Arab Republic of Egypt
Egyptian Health Council
Egyptian Board of Anesthetics, Surgical Intensive Care and Pain Management

Guideline for
Management of Sepsis and Septic Shock 2026

Prepared by

The "Guidelines Development Group" (GDG) of the Scientific Committee of the Egyptian Board of Anesthetics, Surgical Intensive Care and Pain Management.

Contents

Acknowledgements

*The Guideline for Management of Sepsis and Septic Shock 2026 - was prepared by the **Guidelines Development Group (GDG)** of the Egyptian Board of Anesthetics, Surgical Intensive Care and Pain Management group which reserves the right to determine the publication and distribution of the Guideline. The Guideline is subject to revision, and the updated versions will be published when needed, as warranted by the evolution of new-evidenced medical knowledge, new technology, and new practice trends. Although the Egyptian Board of Anesthetics, Surgical Intensive Care and Pain Management encourages Egyptian anesthesiologists to adhere to its practice guideline to ensure high-quality patient care, we cannot guarantee any specific patient outcome. With recognition that successful implementation requires coordinated approaches that align protocols with objectives at the institutional level, anesthesiologists should exercise their own professional judgement in determining the proper course of action for any patient's circumstances. Egyptian Board of Anesthetics, Surgical Intensive Care and Pain Management assumes no responsibility or liability for any error or omission arising from the use of any information contained in its Guideline to the Practice of Management of Sepsis and Septic Shock 2026.*

***This Guideline is intended to apply to all anesthesiologists in Egypt.** The independent practice of anesthesia is a specialized field of medicine, which should be practiced by physicians with appropriate training who continue their education in the practice of anesthetics, surgical intensive care, pain management, perioperative care, and resuscitation.*
All physicians applying for privileges in anesthesia should show satisfactory completion of specialist postgraduate training in anesthesiology certified by either the Egyptian Board training or the standard training in University programs to be able to provide these services. International medical graduates approved for licensure by provincial regulatory bodies should show training equivalent to the Egyptian standard. The only route to specialist recognition in anesthesiology in Egypt is through the "certification process" of the "Egyptian Health Council" (EHC).

*We would like to acknowledge the important contributions to the guideline from members of the Anesthesia **Guidelines Development Group (GDG)** of the Egyptian Board of Anesthetics, Surgical Intensive Care and Pain Management.*

Development Committee for adapting these guidelines

Chair of the GDG:
Prof. Sanaa Abd El-Kareem Helmy, Head of the Scientific Council of the Egyptian Board of Anesthetics, Surgical Intensive Care and Pain Management. Prof. of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Cairo University.

Rapporteur of the GDG:
Prof. Salah El-Sherif, Prof. of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Tanta University.

Members of the GDG are professors of Anesthetics, Intensive Care and Pain Management :

- Prof. Hassan Mohamed, Faculty of Medicine, Cairo University.
- Prof. Hala El-Gendy, Faculty of Medicine, Tanta University.
- Prof. Ghada Ali, Faculty of Medicine, Menofia University.
- Prof. Khaled Maghawry, Faculty of Medicine, Ain Shams University.

Abbreviations

ABG: Arterial Blood Gases
AGREE II: Appraisal of Guidelines for Research and Evaluation II
AI: Artificial Intelligence
AKI: Acute Kidney Injury
AKIN: Acute Kidney Injury Network
ARDS: Acute Respiratory Distress Syndrome.
BMI: Body Mass Index
BP: Blood Pressure
CIs: Confidence Intervals
CO: Cardiac Output
CRE: Carbapenem-resistant *Enterobacterales*
CRRT: Continuous Renal Replacement Therapy
CRT: Capillary Refill Time
CVP: Central venous pressure
dL: deciliter
DVT: Deep venous thrombosis
ECMO: Extracorporeal Membrane Oxygenation
ED: Emergency Department
EMS: Emergency Medical Services
ESBL: Extended spectrum β-lactamase
ESICM: European Society of Intensive Care Medicine
EWS: Early Warning Scores
FiO_2: Fraction of Inspired Oxygen
GDG: Guidelines Development Group
GI: Gastro-intestinal
GPS: Good Practice Statement
GRADE: Grading of Recommendations, Assessment, Development, and Evaluations
HES: Hydroxyethyl starch
HFNC: High flow nasal cannula
IBW: Ideal Body Weight
ICU: Intensive Care Unit
ICU LOS: Intensive Care - Unit Length of Stay
IHD: Intermittent Hemodialysis
iNOS: inducible Nitric Oxide Synthase
IPDMA: Individual patient data meta-analysis
IQR: interquartile range
IV: Intravenous
IVIG: Intravenous Immunoglobulin
Kg: Kilogram
LMICs: Low- and Middle-Income Countries
LMWH: low molecular weight heparin
MAP: Mean arterial pressure
MDR: Multidrug resistant
MDW: Monocyte Distribution Width
MEWS: Modified Early Warning Score
mL: milliliter
MRSA: Methicillin- resistant *S. aureus*
NEWS: National Early Warning Score
NEWS2: National Early Warning Score 2
NIPPV: Noninvasive positive pressure ventilation
NMBA: Neuromuscular Blocking Agents
PE: Pulmonary embolism
PEEP: Positive end-Expiratory Pressure

P/F ratio: PaO_2/FiO_2
PK/PD: pharmacokinetic/pharmacodynamic
POCUS: Point-of-care Ultrasound
PP: Pulse pressure
PPIs: proton-pump inhibitors
PPV: Pulse pressure variation
QI: Quality improvement
qSOFA: quick sepsis-related organ failure assessment
RCTs: Randomized Controlled Trials
RRT: Renal Replacement Therapy
SaO_2: Arterial oxygen saturation. Oxygen saturation in arterial blood.
SBP: Systolic Blood Pressure
SCCM: Society of Critical Care Medicine
S/F: Spo_2/Fio_2
SIRS: Systemic inflammatory response syndrome
Spo_2: Pulse oximeter
Spo_2 : Peripheral oxygen saturation. Oxygenation measured by pulse oximeter.
SSC: Surviving Sepsis Campaign
SV: Stroke volume
SVV: Stroke volume variation
TDM: Therapeutic Drug Monitoring
UFH: unfractionated heparin
UK: United Kingdom
US: United States
VFD: Ventilator free days
VTE: Venous thromboembolism
VV ECMO: Venovenous Extracorporeal Membrane Oxygenation
WHO: World Health Organization

Glossary

Basic Principles and Terminology

The following definitions are used For the purposes of these guidelines:

Definite sepsis: Sepsis is confirmed based on history, clinical examination, and diagnostic testing. An alternative diagnosis is very unlikely.

Possible sepsis: Moderate suspicion for sepsis. Sepsis is a possible diagnosis; however, an alternative diagnosis is also likely based on history, clinical examination, and diagnostic testing.

Probable sepsis: High suspicion for sepsis. Sepsis is the most likely diagnosis based on history, clinical examination, and diagnostic testing. An alternative diagnosis is less likely.

Probiotics: are live microorganisms—usually beneficial bacteria and yeasts—that provide health benefits when consumed in adequate amounts.

Sepsis: life-threatening acute organ dysfunction due to infection.

Septic Shock: a subset of patients with circulatory dysfunction that confers a higher risk of mortality.

Unlikely sepsis: Low suspicion for sepsis. Clinical assessment is not consistent with sepsis, or an alternate diagnosis is more likely based on history, clinical examination, and diagnostic testing.

Executive Summary

This Guideline deals with the recommendations of Management of Sepsis and Septic Shock.

SCREENING AND EARLY MANAGEMENT

1. **Performance Improvement Programs**
   For hospitals and health systems, we "recommend" using a performance improvement program for sepsis, including sepsis screening for acutely ill, high-risk patients; standard operating procedures for treatment; and implementation of sepsis quality improvement strategies. **(Strong)**
2. **Implementation Strategies**
   For hospitals and health systems, we "suggest" using a "code sepsis" or "sepsis huddle" protocol over not using such a protocol. **(Conditional)**
3. **Screening for Sepsis**
   - **3.1** In acutely ill adults en route to hospital by ambulance or flight, we "suggest" using a standard sepsis screening tool over not using a screening tool. **(Conditional)**
   - **3.2** For acutely ill patients in hospital, we "recommend" using NEWS, NEW2, MEWS, or SIRS over qSOFA as a single tool to screen for sepsis. **(Strong)**
4. **Biomarkers and Rapid Diagnostic Tests for Sepsis**
   - **4.1** Sepsis is a clinical diagnosis and should not be ruled in or ruled out using a single biomarker or diagnostic test. **(GPS)**
   - **4.2** There is "insufficient evidence" to make a recommendation regarding use of novel rapid host response diagnostics. **(GPS)**
5. **Blood Cultures**
   For adults with possible, probable, or definite sepsis or septic shock, we "recommend" collecting blood cultures as soon as possible and ideally before the administration of antimicrobial therapy. **(Strong)**
6. **Blood Lactate Measurement**
   For adults with possible, probable, or definite sepsis or septic shock, we "suggest" measuring blood lactate. **(Conditional)**
7. **Initial Fluid Resuscitation**
   - **7.1** Sepsis and septic shock are medical emergencies; treatment and resuscitation should begin immediately. **(Conditional)**
   - **7.2** For adults with sepsis-induced hypoperfusion or septic shock, we "suggest" administering at least 30 mL/kg of IV crystalloid in the first 3 hr. **(Conditional)**
8. **Timing of Vasopressor Initiation Relative to Fluid Resuscitation**
   For adults with sepsis-induced hypotension, we "suggest" initial IV crystalloid fluid bolus resuscitation followed by vasopressor support if hypotension persists. **(Conditional)**
9. **Route of Vasopressor Administration**
   In adults with septic shock, we "suggest" starting vasopressors peripherally to restore mean arterial pressure rather than delaying initiation until central venous access is secured. **(Conditional)**
10. **Mean Arterial Pressure (MAP) Targets**
    - **10.1** For adults with septic shock, we "recommend" an initial MAP target of 65 mm Hg over higher MAP targets. **(Strong)**
    - **10.2** For adults with septic shock 65 years old or older, we "suggest" an initial MAP range of 60–65 mm Hg over higher ranges. **(Conditional)**
11. **Admission to Intensive Care:** For adults with sepsis or septic shock who require ICU admission, we "suggest" admitting the patients to the ICU within 6 hr. **(Conditional)**

