 10.1186/s13613-016-0164-2.
47. Guidet B, Leblanc G, Simon T, Woimant M, Quenot JP, Ganansia O, et al. Effect of systematic intensive care unit triage on long-term mortality among critically ill elderly patients in France a randomized clinical trial. JAMA 2017;318(15):1450–1459. DOI: 10.1001/jama.2017.13889.
48. Hernández AB, de Vega–Ríos E, Ballesteros JS, Braña DU, Domingo LC, Tejerina AF, et al. Impact of the implementation of a sepsis code program in medical patient management: A cohort study in an internal medicine ward. Rev Esp Quimioter 2022;35(2):178–191. DOI: 10.37201/req/132.2021.
49. Boter NR, Deltell JMM, Garcia IC, Blanch GR, Beltran GL, Molas AC. Activation of code sepsis in the emergency department is associated with a decrease in mortality. Med Clin (Barc) 2019;152(7):255–260. DOI: 10.1016/j.medcli.2018.02.013.
50. Faculty of Intensive Care Medicine. Guidance on: The transfer of the critically ill adult. Intensive care society. Available at: https://www.ficm.ac.uk/sites/ficm/files/documents/2021-10/Transfer_of_Critically_Ill_Adult.pdf. Assessed on: 21 December 2023.
51. Warren J, Fromm RE Jr, Orr RA, Rotello LC, Horst HM. Guidelines for the inter- and intrahospital transport of critically ill patients. Crit Care Med 2004;32(1):256–262. DOI: 10.1097/01.CCM.0000104917.39204.0A.
52. Czempik PF, Pluta MP, Krzych ŁJ. Sepsis-associated brain dysfunction: A review of current literature. Int J Environ Res Public Health 2020;17(16):5852. DOI: 10.3390/ijerph17165852.
53. Raith EP, Udy AA, Bailey M, McGloughlin S, MacIsaac C, Bellomo R, et al. Prognostic accuracy of the SOFA score, SIRS criteria, and qSOFA score for in-hospital mortality among adults with suspected infection admitted to the intensive care unit. JAMA 2017;317(3):290–300. DOI:10.1001/jama.2016.20328
54. Lara B, Enberg L, Ortega M, Leon P, Kripper C, Aguilera P, et al. Capillary refill time during fluid resuscitation in patients with sepsis-related hyperlactatemia at the emergency department is related to mortality. PLoS One 2017;12(11):e0188548. DOI: 10.1371/journal.pone.0188548.
55. Hu T, Qiao Z, Mei Y. Urine output is associated with in-hospital mortality in intensive care patients with septic shock: A propensity score matching analysis. Front Med (Lausanne) 2021;8:737654. DOI: 10.3389/fmed.2021.737654.
56. Kushimoto S, Akaishi S, Sato T, Nomura R, Fujita M, Kudo D, et al. Lactate, a useful marker for disease mortality and severity but an unreliable marker of tissue hypoxia/hypoperfusion in critically ill patients. Acute Med Surg 2016;3(4):293–297. DOI: 10.1002/ams2.207.
57. Rawat N, Sahni N, Yaddanapudi L. Comparison of commercially available balanced salt solution and Ringer's lactate on extent of correction of metabolic acidosis in critically ill patients. Indian J Crit Care Med 2020;24(7):539–543. DOI: 10.5005/jp-journals-10071-23488.
58. Raghunathan K, Shaw A, Nathanson B, Stürmer T, Brookhart A, Stefan MS, et al. Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis. Crit Care Med 2014;42(7):1585–1591. DOI: 10.1097/CCM.0000000000000305.
59. Vincent JL. Relevance of albumin in modern critical care medicine. Best Pract Res Clin Anaesthesiol 2009;23(2):183–191. DOI: 10.1016/j.bpa.2008.11.004.
60. 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):1412–1421. DOI: 10.1056/NEJMoa1305727.
61. 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. Crit Care 2014;18(6):702. DOI: 10.1186/s13054-014-0702-y.
62. Rochwerg B, Alhazzani W, Sindi A, Heels–Ansdell D, Thabane L, Fox–Robichaud A, et al. Fluid resuscitation in sepsis: A systematic review and network meta-analysis. Ann Intern Med 2014;161(5):347–355. DOI: 10.7326/M14-0178.
63. Zhou S, Zeng Z, Wei H, Sha T, An S. Early combination of albumin with crystalloids administration might be beneficial for the survival of septic patients: A retrospective analysis from MIMIC-IV database. Ann Intensive Care 2021;11(1):42. DOI: 10.1186/s13613-021-00830-8.
64. Martin C, Cortegiani A, Gregoretti C, Martin–Loeches I, Ichai C, Leone M, et al. Choice of fluids in critically ill patients. BMC Anesthesiol 2018;18(1):200. DOI: 10.1186/s12871-018-0669-3.
65. García MIM, González PG, Romero MG, Cano AG, Oscier C, Rhodes A, et al. Effects of fluid administration on arterial load in septic shock patients. Intensive Care Med 2015;41(7):1247–1255. DOI: 10.1007/s00134-015-3898-7.
66. Pierrakos C, Velissaris D, Scolletta S, Heenen S, De Backer D, Vincent JL. Can changes in arterial pressure be used to detect changes in cardiac index during fluid challenge in patients with septic shock? Intensive Care Med 2012;38(3):422–428. DOI: 10.1007/s00134-011-2457-0.