INFECTION

12. Timing of Antibiotic Initiation in Hospital and En Route to Hospital

12.1 For adults with possible, probable, or definite septic shock, we "recommend" administering antimicrobial therapy immediately, ideally within 1 hr of recognition. **(Strong)**

12.2 For adults with probable or definite sepsis without shock, we "recommend" administering antimicrobial therapy immediately, ideally within 1 hr of recognition. **(Strong)**

12.3 For adults with possible sepsis without shock, we "suggest" a time-limited course of rapid investigation and if concern for infection persists, the administration of antimicrobial therapy within 3 hours from the time when sepsis was first suspected. **(Conditional)**

12.4 Clinicians should perform a rapid assessment of the likelihood of infectious vs. non-infectious causes of acute illness in adults with possible sepsis without shock. **(GPS)**

12.5 For adults with a low likelihood of infection and without shock, we "suggest" deferring antimicrobial therapy while continuing to closely monitor the patient. **(Conditional)**

12.6 For adults with definite or probable sepsis and hypotension (i.e., septic shock) and who have an anticipated time to in-hospital medical evaluation of over 60 min, we "suggest" administering antimicrobial therapy in ambulance or flight. **(Conditional)**

13. Biomarker-Guided Initiation of Antimicrobial Therapy

For adults with possible or probable sepsis or septic shock, we "suggest" using clinical evaluation alone over procalcitonin plus clinical evaluation to decide whether to start antimicrobial therapy. **(Conditional)**

14. Source Control

14.1 Adults with sepsis or septic shock should be rapidly evaluated for specific anatomical diagnoses or sources of infection that require emergent source control. **(GPS)**

14.2 For adults with sepsis or septic shock and a specific anatomical diagnosis or source of infection that requires source control, we "suggest" early source control over late source control, ideally within 6 hr of diagnosis of sepsis or septic shock requiring source control. **(Conditional)**

15. Empiric Multidrug Resistant (MDR) Pathogen Coverage, Empiric Antifungal Coverage, and Empiric Anaerobic Coverage

15.1 For adults with sepsis or septic shock at high risk of infection with a specific multidrug resistant (MDR) pathogen, we "suggest" using empirical antimicrobial therapy with coverage for this MDR pathogen. **(Conditional)**

15.2 For adults with sepsis or septic shock at low risk of infection with a specific MDR pathogen, we "suggest against" using empirical antimicrobial therapy with coverage for this MDR pathogen. **(Conditional)**

15.3 For adults with sepsis or septic shock, we "suggest against" using empirical antifungal therapy. **(Conditional)**

15.4 For adults with sepsis or septic shock without risk factors for anaerobic infection, we "suggest" using an empiric antibiotic regimen without anaerobic coverage. **(Conditional)**

15.5 For adults with sepsis or septic shock with specific risk factors for anaerobic infection, we "suggest" using an empiric antibiotic regimen that includes anaerobic coverage. **(Conditional)**

16. Pathogen-Specific Rapid Diagnostic Tests

For adults with sepsis or septic shock, we "suggest" using pathogen-specific rapid diagnostic tests on a case-by-case basis in selected patients based on clinical features, local pathogen- and resistance patterns, seasonality, and availability of tests and antibiotic stewardship guidance. **(Conditional)**

17. Prolonged Infusion of β-Lactam Antibiotics

For adults with sepsis or septic shock, we "recommend" using prolonged infusion of beta-lactams for maintenance (after an initial loading dose) over bolus administration. **(Strong)**

18. Therapeutic Drug Monitoring (TDM) of Antimicrobial Therapy

For adults with sepsis or septic shock, we "suggest" using antimicrobial therapeutic drug monitoring (TDM) on a case-by-case basis in selected patients, based on clinical features, local pathogen- and resistance patterns, drug class, and availability of TDM. **(Conditional)**

19. Antimicrobial De-escalation and Discontinuation

19.1 Clinicians should continuously reevaluate patients, search for alternative diagnoses, and discontinue empiric antimicrobial therapy if an alternative cause of illness is demonstrated or strongly suspected in adults with suspected sepsis or septic shock but unconfirmed infection. **(GPS)**

19.2 For adults with sepsis or septic shock, we "recommend" de-escalation of antimicrobial therapy over no de-escalation when a confirmed microbiological diagnosis and susceptibility profile is available. **(Strong)**

19.3 For adults with sepsis or septic shock, we "suggest" de-escalation of antimicrobial therapy over no de-escalation when no pathogens are identified on final culture results. **(Conditional)**

19.4 For adults with an initial diagnosis of sepsis or septic shock and adequate source control where optimal duration of therapy is unclear, we "suggest" using procalcitonin AND clinical evaluation to decide when to discontinue antimicrobial therapy over clinical evaluation alone. **(Conditional)**

HEMODYNAMIC MANAGEMENT

20. Blood Pressure Monitoring

For adults with septic shock, we "suggest" using either invasive or noninvasive blood pressure monitoring. **(Conditional)**

21. Fluid Type

21.1 For adults with sepsis or septic shock, we "recommend" using crystalloids as first-line fluid for resuscitation. **(Strong)**

21.2 For adults with sepsis or septic shock undergoing initial resuscitation, we "suggest" using balanced crystalloids over 0.9% saline. **(Conditional)**

21.3 For adults with sepsis or septic shock, we "suggest" using crystalloids alone over crystalloids with supplemental albumin for fluid resuscitation. **(Conditional)**

21.4 For adults with sepsis or septic shock, we "recommend against" using starches for resuscitation. **(Strong)**

21.5 For adults with sepsis and septic shock, we "suggest against" using gelatin for resuscitation. **(Conditional)**

22. Liberal Vs. Conservative Approach to Resuscitation

For adults with sepsis or septic shock who have already received fluid resuscitation with 30 mL/kg and have persistent hypoperfusion, we "suggest" using either a liberal or a restrictive fluid resuscitation strategy based on individual patient and health system factors. **(Conditional)**

23. Fluid Resuscitation Guided by Dynamic Measures, Capillary Refill Time & Cardiac Output Monitoring Devices

23.1 For adults with sepsis or septic shock, we "suggest" using dynamic measures to guide fluid resuscitation over physical examination or static measures alone. **(Conditional)**

23.2 For adults with sepsis or septic shock, we "suggest" using capillary refill time to guide resuscitation as an adjunct to other measures of perfusion. **(Conditional)**

23.3 For adults with septic shock, there is "**insufficient evidence**" to make a recommendation on using minimally invasive or noninvasive cardiac output monitoring in addition to usual care.

24. Serial Lactate Measurement

For adults with sepsis and elevated lactate or septic shock, we "suggest" using serial lactate measurements to guide resuscitation. **(Conditional)**

25. Vasopressors

25.1 For adults with septic shock, we "recommend" using norepinephrine as the first-line agent over dopamine, epinephrine, or selepressin. **(Strong)**

25.2 For adults with septic shock, we "suggest against" using terlipressin. **(Conditional)**

25.3 For adults with septic shock, we "suggest" using norepinephrine as the first-line agent over vasopressin or angiotensin II. **(Conditional)**

25.4 For adults with septic shock on escalating doses of norepinephrine, we "suggest" adding vasopressin. **(Conditional)**

25.5 For adults with septic shock and inadequate MAP levels despite norepinephrine and vasopressin, we "suggest" adding epinephrine. **(Conditional)**

25.6 For adults with septic shock with concomitant cardiac dysfunction, we "suggest" using either norepinephrine or epinephrine as first line vasopressor. **(Conditional)**

26. Inotropes

26.1 For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate fluid status and arterial blood pressure, we "suggest" using inotropes over no inotropes.**(Conditional)**

26.2 For adults with septic shock with persistent hypoperfusion and cardiac dysfunction despite adequate fluid resuscitation and arterial blood pressure, we "suggest" adding dobutamine to norepinephrine or using epinephrine alone. **(Conditional)**

26.3 For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we "suggest against" using levosimendan. **(Conditional)**

27. Beta-Blockers, Oral Midodrine and Methylene Blue

27.1 For adults with septic shock, we "suggest against" using beta-blockers as a treatment for septic shock. **(Conditional)**

27.2 For adults with septic shock and ongoing requirement for vasopressors, there is "insufficient evidence" to make a recommendation on use of oral midodrine.

27.3 For adults with refractory septic shock and escalating vasopressor requirements, there is "insufficient evidence" to make a recommendation on IV methylene blue.

RESPIRATORY SUPPORT

28. Monitoring of Hypoxemia

For adults with sepsis, we "suggest" measuring oxygenation by either pulse oximeter (Spo_2) or arterial blood gas (Sao_2) in conjunction with physical examination and clinical acumen. **(Conditional)**

29. Oxygen Targets

For adults with sepsis and acute hypoxemic respiratory failure, we "suggest" titrating Fio_2 to target either higher, more liberal oxygen levels or lower, conservative oxygen levels depending on patient factors and resource limitations. **(Conditional)**

30. Noninvasive Respiratory Support & Awake Proning

30.1 For adults with sepsis and acute hypoxemic respiratory failure, we "suggest" using high flow nasal cannula (HFNC) therapy over conventional oxygen therapy. **(Conditional)**

30.2 For adults with sepsis and acute hypoxemic respiratory failure, we "suggest" using HFNC as the initial therapy over noninvasive positive pressure ventilation. **(Conditional)**

30.3 For adults with sepsis and acute hypoxemic respiratory failure, we "suggest" using HFNC over high flow alternating with noninvasive positive pressure ventilation. **(Conditional)**

30.4 For adults with sepsis and acute hypoxemic respiratory failure who are not intubated, we "suggest" a trial of awake proning. **(Conditional)**

31. Invasive Mechanical Ventilation

31.1 For adults with sepsis and ARDS, we "recommend" using a low tidal volume ventilation strategy (6 mL/kg) over a high tidal volume strategy (> 10 mL/kg). **(Strong)**

31.2 For adults with sepsis-associated hypoxemic respiratory failure without ARDS, we "suggest" using a tidal volume of 6—8 mL/kg ideal body weight (IBW) over a lower (4 to < 6 mL/kg IBW) tidal volume. **(Conditional)**

31.3 For adults with sepsis and ARDS, we "recommend" using an upper limited goal for plateau pressure of 30 cm H_2o) over higher plateau pressures. **(Strong)**

31.4 For adults with sepsis and moderate-severe ARDS, we "suggest" using higher positive end-expiratory pressure (PEEP) over lower PEEP. **(Conditional)**

31.5 For adults with sepsis and moderate-severe ARDS, we "recommend against" using an incremental PEEP titration strategy. **(Strong)**

31.6 For adults with sepsis and moderate-severe ARDS, we "suggest" using prone ventilation for greater than 12 hr daily. **(Conditional)**

31.7 For adults with sepsis and moderate-severe ARDS, we "suggest" using intermittent NMBA boluses over continuous NMBA infusion. **(Conditional)**

32. Venovenous ECMO

For adults with severe ARDS due to sepsis, we "suggest" using veno-venous ECMO when conventional mechanical ventilation fails in experienced centers with infrastructure to support its use. **(Conditional)**

ADJUNCTIVE THERAPIES FOR THE MANAGEMENT OF SEPSIS

33. Adjunctive Therapies for the Management of Sepsis

33.1 **IV Corticosteroids:** For adults with septic shock, we "suggest" using IV corticosteroids. **(Conditional)**

33.2 **Antipyretics:** For adults with sepsis or septic shock, we "suggest against" the use of antipyretic therapy, either pharmacologic or surface cooling, for the purpose of improving clinical outcomes. **(Conditional)**

33.3 **IV Vitamin C:** For adults with sepsis or septic shock, we "suggest against" using IV vitamin C in patients with sepsis or septic shock. **(Conditional)**

33.4 **IV Immunoglobulin (IVIG):** For adults with sepsis or septic shock, we "suggest against" using IV immunoglobulins. **(Conditional)**

33.5 **Vitamin D**: For adults with sepsis and septic shock, we "suggest against" using Vitamin D therapy for sepsis treatment. **(Conditional)**

33.6 **IV XueBiJing:** For adults with sepsis or septic shock, we "suggest against" using XueBiJing injection outside of jurisdictions where it has regulatory approval. **(Conditional)**

33.7 **Blood Purification:**

33.7.1 For adults with sepsis or septic shock, we "suggest against" using blood purification techniques, including hemoperfusion, high- dose hemofiltration, or plasma exchange. **(Conditional)**

33.7.2 For adults with sepsis or septic shock we "suggest against" using polymyxin B hemoperfusion. **(Conditional)**

ADDITIONAL SUPPORTIVE THERAPIES IN PATIENTS WITH SEPSIS

34. Insulin Therapy

For adults with sepsis or septic shock, we "recommend" initiating insulin therapy at a glucose level of ≥180 mg/dL (10 mmol/L). **(Strong)**

35. Blood Transfusion

For adults with sepsis or septic shock, we "recommend" using a restrictive transfusion strategy over a liberal transfusion strategy. **(Strong)**

36. Stress Ulcer Prophylaxis

For adults with sepsis or septic shock, and who have risk factors for GI bleeding, we "suggest" using stress ulcer prophylaxis with proton-pump inhibitors over not using stress ulcer prophylaxis. **(Conditional)**

37. Renal Replacement Therapy

37.1 For adults with sepsis or septic shock and acute kidney injury, with no definitive indication for renal replacement therapy, we "suggest against" using renal replacement therapy. **(Conditional)**

37.2 For adults with sepsis or septic shock and acute kidney injury warranting renal replacement therapy, we "suggest" either continuous or intermittent renal replacement therapy. **(Conditional)**

38. Enteral Nutrition

For adults with sepsis or septic shock, we "suggest" early (within 72 h) initiation of enteral nutrition. **(Conditional)**

39. Sodium Bicarbonate

38.1 For adults with septic shock and hypoperfusion-induced lactic acidemia, we "suggest against" using sodium bicarbonate therapy to improve hemodynamics or to reduce vasopressor requirements. **(Conditional)**

38.2 For adults with septic shock, severe metabolic acidemia (pH ≤7.2), & acute kidney injury (AKIN score 2 or 3), we "suggest" using sodium bicarbonate therapy. **(Conditional)**

40. Active Fluid Removal

For adults with septic shock after the acute resuscitation phase, we "suggest" using active fluid removal. **(Conditional)**

41. Probiotics

For adults with sepsis or septic shock, we "suggest against" using probiotics. **(Conditional)**

42. Venous Thromboembolism Prophylaxis

42.1 For adults with sepsis or septic shock, we "recommend" using pharmacologic venous thromboembolism (VTE) prophylaxis unless a contraindication exists. **(Strong)**

42.2 For adults with sepsis or septic shock, we "recommend" using low molecular weight heparin over unfractionated heparin for VTE prophylaxis. **(Strong)**

42.3 For adults with sepsis or septic shock, we "suggest" using pharmacological VTE prophylaxis alone over pharmacological VTE prophylaxis plus mechanical VTE prophylaxis. **(Conditional)**

Introduction

Sepsis, life-threatening acute organ dysfunction due to infection, is a global health priority. Beyond being acutely deadly, sepsis contributes to new and worsened physical, cognitive, and mental health problems in many survivors. Early identification and treatment are critical to improving outcomes.

The Egyptian Guideline was made in accordance with "The Surviving Sepsis Campaign (SSC): The international guidelines for Management of Sepsis and Septic Shock 2026" [1] which were fully funded by Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM), with methodological support from the Guidelines in Intensive Care Medicine, Development, and Evaluation group. These Guidelines are intended to support clinicians caring for adult patients with sepsis and septic shock.

The guidelines define sepsis as life-threatening acute organ dysfunction due to infection, and septic shock as a subset of patients with circulatory dysfunction that confers a higher risk of mortality, consistent with the third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [2]. Because the diagnosis of sepsis may be uncertain in clinical practice, they developed standardized language for definite, probable, possible, and unlikely sepsis, which are used throughout the guidelines (Table 1).

In clinical practice, diagnosis of sepsis and septic shock should be based on holistic clinical assessment, which may vary across settings depending on local resources such as laboratory testing availability. The recommendations in the guidelines are intended to be applied pragmatically to patients diagnosed with sepsis and septic shock according to local practice, with recognition that successful implementation requires coordinated approaches that align sepsis protocols with stewardship objectives at the institutional level.

Purpose and Scope of the guidelines

The purpose of these guidelines is to assist anesthesiologists to enhance the quality of their practice, make choices of care based on evidence to improve patient safety, improve in health indicators such as mortality and incidence and severity of sepsis-related complications, and support improvements in management and overall patient outcomes of sepsis and septic Shock.

Given the high risk of death with septic shock and the more consistent and stronger association of antimicrobial timing and short-term mortality in patients with septic shock, implementation strategies, biomarkers and rapid diagnostic tests for sepsis, identifying the causative organism helping to optimize antimicrobial therapy, timely effective fluid resuscitation and timing of vasopressor initiation among other measures are crucial for proper management strategies.

The intended patient population: the recommendations in the guidelines are intended to be applied pragmatically to adult patients presenting with sepsis and septic shock.
The following guidelines are aimed at providing basic guidelines for management, incorporating principles of recommendations of sepsis and septic shock stabilization and ongoing effort to improve evidence-based care processes, such as timely antibiotic administration, with the aim of improving clinical outcomes. They are intended as a framework for reasonable and acceptable patient care and should be interpreted as such to allow for some degree of flexibility in different circumstances and according to local practice.

Target Audience

These guidelines are intended for use by healthcare professionals working as Anesthesiologists managing sepsis and septic shock in the surgical intensive care. They also may serve as a resource for healthcare professionals such as ward and intensive care nurses, perioperative care teams, policy makers, hospital managers, and other stakeholders who advise or care for patients presenting with sepsis and septic shock .

All physicians applying for privileges in surgical intensive care should show satisfactory completion of specialist postgraduate training in anesthesiology, surgical intensive care and pain management, standard training in the Egyptian Board program, University programs or equivalent.

METHODOLOGY

A comprehensive search for guidelines was done to identify the most relevant ones to consider for adaptation. For the literature review, potentially relevant clinical studies were identified *via* electronic and manual searches of the literature. The updated searches covered a 10-year period from January 1, 2016, to April 30, 2026. The inclusion/exclusion criteria that were followed in the search and retrieval of guidelines are adapted.

We selected guidelines only if they are:

- Evidence-based guidelines.
- National and/or international guidelines.
- Guidelines published from 2016 to April 2026.
- Peer reviewed publications.
- Guidelines written in English language.

We Excluded guidelines that are:

- Written by a single author not on behalf of an organization as guideline to be valid and comprehensive, ideally requires multidisciplinary input.
- Published without references as the GDG panel needs to know whether a thorough literature review was conducted and whether the current evidence was used in the preparation of the recommendations.

All retrieved Guidelines were screened and appraised using AGREE II instrument (www.agreetrust.org) by at least three members of the GDG. The panel decided on a cut-off point or ranked the guidelines (any guideline scoring above 50% on the rigor dimension was retained).