67. Monnet X, Letierce A, Hamzaoui O, Chemla D, Anguel N, Osman D, et al. Arterial pressure allows monitoring the changes in cardiac output induced by volume expansion but not by norepinephrine. Crit Care Med 2011;39(6):1394–1399. DOI: 10.1097/CCM.0b013e31820edcf0.

68. Kattan E, Hernández G. The role of peripheral perfusion markers and lactate in septic shock resuscitation. J Intensive Med 2021;2(1):17–21. DOI: 10.1016/j.jointm.2021.11.002.
69. Samoni S, Vigo V, Reséndiz LIB, Villa G, De Rosa S, Nalesso F, et al. Impact of hyperhydration on the mortality risk in critically ill patients admitted in intensive care units: Comparison between bioelectrical impedance vector analysis and cumulative fluid balance recording. Crit Care 2016;20:95. DOI: 10.1186/s13054-016-1269-6.
70. Sadaka F, Juarez M, Naydenov S, O'brien J. Fluid resuscitation in septic shock: The effect of increasing fluid balance on mortality. J Intensiv Care Med 2013;29(4):213–217. DOI: 10.1177/0885066613478899.
71. Smith SH, Perner A. Higher vs. lower fluid volume for septic shock: Clinical characteristics and outcome in unselected patients in a prospective, multicenter cohort. Crit Care 2012;16:R76. DOI: 10.1186/cc11333.
72. Teboul JL, Monnet X, Chemla D, Michard F. Arterial pulse pressure variation with mechanical ventilation. Am J Respir Crit Care Med 2019;199(1):22–31. DOI: 10.1164/rccm.201801-0088CI.
73. Myatra SN, Monnet X, Teboul JL. Use of "tidal volume challenge" to improve the reliability of pulse pressure variation. Crit Care 2017;21(1):60. DOI: 10.1186/s13054-017-1637-x.
74. 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):981–991. DOI: 10.1097/CCM.0000000000001556.
75. Vincent JL, Weil MH. Fluid challenge revisited. Crit Care Med 2006;34(5):1333–1337. DOI: 10.1097/01.CCM.0000214677.76535.A5.
76. Granado RCD, Mehta RL. Fluid overload in the ICU: Evaluation and management. BMC Nephrol 2016;17(1):109. DOI: 10.1186/s12882-016-0323-6.
77. Ogbu OC, Murphy DJ, Martin GS. How to avoid fluid overload. Curr Opin Crit Care 2015;21(4):315–321. DOI: 10.1097/MCC.0000000000000211.
78. Annane D, Vignon P, Renault A, Bollaert PE, Charpentier C, Martin C, et al. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: A randomised trial. Lancet 2007;370(9588):676–684. DOI: 10.1016/S0140-6736(07)61344-0.
79. Georger JF, Hamzaoui O, Chaari A, Maizel J, Richard C, Teboul JL. Restoring arterial pressure with norepinephrine improves muscle tissue oxygenation assessed by near-infrared spectroscopy in severely hypotensive septic patients. Intensive Care Med 2010;36(11):1882–1889. DOI: 10.1007/s00134-010-2013-3.
80. Ricard JD, Salomon L, Boyer A, Thiery G, Meybeck A, Roy C, et al. Central or peripheral catheters for initial venous access of ICU patients: A randomized controlled trial. Crit Care Med 2013;41(9):2108–2115. DOI: 10.1097/CCM.0b013e31828a42c5.
81. Lewis T, Merchan C, Altshuler D, Papadopoulos J. Safety of the peripheral administration of vasopressor agents. J Intensive Care Med 2019; 34(1):26–33. DOI: 10.1177/0885066616686035.
82. Kappagoda S, Singh U, Blackburn BG. Antiparasitic therapy. Mayo Clin Proc 2011;86(6):561–583. DOI: 10.4065/mcp.2011.0203.
83. Baldomero AK, Melzer AC, Greer N, Majeski BN, MacDonald R, Linskens EJ, et al. Effectiveness and harms of high-flow nasal oxygen for acute respiratory failure: An evidence report for a clinical guideline from the American College of Physicians. Ann Intern Med 2021;174(7):952–966. DOI:10.7326/M20-4675.
84. Ferreyro BL, Angriman F, Munshi L, Del Sorbo L, Ferguson ND, Rochwerg B, et al. Association of noninvasive oxygenation strategies with all-cause mortality in adults with acute hypoxemic respiratory failure: A systematic review and meta-analysis. JAMA 2020;324(1):57–67. DOI:10.1001/jama.2020.9524.
85. Kahn JM, Gunn SR, Lorenz HL, Alvarez J, Angus DC. Impact of nurse-led remote screening and prompting for evidence-based practices in the ICU. Crit Care Med 2014;42(4):896–904. DOI: 10.1097/CCM.0000000000000052.
86. Vranas KC, Slatore CG, Kerlin MP. Telemedicine coverage of intensive care units: A narrative review. Ann Am Thorac Soc 2018;15(11):1256–1264. DOI: 10.1513/AnnalsATS.201804-225CME.
87. Tu KJ, Wymore C, Tchangalova N, Fuller BM, Mohr NM. The impact of telehealth in sepsis care: A systematic review. J Telemed Telecare 2023:1357633X231170038. DOI:10.1177/1357633X231170038
88. Mohr NM, Campbell KD, Swanson MB, Ullrich F, Merchant KA, Ward MM. Provider-to-provider telemedicine improves adherence to sepsis bundle care in community emergency departments. J Telemed Telecare 2021;27(8):518–526. DOI: 10.1177/1357633X19896667.