Guidelines used in the Adaptation Process:

The basic elements of the international guidelines for the management of sepsis and septic shock published by international societies can be successfully implemented in the practice of surgical intensive care worldwide. The Guidelines Development Group (GDG) for the Egyptian Board of Anesthetics, Surgical Intensive Care, and Pain Management has adopted with modification:

1. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic shock 2026. Critical Care Medicine April 2026; 54 (4):715-812 **(Reference No. 1)**

2. Singer M, Deutschman CS, Seymour CW, et al: The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016; 315:801–810 **(Reference No. 2)**

3. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Evans L, Rhodes A, Alhazzani W, et al: Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock 2021. *Intensive Care Med* 2021; 47:1181–1247 This article was simultaneously published in *Critical Care Medicine* (DOI: https://doi.org/10.1097/ CCM.0000000000005337) and *Intensive Care Medicine* (DOI: https://doi.org/10.1007/ s00134-021-06506-y). **(Reference No. 24)**

4. Rhodes A, Evans LE, Alhazzani W, et al: Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med* 2017; 45:486–552 **(Reference No. 32)**

5. Mekontso Dessap A, AlShamsi F, Belletti A, et al: European Society of Intensive Care Medicine: European Society of Intensive Care Medicine (ESICM) 2025 clinical practice guideline on fluid therapy in adult critically ill patients: Part 2-the volume of resuscitation fluids. *Intensive Care Med* 2025; 51:461–477 **(Reference No. 41)**

6. Thwaites L, Nasa P, Abbenbroek B, et al: Management of adult sepsis in resource-limited settings: Global expert consensus statements using a Delphi method. *Intensive Care Med* 2025; 51:21–38 **(Reference No. 77)**

7. Ostermann M, Alshamsi F, Artigas Raventos A, et al: European society of intensive care medicine clinical practice guideline on fluid therapy in adult critically ill patients: Part 3-fluid removal at de-escalation phase. *Intensive Care Med* 2025; 51:1749–1763 **(Reference No. 217)**

Strength of Recommendations

The strength of a recommendation communicates the importance of adherence to the recommendation.

Strong Recommendations	The GDG found that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This means that in most situations the recommendation can be adopted.
Conditional Recommendations	This means that the GDG found that there is: ▪ Greater uncertainty about the strength of evidence, or ▪ The recommendation may account for a greater variety in patient values and preferences, or ▪ The resource use makes the intervention suitable for some, but not for other locations. Conditional recommendations are still the best available evidence to date, and it can be adopted if it meets the conditions mentioned with it.
Good Practice Statement (GPS)	Statements based on expert opinion of respected authorities, and the guidelines development group.

Evidence level

Evidence Assessment

According to WHO Handbook for Guidelines, we used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to assess the quality of a body of evidence, develop and report recommendations. GRADE methods are used by WHO because these represent internationally agreed standards for making transparent recommendations.

Detailed GRADE information is available on the following sites:

- GRADE working group: https://www.gradeworkinggroup.org/
- GRADE online training modules: http://cebgrade.mcmaster.ca/

Quality Definition Implications

Evidence is categorized as High, Moderate, Low and Very low.

Table 1: Quality and Significance of the Four Levels of Evidence in GRADE:

Quality	Definition	Implications
High	The guideline development group is very confident that the true effect lies close to that of the estimate of the effect.	Further research is very unlikely to change confidence in the estimate of effect
Moderate	The guideline development group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect.	Further research is very likely to have an important impact on confidence in the estimate of effect and is unlikely to change the estimate
Very low	The group has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.	Any estimate of effect is very uncertain

RECOMMENDATIONS

These Guidelines deal with the cornerstone steps of Management of Sepsis and Septic shock in the Surgical Intensive Care.

The Guidelines Development Group (GDG) for the Egyptian Board of Anesthetics, Surgical Intensive Care, and Pain Management has adopted with modification:
Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic shock 2026. Critical Care Medicine April 2026; 54 (4): 715-812 (Reference No. 1)

SCREENING AND EARLY MANAGEMENT

1. Performance Improvement Programs

For hospitals and health systems, we "recommend" using a performance improvement program for sepsis, including sepsis screening for acutely ill, high-risk patients; standard operating procedures for treatment; and implementation of sepsis quality improvement strategies. (Strong, Moderate, Very low and Moderate evidence)

	Performance Improvement Programs
Strength	**Strong**
Benefit of Direction	Beneficial. QI initiatives likely improve sepsis processes of care and may have small effects on mortality.
Evidence	**Moderate certainty evidence** for Screening: Carried over from 2021 SSC*, RCT SCREEN** **Very low certainty evidence** for standard operating procedures: Carried over from 2021 SSC*, one recent RCTs*** **Moderate certainty evidence** for quality improvement strategies: Meta-analysis †, SSC 2026 recent RCT ††**,** the U.S. Centers' for Disease Control and Prevention's Hospital Sepsis Program Core Elements guidance †††**.**
Remarks	Performance improvement programs and quality improvement strategies may vary by setting and in accordance with a hospital/ healthcare system's ability to implement.

*The recommendations for sepsis **screening** and **standard operating procedures** were carried over from **2021 SSC guidelines**, so did not undergo formal updated evidence synthesis at SSC 2026. However, several relevant randomized controlled trials (RCTs) have been published since the 2021 SSC guidelines **further supporting these recommendations**. **In the large stepped-wedge, cluster **RCT SCREEN** evaluating 60,055 patients, implementation of an electronic alert system, staff education, and feedback was associated with lower 90-day in-hospital mortality in patients with and without sepsis [3]**.** ***One recent **RCT** with 872 patients evaluated hour-1 bundle implementation in the emergency department and showed this **standard operating procedure** was associated with shorter time to antibiotics and an uncertain effect on mortality with a point estimate suggesting a possible large decrease [4]**.**

† **Quality improvement** (QI) strategies represent a potentially scalable intervention for improving systems performance and patient care. **In a meta-analysis** of 50 observational studies, sepsis QI initiatives were associated with improved delivery of recommended care practices and reduced mortality [5]. Furthermore, multiple before-and-after and differences-in-differences studies have shown improvements in both processes of care and clinical outcomes in hospitals participating in multi-hospital sepsis QI initiatives.
†† **SSC 2026 panel** identified **one recent RCT** testing a QI intervention involving the display of a sepsis early warning system-triggered flag in the electronic health record combined with electronic health record-

based emergency department pharmacist notification [6]. Patients randomized to this QI intervention had shorter time to antimicrobial therapy and increased days alive and out of hospital at 28 days [6]. ††† These recommendations are consistent with the **U.S. Centers' for Disease Control and Prevention's Hospital Sepsis Program Core Elements guidance** [7].

2. Implementation Strategies

For hospitals and health systems, we "suggest" using a "code sepsis" or "sepsis huddle" protocol over not using such a protocol. (Conditional, Low evidence)

	Implementation Strategies
Strength	**Conditional**
Benefit of Direction	Beneficial. Provide more benefit in settings with less robust infra-structure for sepsis recognition and treatment,
Evidence	**Low certainty evidence.** Stepped-wedge, cluster randomized trial* & Recent study in 66 hospitals in 24 LMICs**, SSC 2026**
Remarks	"Code sepsis" or "sepsis huddle" protocols involve a multidisciplinary team huddle at bedside to discuss and expedite sepsis diagnosis and treatment following a positive sepsis screen.

As with rapid response systems, code sepsis implementation requires an institutional commitment and designated leadership to oversee its performance and effectiveness [8].

*In a large **stepped-wedge, cluster randomized trial** evaluating 60,055 patients, implementation of an electronic alert system, staff education, and feedback was associated with lower 90-day in-hospital mortality in patients with and without sepsis [3]. Meanwhile, some studies showed no difference in time to sepsis recognition [9], administration of antibiotics [6], fluid resuscitation [9], escalation of care [6], use of vasopressors [8], and mortality [6].

A **recent study on sepsis management in 66 hospitals in 24 **Low- and Middle-Income Countries (LMICs)** identified nearly one-third (28%) used an ICU outreach service [10], which could potentially be used for a code sepsis response team. Overall, the **SSC 2026** [1] panel assessed that the balance of evidence favored implementation of a multidisciplinary "code sepsis" response to improve outcomes in patients with sepsis.

3. Screening for Sepsis

3.1 In acutely ill adults en route to hospital by ambulance or flight, we "suggest" using a standard sepsis screening tool over not using a screening tool. (Conditional, Very low evidence)

3.2 For acutely ill patients in hospital, we "recommend" using NEWS, NEW2, MEWS, or SIRS over qSOFA as a single tool to screen for sepsis.(Strong, Moderate evidence)

	Screening for Sepsis
Strength	**Conditional** for en route to hospital **Strong** for in hospital
Benefit of Direction	Beneficial, Prehospital notification can improve timeliness of care.
Evidence	**Very low certainty evidence for en route:** SSC 2026 Comparative study of 221,429 prehospital medical records*, Several single-center studies**, **Moderate certainty evidence for in hospital:** Large cohort study†, Four systematic reviews and meta-analyses††, recently published stepped wedge trial†††
Remarks	The use of artificial intelligence (AI) is receiving increasing attention as a tool for early screening and prediction of sepsis.

*In a **comparative study** of 221,429 **prehospital** medical records that calculated the following early warning scores: National Early Warning Score (NEWS), National Early Warning Score 2 (NEWS2), Modified Early Warning Score (MEWS), systemic inflammatory response syndrome (SIRS), and quick sepsis-related organ failure assessment (qSOFA), NEWS2 had the best absolute test performance of studied screening tools [11]. However, due to the lower specificity, high rate of false-positive screens, and perceived difficulty of use in the prehospital environment, the **SSC 2026** panel refrained from recommending a specific screening tool. ****Several single-center studies** evaluated the impact of implementing prehospital sepsis notification on process and clinical outcomes. Three of these studies showed that time-to-treatment on sepsis quality measures or time-to-antibiotics were shorter with prehospital sepsis notification, but only one study reported a reduction in sepsis mortality [12–15]. Based on available evidence, the **SSC 2026** [1] panel determined that the balance of effects probably favors prehospital ambulance-based sepsis screening for identifying patients with sepsis and improving the timeliness of sepsis care.

† There is no ideal tool to screen for sepsis that has both high sensitivity and specificity. Screening tools should have high sensitivity to limit the number of false negative results. A **large cohort study of over 221,000 patients** demonstrated NEWS2 had the greatest sensitivity and specificity compared with MEWS, SIRS, and qSOFA [11]. ††**Four systematic reviews and meta-analyses** have reported that Early Warning Scores (EWS), including NEWS, NEWS2, MEWS, and SIRS were more sensitive for the diagnosis of sepsis than qSOFA [16-19]. Bedside clinicians need to understand the limitations of each tool. The presence of a positive qSOFA should alert clinicians to the possibility of sepsis in all resource settings but given qSOFA's poor sensitivity for the diagnosis of sepsis, the panel issued a strong recommendation in favor of using NEWS, NEW2, MEWS, or SIRS over qSOFA as a single screening tool. †††However, a recently published **stepped wedge trial** showed that electronic qSOFA screening with activation of an alert system triggering subsequent nurse and physician assessment and interventions resulted in improved 90-day in-hospital mortality [3].

4. Biomarkers and Rapid Diagnostic Tests for Sepsis

4.1 Sepsis is a clinical diagnosis and should not be ruled in or ruled out using a single biomarker or diagnostic test. (GPS)

4.2 There is "insufficient evidence" to make a recommendation regarding use of novel rapid host response diagnostics. (GPS)

	Biomarkers and Rapid Diagnostic Tests for Sepsis
Strength	**Good Practice Statement**
Benefit of Direction	Novel host response diagnostics could prompt the re-evaluation of patients with non-classical presenting features for sepsis.
Evidence	**Insufficient evidence**: SSC 2026*
Remarks	It is reasonable for health systems and clinicians make use of these novel host response diagnostics when feasible, whereas studying their impact on patient outcomes and resource utilization.

Several novel host response diagnostic tests are approved by regulatory bodies and available as diagnostic aids for sepsis. Sepsis diagnostic tests use several approaches to assess the likelihood of sepsis. None of these novel host response diagnostics provides a "positive" or "negative" result. Instead, they categorize the post-test risk of sepsis into categories, ranging from low risk to very high risk. However, the post-test likelihood ratios for sepsis associated with those categories are not uniform from one test to another. None of the tests should be considered definitive except for monocyte distribution width (MDW).

*Some tests use WBC characteristics, for example, **monocyte distribution width (MDW)** which evaluate size characteristics of circulating monocytes [20]. Except for MDW, clinicians must suspect sepsis before ordering the test. MDW, once activated on the appropriate hematological analyzer, is available for all complete blood counts with leukocyte differential. Thus, increased MDW values could prompt the re-evaluation of patients with non-classical presenting features, specifically to reassess for sepsis.

*Each of these novel host response diagnostics is designed to help clinicians to assess a patient's likelihood of having or developing sepsis with potentially greater accuracy than standard clinical evaluation, especially for patients with non-classic presentations. Due to the costs of these diagnostic aids, and lack of evidence that they improve patient-centered outcomes or resource utilization, **the SSC 2026** [1] panel did not recommend the use of any specific sepsis diagnostic aids.

5. Blood Cultures

For adults with possible, probable, or definite sepsis or septic shock, we "recommend" collecting blood cultures as soon as possible and ideally before the administration of antimicrobial therapy. (Strong, Low evidence)

	Blood cultures
Strength	**Strong**
Benefit of Direction	Beneficial. Cultures help to elucidate the source of infection.
Evidence	**Low certainty evidence**. SSC 2026*, systematic review**, 2025 German National Guidelines based on 2025 systematic review of 7 studies *** and **a** multi-center study†.
Remarks	Repeat cultures are recommended to confirm clearance of bacteremia or fungemia for *Staphylococcus au- reus*, *Staphylococcus lugdunensis*, and *Candida* species.

*Given the high mortality and morbidity associated with sepsis and the importance of appropriate antimicrobial coverage, the **SSC 2026** [1] panel issued **a strong recommendation for collection of blood cultures.** Blood cultures should be collected as soon as possible to avoid delay in initiating antimicrobial therapy.

** In **a systematic review** in 2025, several factors affect the yield of blood cultures, including the pretest probability of bacteremia, number of sets collected, the blood volume collected, the use of anaerobic bottles, and prior antibiotic use [21]. Blood cultures are generally obtained from two different sites**,** using 10-mL blood volume per tube. Multi-site collection is often recommended. One study showed sensitivity for detecting bacteremia increased from 91.5% to 99.3% when two sets of blood cultures were collected vs. one [21]. ***However, **2025 German National Guidelines** [22] recommend collecting blood cultures from a single site based on a **2025 systematic review of seven studies** (18,901 patients, 24,955 blood culture samples) that showed single site cultures may result in a higher proportion of cultures having the recommended 10mL, improved pathogen detection, less contamination, and require less venipuncture [21].

The **number of blood cultures** and the use of anaerobic bottles should be individualized, especially in low resource settings. The use of **aerobic bottles** alone can be justified since anaerobic cultures may not confer substantial additional benefit unless anaerobic pathogens are highly suspected. Attention to the technical aspects of blood culture collection is important to limit contamination, unnecessary diagnostic and therapeutic interventions, and additional costs.

† Clinicians should be aware that administration of **antimicrobial therapy before blood culture collection** may reduce their yield. In a **multi-center study of 325 patients** presenting to the emergency department with sepsis-induced hypotension or hypoperfusion (systolic blood pressure < 90 mm Hg or lactate ≥ 4 mmol/L), blood culture positivity decreased from 31.4% pre-antimicrobial to 19.4% at a median 70 minutes

(interquartile range [IQR], 50–110min) post-antimicrobial, a 12.0% absolute reduction and 38.2% relative reduction in blood culture sensitivity [23]. Wherever possible, blood cultures should be collected before administration of antimicrobial, but should not delay the initiation antimicrobial therapy, particularly in patients with hypotension.

6. Blood Lactate Measurement

For adults with possible, probable, or definite sepsis or septic shock, we "suggest" measuring blood lactate. (Conditional, Low evidence)

	Blood lactate Measurement
Strength	**Conditional**
Benefit of Direction	Beneficial. Helps to identify sepsis in patients with suspected but not confirmed sepsis.
Evidence	**Low certainty evidence.** SSC 2026, 2021 SSC, Systematic review, meta-analysis and several studies*. A systematic review of patient outcomes **
Remarks	Lactate testing may not be readily available in many resource-limited settings.

*The **SSC 2026** [1] carried over the statement on measuring blood lactate from **2021 SSC** guidelines **[24,25]. A systematic review and a meta-analysis** showed that the association of lactate level with mortality in patients with suspected infection and sepsis is well established [26,27]. Its use is currently recommended as part of the SSC Hour-1 sepsis bundle for those patients with sepsis [28], and an elevated lactate is part of the Sepsis-3 definition of septic shock [29]. It has been suggested that lactate can also be used to screen for the presence of sepsis among undifferentiated adult patients with clinically suspected (but not confirmed) sepsis. Ljungström et al. **among several studies** have assessed the use of lactate in this context [30]. The lactate cutoffs determining an elevated level ranged from 1.6−2.5 mmol/L, although diagnostic characteristics were similar regardless of the cutoff. Sensitivities range from 66−83%, with specificities ranging from 80−85%.

****A systematic review of patient outcomes** showed an association between the use of point-of-care lactate measurements at presentation and reduced mortality; however, the results are inconsistent [31]. In summary, the presence of an elevated or normal lactate level significantly increases or decreases, respectively, the likelihood of a final diagnosis of sepsis in patients with suspected sepsis. However, lactate alone is neither sensitive nor specific enough to rule-in or rule-out the diagnosis on its own. Therefore, **2021 SSC panel** [24,25] issued a weak recommendation favoring the use of serum lactate as an adjunctive test to modify the pretest probability of sepsis in patients with suspected but not confirmed sepsis.

7. Initial Fluid Resuscitation

7.1 Sepsis and septic shock are medical emergencies; treatment and resuscitation should begin immediately. (Conditional, Low evidence)

7.2 For adults with sepsis-induced hypoperfusion or septic shock, we "suggest" administering at least 30 mL/kg of IV crystalloid in the first 3 hr. (Conditional, Low evidence)

	Initial Fluid Resuscitation
Strength	**Conditional**
Benefit of Direction	Beneficial. A survival benefit was observed when 30mL/kg was completed within 3 hours
Evidence	**Low certainty evidence.** SSC 2026, 2021 SSC and SSC 2016, mainly from observational studies & Sepsis-3 definitions* Retrospective analysis & observational study**

	ARISE, ProCESS, and PROMISE trials, recent systematic review & meta-analysis, and ESCIM clinical practice guidelines***
Remarks	Consideration should be given to individual patient characteristics and context when selecting initial fluid volume. Clinicians prescribing fluids should perform frequent, ongoing reassessment and closely monitor patients to avoid harms of under- or over-resuscitation. Weight-based fluid volume should be calculated based on actual body weight, or by adjusted or ideal body weight in patients with BMI > 30 kg/m^2 (**Table 2**).

***SSC 2026** [1] recommended as consistent with previous SSC guidelines (**SSC 2016** and **2021 SSC**), resuscitation should begin immediately upon recognition of sepsis or septic shock, and clinicians should have a low threshold for commencing resuscitation in patients with possible sepsis **[**24,32]. Also, consistent with 2016 and 2021 SSC guidelines, SSC 2026 panel suggested administering at least 30mL/kg of IV crystalloids for initial fluid resuscitation in patients with sepsis-induced hypoperfusion or septic shock [24, 32]. Clinicians should consider fluid resuscitation in patients presenting with intermediate lactate elevation consistent with lactate threshold for the **Sepsis-3 definitions** of septic shock (> 2 mmol/L) [33]; particularly if there are no contraindications to fluid administration.

****A retrospective analysis** of adults presenting to an emergency department with sepsis or septic shock showed that failure to receive 30 mL/kg of crystalloid fluid therapy within 3 hours of sepsis onset was associated with increased odds of in-hospital mortality, delayed resolution of hypotension, and increased ICU length of stay (LOS), including in patients with end-stage kidney disease and heart failure [34]. **An observational study** of 612 hospitals in the United States demonstrated a reduced risk of in-hospital mortality for patients with sepsis who received moderate volume fluid resuscitation (4.0 L; IQR, 2.4–5.1 L) compared with very low volume resuscitation (1.6 L; IQR, 1.0–2.5 L) or very high volume resuscitation (6.1 L; IQR, 4.0–9.0 L) $p < 0.01$ [35].

***In the **ARISE [36]**, **ProCESS [37]**, and **PROMISE** [38] trials, the average volume of fluid received pre-randomization was also in the range of 30 mL/kg, suggesting that this fluid volume has been adopted in routine clinical practice. A **recent systematic review and meta-analysis** addressing the effect of early fluid resuscitation on mortality in sepsis reported that a survival benefit was observed when 30mL/kg was completed within 3 hours (low certainty) [39]. **The SSC 2026** panel determined that fluid volumes may be calculated using adjusted or ideal body weight in patients with high body mass index [40]. It is important that fluid resuscitation be tailored to actual body weight in cachectic or underweight patients to avoid over-resuscitation. The **SSC 2026 panel** emphasized the need for clinical reassessment during and following initial fluid resuscitation to reduce the risk of either under or over-resuscitation. The **SSC 2026** guidelines' conditional recommendation to administer greater than or equal to 30 mL/kg of initial resuscitation differs from the **ESCIM clinical practice guidelines** which "suggest administering up to 30 mL/ kg of IV crystalloids in the initial phase" [41]. The SSC 2026 panel acknowledges that fluid volume requirements vary across patients and encourages frequent reassessment to avoid under- or over-resuscitation. However, most patients with sepsis-induced hypotension and hypoperfusion benefit from greater than or equal to 30 mL/kg fluid resuscitation and fluid-related harms generally occur with far larger volumes (e.g., > 50 mL/kg).

8. Timing of Vasopressor Initiation Relative to Fluid Resuscitation

For adults with sepsis-induced hypotension, we "suggest" initial IV crystalloid fluid bolus resuscitation followed by vasopressor support if hypotension persists. (Conditional, Very low evidence)

	Timing of Vasopressor Initiation Relative to Fluid Resuscitation
Strength	**Conditional**

Benefit of Direction	Earlier vasopressor initiation in septic shock includes faster restoration of blood pressure and prevention of fluid overload
Evidence	**Very low evidence.** SSC 2026, 4 Systematic reviews and meta-analyses & 2 single-center RCTs*. Observational studies & the multicenter CLOVERS RCT**
Remarks	In patients with unstable septic shock, immediate concurrent administration of vasopressors together with IV crystalloid fluid may be warranted on a case-by-case basis. Presence of unstable shock should be determined by physical examination. Suggestive clinical features of unstable shock include severely reduced blood pressure, mottled skin, ashen appearance, cyanosis/decreased oxygen saturation, tachycardia, and altered mentation.

Sepsis-induced hypotension is a critical condition that requires prompt and appropriate intervention to restore perfusion and the mitigate risk of end-organ damage. The timing of vasopressor initiation remains a topic of debate. The rationale for earlier vasopressor initiation in septic shock includes faster restoration of blood pressure and prevention of fluid overload [42,43]. Persistent hypotension is associated with worse outcomes in observational studies.

*Recent studies provide mixed evidence on the timing of vasopressor administration. Four relevant **systematic reviews** and **meta-analyses** were identified [42,44–46]. **Two small, single-center RCTs** suggest that early administration of fixed, low-dose norepinephrine is associated with reduced fluid requirements and lower short-term mortality [43,47]. However, these trials were limited by a prolonged time to shock resolution, several hours in both arms**.**

Nonetheless, the findings of these trials were similar to **observational studies suggesting that early vasopressor use may be associated with lower mortality [48,49]. **The multicenter CLOVERS RCT**, however, found no difference in 90-day mortality, organ support-free days, or receipt of invasive ventilation between resuscitation algorithms with early vs. delayed vasopressor initiation [50]. Recent observational studies have indicated that peripheral administration of vasopressors is both feasible and safe [51, 52], so early vasopressor administration is adaptable to all settings.

The **SSC 2026** [1] panel based its recommendations on a careful review of available evidence, balancing the potential benefits of early vasopressor administration in patients with life-threatening end-organ hypoperfusion against the lack of clear evidence supporting its use in all patients, as well as the potential harms of unnecessary catecholamine exposure in patients whose hypotension could be rapidly corrected with fluid resuscitation.

9. Route of Vasopressor Administration

In adults with septic shock, we "suggest" starting vasopressors peripherally to restore mean arterial pressure rather than delaying initiation until central venous access is secured. (Conditional, Very low evidence)

	Route of Vasopressor Administration
Strength	**Conditional**
Benefit of Direction	Starting vasopressors peripherally to restore arterial blood pressure rather than delaying initiation until central venous access is secured.
Evidence	**Very low certainty evidence.** RCT of 263 general ICU patients, 5 observational studies via meta-analysis, and pooled complication rate across 7 studies*. The SSC 2026 in line with the 2021 SSC guidelines**.
Remarks	Data are insufficient to recommend a duration of use, dose, or access route (size of peripheral IV line or anatomic location). Midline catheters were not considered.

Traditionally, vasopressors were administered exclusively through central venous catheters out of concern for tissue necrosis associated with extravasation from peripheral IV lines. **Recent data** suggest that clinicians and hospital policies are more comfortable with peripheral vasopressor administration than with delayed initiation of vasopressors if no central access is present. *The SSC 2026 panel considered **one RCT** [53] of **263 general ICU patients** (of whom 70% required vasopressors) randomized to immediate central venous catheter placement vs. no catheter placement, which found an uncertain effect on mortality (very low certainty evidence). **SSC 2026 panel** [1] also considered **observational studies** which, when evaluated via **meta-analysis**, found an uncertain effect on mortality with peripheral vasopressor administration (two studies [53,54] with 611 patients, 28-day mortality; 3 studies [55-57] with 1,868 patients, 90-day mortality; both very low certainty). **Across seven studies** [53, 55–60] (1657 patients), the pooled complication rate for peripheral vasopressor administration was 5.97%, very low certainty).
The **SSC 2026 [1] panel determined that balance of effects and resource use probably favors initial peripheral vasopressor administration; however, evidence certainty was very low. Thus, they suggest starting vasopressors peripherally to restore arterial blood pressure rather than delaying initiation until central venous access is secured, in line with the **2021 SSC** guidelines [24,25].

10. Mean Arterial Pressure (MAP) Targets

10.1 For adults with septic shock, we "recommend" an initial MAP target of 65 mm Hg over higher MAP targets. (Strong, Moderate evidence)

10.2 For adults with septic shock 65 years old or older, we "suggest" an initial MAP range of 60–65 mm Hg over higher ranges. (Conditional, Low evidence)

	Mean Arterial Pressure (MAP) Targets
Strength	**Strong** for adults. **Conditional** for 65 years old or older.
Benefit of Direction	Beneficial. Benefit with a lower BP target compared with a higher target.
Evidence	**Moderate certainty evidence** for adults: 2021 SSC, RCT and meta-analysis of 2 RCTs* **Low certainty evidence** for 65 years old or older: The 65 trial, Meta-analysis of 3 trials, SSC 2026 open-label trial of 518 patients **
Remarks	In practice, it is not feasible to maintain MAP at exactly 65 mm Hg, so a reasonable range (e.g., within 5 mm Hg) should be used. Vasopressors should be titrated to maintain MAP within this range.

Mean arterial pressure (MAP) is a key determinant of mean systemic filling pressure, which in turn is a major driver of venous return and cardiac output. Increasing MAP therefore usually results in increased blood flow and augments the supply side of tissue perfusion. Although some organs, such as the brain and kidneys can auto-regulate blood flow, MAPs below a threshold, often understood to be approximately 60mm Hg, are associated with decreased organ perfusion, which tracks linearly with MAP [61].
***The 2021 SSC** [1] guidelines recommended targeting an MAP of 65 mm Hg or higher for initial resuscitation [24,25]. The recommendation was based principally on an **RCT in septic shock** comparing patients who were prescribed vasopressors to target a MAP of 65–70 mm Hg, vs a target of 80–85 mm Hg [62]. A **meta-analysis of two RCTs** indicated that higher MAP targets may result in little to no difference in short-term mortality in septic shock (low certainty) [63].

****The 65 trial subsequently** compared "permissive hypotension" (MAP 60–65 mm Hg) to "usual care" in patients 65 years old and older with distributive shock [64]. The intervention arm achieved a mean MAP of 67 mm Hg, compared with 73 mm Hg in the usual care arm**.** An individual patient level **meta-analysis** that included **this trial and two others** reported a point estimate for mortality that suggested benefit with a lower blood pressure target compared with a higher target, but the CI did not exclude the possibility of

harm (low certainty) [65]. In **a meta-analysis** done for the guidelines limited to patients 65 years old or older, a lower BP target was associated with reduced mortality at longest follow-up (high certainty).

An **open-label trial of 518 patients 65 years old or older randomized to a lower BP target (MAP 65–70 mm Hg) compared with a higher BP target (MAP 80–85 mm Hg) was published **after the guidelines meta-analysis was completed** [66]. This trial reported increased mortality associated with the higher MAP target. In the absence of data to support a higher MAP target, the **SSC 2026 panel** continues to recommend an initial MAP target of 65 mm Hg over higher MAP targets and makes a new conditional recommendation for an initial MAP target of 60–65 mm Hg over higher targets in adults 65 years old or older (conditional recommendation, low certainty evidence) in the setting of new evidence suggesting potential benefit of a lower MAP target [64,65].

11. Admission to Intensive Care

For adults with sepsis or septic shock who require ICU admission, we "suggest" admitting the patients to the ICU within 6 hr. (Conditional, Low evidence)

	Admission to Intensive Care
Strength	**Conditional**
Benefit of Direction	Beneficial. Timely admission of critically ill patients to an ICU environment may result in better patient outcomes.
Evidence	**Low certainty evidence.** 2021 SSC carried over to SSC 2026* Observational studies and registry databases of 401 ICU patients, Retrospective observational study of 14,788 patients, study of 50,322 ED patients admitted to 120 US ICUs, and the UK study of 12,380 ward patients in 48 hospitals**.
Remarks	Delayed admissions are associated with decreased sepsis bundle compliance and increased mortality, ventilator duration, and ICU and hospital length of stay. Where ICU bed availably can be limited, regular assessment, evaluation, and appropriate treatment should not be delayed, independent of patient location.

*The SSC 2026 [1] recommendations for admitting the patients to the ICU within 6 hr was carried over from **2021 SSC** guidelines [24,25]. The outcome of critically ill patients depends on timely application of critical care interventions in an appropriate environment. Outside the ICU, septic patients are typically seen in the Emergency Department (ED) and hospital wards and delayed admissions from ED are associated with decreased sepsis bundle compliance and increased mortality, ventilator duration, and ICU and hospital length of stay.

Data on the optimal time for transfer to the ICU stem from **observational studies and **registry databases**. In an **observational study of 401 ICU patients**, authors reported an increase in ICU mortality of 1.5% for each hour delay of ED to ICU transfer [67]. A **retrospective observational study of 14,788 critically ill patients** in the Netherlands showed a higher hospital mortality for the higher ED to ICU time quintiles (2.4– 3.7hr and > 3.7hr) compared with the lowest ED to ICU time quintile (< 1.2hr) [68]. When adjusted for severity of illness, an ED to ICU time > 2.4hr was associated with increased hospital mortality in patients with higher illness severity. Patients with sepsis were not studied separately. **Another study evaluated 50,322 ED patients admitted to 120 US ICUs** [69]. Mortality increased when ED stay exceeded 6 hours (17% vs 12.9%, $p < 0.001$). Among hospital survivors, the delayed admission group had a longer hospital stay, higher mortality, and higher rates of mechanical ventilation and central venous catherization. Similarly, **another study of 12,380 ward patients in 48 hospitals** in the **United Kingdom** showed that [70] delayed admission to ICU led to higher 90-day mortality and further physiological deterioration. Based on existing data, timely admission of critically ill patients to an ICU environment may result in better patient outcomes. There is also evidence of improved patient satisfaction, increased patient safety, better patient flow and improved staff morale.

12. Timing of Antibiotic Initiation in Hospital and En Route to Hospital

12.1 For adults with possible, probable, or definite septic shock, we "recommend" administering antimicrobial therapy immediately, ideally within 1 hr. of recognition. (Strong, Very low evidence)

12.2 For adults with probable or definite sepsis without shock, we "recommend" administering antimicrobial therapy immediately, ideally within 1 hr. of recognition. (Strong, Very low evidence)

12.3 For adults with possible sepsis without shock, we "suggest" a time-limited course of rapid investigation and if concern for infection persists, the administration of antimicrobial therapy within 3 hours from the time when sepsis was first suspected. (Conditional, Very low evidence)

12.4 Clinicians should perform a rapid assessment of the likelihood of infectious vs. non-infectious causes of acute illness in adults with possible sepsis without shock. (GPS)

12.5 For adults with a low likelihood of infection and without shock, we "suggest" deferring antimicrobial therapy while continuing to closely monitor the patient. (Conditional, Very low evidence)

12.6 For adults with definite or probable sepsis and hypotension (i.e., septic shock) and who have an anticipated time to in-hospital medical evaluation of over 60 min, we "suggest" administering antimicrobial therapy in ambulance or flight. (Conditional, Very low evidence)

	Timing of Antibiotic Initiation in Hospital and En Route to Hospital
Strength	**Strong** for possible, probable, or definite septic shock or with probable or definite sepsis without shock **Conditional** for possible sepsis without shock, for a low likelihood of infection and without shock & en route to Hospital with definite or probable sepsis and hypotension. **GPS** for rapid assessment for possible sepsis without shock.
Benefit of Direction	Beneficial. Early administration of appropriate antimicrobial therapy is the most effective initial intervention to reduce mortality in patients with sepsis or septic shock, along with fluid resuscitation.
Evidence	**Very low certainty evidence.** SSC 2026 systematic review & meta-analysis which included 42 observational studies combined with 2 additional observational studies and 2 RCTs*, 2021 SSC & SSC 2026 panel** and Delphi panel of global experts *** **En route:** 3 systematic reviews & Meta-analysis of observational studies & RCTs†
Remarks	Prehospital antibiotic delivery should be implemented only after having a structured process in place to screen for sepsis in ambulance or flight, as discussed in recommendation 3

Early administration of appropriate antimicrobial therapy is the most effective initial intervention to reduce mortality in patients with sepsis or septic shock, along with fluid resuscitation [71]. Delivering antimicrobial therapy to patients with sepsis or septic shock should therefore be treated as an emergency. The imperative to administer appropriate antimicrobial therapy as early as possible, however, must be balanced against the potential undesirable effects of unnecessary antimicrobial use in patients without infection [72].

***SSC 2026 panel** [1] identified a **systematic review** and **meta-analysis** which **included 42 observational studies** through May 22, 2022, comprising 190,896 patients [73]. They combined the data from this meta-analysis with **two additional observational studies** published after May 22, 2022 [74, 75] and **two RCTs** [4,76]. Overall, early antimicrobial therapy was associated with a reduction in short-term mortality for adults with sepsis or septic shock, including patients who received antibiotics within 1 hour (vs. longer), 3 hours (vs. longer), and 6 hours (vs. longer) from presentation, albeit with wide CIs **(**Confidence Intervals) that included no difference. The observed mortality reduction associated with early antimicrobial therapy appeared strongest and most consistent in patients with septic shock. The recommended thresholds for administering antimicrobial therapy, that is, within 1 and 3 hours, were selected based on the available summary estimates.

**Despite the growth in evidence since the 2021 SSC guidelines [24,25], the overall certainty of evidence was adjudicated as very low due to persistent risk of bias (the main body of evidence comprised of observational studies with an inherent risk of residual confounding, and most studies used inadequate risk adjustment), inconsistency, indirectness (variations in population /intervention/comparator and in the definition of time zero), and imprecision.

The recommendations on timing of antimicrobial therapy are **unchanged from the 2021 SSC** guidelines.
***Given the high risk of death with septic shock and the more consistent and stronger association of anti-microbial timing and short-term mortality in patients with septic shock, the **SSC 2026 panel** issued a strong recommendation to administer antimicrobial therapy immediately (within 1 hr.) in adults with possible, probable, and definite septic shock and in adults with probable or definite sepsis. For adults with possible sepsis without shock, where the diagnosis of bacterial infection is less clear, the panel issued a conditional recommendation for a rapid (within 3 hr) assessment of infectious and noninfectious etiologies of illness.
In recognition of the variation in diagnostic testing capabilities, a recent **Delphi panel of global experts** recommended: "for adults with possible sepsis without shock, where investigators (such as laboratory or imaging) to exclude a noninfectious source of acute illness are not readily available and if concern for infection persists, antimicrobial therapy should be administered without delay" [77].

† En Route to Hospital in ambulance or flight, for administering antimicrobial therapy **3 systematic reviews** evaluated the impact of prehospital IV antibiotics on survival [78-80]. Most studies were **observational. Meta-analysis** of observational studies was uncertain but suggested a possible reduction in mortality with prehospital antibiotics. Meta-analysis of **RCTs** also suggested that prehospital antibiotics may reduce 28-day mortality, with most of the estimate weight attributed to a single trial. **One high-quality trial** showed no difference in 28-day mortality when antibiotics were given 96 min sooner in the prehospital intervention arm, but the control arm mortality was only 8%, suggesting a low aggregate illness severity [76]. The **SSC 2026 panel** tailored this recommendation to patients with evidence of septic shock, as demonstrated by definite or probable sepsis and hypotension (e.g., SBP < 90; MAP < 65; SBP < 100 in patients with known hypertension). Also, the SSC 2026 panel limited this recommendation to those in whom the total medical contact delay (time from EMS arrival to in-hospital evaluation) was projected to exceed 60 minutes, consistent with the recommendation to administer antimicrobial therapy within 1 hour for patients with septic shock.

13. Biomarker-Guided Initiation of Antimicrobial Therapy

For adults with possible or probable sepsis or septic shock, we "suggest" using clinical evaluation alone over procalcitonin plus clinical evaluation to decide whether to start antimicrobial therapy. (Conditional, Very low evidence)

	Biomarker-Guided Initiation of Antimicrobial Therapy
Strength	**Conditional**

Benefit of Direction	Beneficial to use clinical evaluation alone due to the limited availability of procalcitonin level measurements in some settings.
Evidence	**Very low certainty evidence**. SSC 2026 recommendation was carried over from 2021 SSC*, Meta-analysis of 30 studies, meta-analysis of 3 RCTs, and guidelines for the management of community acquired pneumonia**
Remarks	With no apparent benefit, unknown costs, and limited availability in some settings including LMICs, the 2021 SSC panel issued a weak recommendation against using procalcitonin to guide antimicrobial initiation in addition to clinical evaluation.

*The **SSC 2026 recommendation** to "suggest" using clinical evaluation alone over procalcitonin plus clinical evaluation to decide whether to start antimicrobial therapy was **carried over from 2021 SSC** guidelines. Procalcitonin is undetectable in healthy states, but rises rapidly in response to pro-inflammatory stimuli, especially bacterial infections [81]. In theory, procalcitonin levels in combination with clinical evaluation may facilitate the diagnosis of serious bacterial infections and prompt early initiation of antimicrobials.

****The 2021 SSC** panel in a **meta-analysis of 30 studies** (3,244 patients), procalcitonin had a pooled sensitivity of 77% and specificity of 79% for sepsis in critically ill patients [82]. The panel identified direct evidence from **three RCTs** that compared procalcitonin-guided protocols for antibiotic initiation vs usual care [83-85]. A **meta-analysis of the three trials** (n = 1,769 ICU patients) found no difference in short-term mortality, length of ICU stays, or length of hospitalization. Long-term mortality, readmission rates, and hospital-free days were not reported in any of the trials, and no relevant studies on the costs associated with use of procalcitonin were found. In general, knowledge about the undesirable effects was lacking, and the quality of evidence was very low. Published **guidelines for the management of community acquired pneumonia** recommend initiation of antimicrobials for patients with community acquired pneumonia regardless of procalcitonin level [86].

14. Source Control

14.1 Adults with sepsis or septic shock should be rapidly evaluated for specific anatomical diagnoses or sources of infection that require emergent source control. (Good Practice Statement)

14.2 For adults with sepsis or septic shock and a specific anatomical diagnosis or source of infection that requires source control, we "suggest" early source control over late source control, ideally within 6 hr of diagnosis of sepsis or septic shock requiring source control. (Conditional, Very low evidence)

	Source Control
Strength	**Good Practice Statement** (GPS) for rapid evaluation. **Conditional** for early source control within 6 hours
Benefit of Direction	Early source control (≤6 hours) is associated with reduced short-term mortality and shorter ICU length of stay compared to late source control,
Evidence	**Very low certainty evidence.** SSC 2026 Meta-analysis of 11 observational studies*. Recommendation of SSC 2026 is consistent with the 2021 SSC** as well as other guidelines.
Remarks	Prolonged medical stabilization without source control in severely ill patients with septic shock is unlikely to succeed. Source control should be implemented as soon as medically and logistically practical after diagnosis.

*Source control should be achieved as soon as possible following initial resuscitation, but the optimal timeframe is unclear. The **SSC 2026 panel** [1] identified **11 relevant observational studies.** Studies defined early source control in various ways, most commonly as source control within 6 hours from either diagnosis or sepsis, diagnosis of septic shock, or identification of the need for source control. **Meta-analysis** of these studies yielded uncertain findings due to the very low certainty of evidence. However, point estimates suggest early source control may possibly reduce short-term (up to day 90) mortality, as compared with late source control. **One study** evaluated mortality beyond 90 days and suggested that early source control may result in a large reduction in one-year mortality, as compared with late source control. ICU LOS may be slightly reduced, while impact of hospital LOS was trivial. **The recommendation of **SSC 2026** for early source control is consistent with the **2021 SSC guidelines**, which included a best practice statement in favor of early source control, as well as **other guidelines** [87,88].

15. Empiric Multidrug Resistant (MDR) Pathogen Coverage, Empiric Antifungal Coverage, and Empiric Anaerobic Coverage

15.1 For adults with sepsis or septic shock at high risk of infection with a specific multidrug resistant (MDR) pathogen, we "suggest" using empirical antimicrobial therapy with coverage for this MDR pathogen. (Conditional, Very low evidence)

15.2 For adults with sepsis or septic shock at low risk of infection with a specific MDR pathogen, we "suggest against" using empirical antimicrobial therapy with coverage for this MDR pathogen. (Conditional, Low evidence)

15.3 For adults with sepsis or septic shock, we "suggest against" using empirical antifungal therapy. (Conditional, Very low evidence)

15.4 For adults with sepsis or septic shock without risk factors for anaerobic infection, we "suggest" using an empiric antibiotic regimen without anaerobic coverage. (Conditional, Very low evidence)

15.5 For adults with sepsis or septic shock with specific risk factors for anaerobic infection, we "suggest" using an empiric antibiotic regimen that includes anaerobic coverage. (Conditional, Very low evidence)

	Empiric Multidrug Resistant (MDR) Pathogen Coverage, Empiric Antifungal Coverage, and Empiric Anaerobic Coverage
Strength	**Conditional** for all
Benefit of Direction	Beneficial. Selective MDR coverage reduces mortality in high-risk patients; routine use in all patients is harmful. Beneficial empiric antifungal only in high-risk individuals, but in a patient without a fungal infection may also be harmful. Beneficial empiric anaerobic coverage in an adult with anaerobic infection but unnecessary in an adult without anaerobic infection and may also be harmful.
Evidence	**Very low certainty of evidence** **MDR Coverage:** SSC 2026 meta-analysis of one RCT examining *A. baumannii*, 4 RCTs examining ESBL, 5 RCTs examining CRE, and a systematic review of 15 observational studies*. **Antifungal Coverage:** SSC 2026 systematic review and meta-analysis of 7 RCTs including EMPIRICUS trial, evidence base was unchanged from the 2021 SSC**. **Anaerobic Coverage:** The SSC 2026 identified a relevant systematic review and meta-analysis of two RCTs, observational studies, other guidelines and research on the anaerobic microbiome†.

Remarks	Risk factors for MDR pathogens include colonization with the MDR pathogen of concern, previous infection with the MDR pathogen of concern, prolonged use of broad-spectrum antibiotics, and prolonged hospitalization in a unit with a high prevalence of the MDR pathogen of concern. Empiric antifungal therapy should be considered on a case-by-case basis in selected patients with sepsis or septic shock and risk factors for fungal infection, including immunosuppression, prolonged use of antibiotics, prolonged hospitalization, and intra-abdominal sources of infection. When coverage of potential multidrug-resistant (MDR) pathogens is required, agents with anaerobic activity (e.g., piperacillin– tazobactam or carbapenems) are appropriate when alternative agents lacking anaerobic coverage are insufficient. Risk factors for anaerobic infection include intra-abdominal or deep seated gynecological/ obstetric source of infection, necrotizing soft- tissue infection, head and neck infection, and CNS abscesses or empyema.

MDR pathogens**, are defined as those with acquired non-susceptibility to least one agent in three of more antimicrobial categories [89], including *Acinetobacter baumannii*, extended spectrum β-lactamase (ESBL)-producing Gram-negative bacteria, carbapenem-resistant *Enterobacterales* (CRE), vancomycin-resistant *Enterococcus*, MDR *pseudomonas*, and methicillin- resistant *S. aureus* (MRSA). **The SSC 2026** panel identified **one relevant RCT** examining *A. baumannii, 4 RCTs** examining ESBL-producing Gram-negative bacteria, **5 RCTs** examining CRE, and a **systematic review of 15 observational studies** examining MRSA infections [90]. **Meta-analysis** of these studies yielded very low certainty evidence but suggested a possible reduction in short-term mortality with the use of empiric antimicrobial therapy with MDR coverage, as compared with no MDR coverage.

**** Antifungal Coverage: The SSC 2026** panel identified a relevant **systematic review** and **meta-analysis** of **seven RCTs** [91], including the **EMPIRICUS trial** [92]. No additional trials were identified, and the evidence base was unchanged from the **2021 SSC** guidelines [24,25]. **Meta-analysis** suggested that there may be no important reduction in short-term mortality with the use of empiric antifungal therapy, as compared with no antifungal therapy. The panel agreed that empiric antifungal therapy is not indicated in every adult with sepsis or septic shock. Generalized use of empiric antifungal therapy in all adults with sepsis or septic shock may result in reduced equity globally.

† **Empiric Anaerobic Coverage.** the decision to include or withhold anaerobic coverage depends on the anatomical site of infection, which influences likelihood of anaerobic infection. **The SSC 2026 panel** identified a relevant **systematic review** and **meta-analysis** of **two RCTs** [93] that comprised the primary evidence base. In meta-analysis of the two RCTs, there was an uncertain impact of empiric anti-anaerobic coverage in general population of adult patients with sepsis or septic shock, as compared with no anaerobic coverage. **Observational studies** suggested an increased risk of adverse outcomes, including increased mortality in patients treated with empiric anti-anaerobic antibiotics [94]. The recommendation is consistent with **other guidelines** [95,96] and research on the **anaerobic microbiome** [97]. t is also applicable to low resource settings.

16. Pathogen-Specific Rapid Diagnostic Tests

For adults with sepsis or septic shock, we "suggest" using pathogen-specific rapid diagnostic tests on a case-by-case basis in selected patients based on clinical features, local pathogen- and resistance patterns, seasonality, and availability of tests and antibiotic stewardship guidance. (Conditional, Low evidence)

	Pathogen-Specific Rapid Diagnostic Tests
Strength	**Conditional**

Benefit of Direction	Beneficial. This may enable clinicians to better target antimicrobial therapy and reducing both the unnecessary prescription of broad-spectrum antimicrobial therapy and the development of antimicrobial resistance.
Evidence	**Low certainty evidence.** SSC 2026 systematic review and meta-analysis of 6 RCTs + 1 additional RCT*
Remarks	Pathogen-specific rapid diagnostic tests are used to guide empiric antimicrobial therapy which may include molecular PCR-based tests, phenotypic assays, respiratory and other syndromic panels, or antimicrobial resistance detection, each offering either rapid identification of pathogens or resistance detection to guide anti-microbial therapy.

*The SSC 2026 panel evaluated a **systematic review and meta-analysis of 6 RCTs** [98] supplemented by one additional RCT [99] assessing molecular testing platforms and phenotypic assays in adults with bloodstream infection. Meta-analysis showed possibly little to no difference in short-term mortality with the use of pathogen-specific rapid diagnostic tests, as compared with not using them. The use of these tests in isolation may have a limited impact on patient-important outcomes, but mortality benefits have been observed when rapid diagnostic tests are paired with effective antimicrobial stewardship programs [100].

17. Prolonged Infusion of β-Lactam Antibiotics

For adults with sepsis or septic shock, we "recommend" using prolonged infusion of beta-lactams for maintenance (after an initial loading dose) over bolus administration. (Strong, Moderate evidence)

	Prolonged Infusion of β-Lactam Antibiotics
Strength	**Strong**
Benefit of Direction	Beneficial. Prolonged infusion significantly reduces short-term mortality and increases days alive outside ICU & hospital compared to bolus administration.
Evidence	**Moderate certainty evidence.** SSC 2026 panel recent systematic review and meta-analysis of 18 RCTs, including the large international BLING III RCT*
Remarks	A loading dose before prolonged infusion is essential to avoid delays in reaching effective beta-lactam concentrations. Drug stability and drug-drug compatibility must be considered throughout therapy.

Key pharmacokinetic parameters of beta-lactam antibiotics can change in patients with sepsis and septic shock, potentially leading to sub-therapeutic concentrations [101]. Unlike traditional intermittent bolus infusion (lasting 30 min or less), administering beta-lactam antibiotics via prolonged IV infusion—either as an extended infusion (over at least half of the dosing interval) or as a continuous infusion—maintains consistent beta-lactam concentrations that maximize the pharmacodynamics of these drugs [102]. The shorter the drug half-life, the greater the benefit.

***The SSC 2026 panel** identified **a recent systematic review** and **meta-analysis of 18 RCTs** (9,108 participants) [103], including the large international **BLING III RCT [104]**. Meta-analysis of these trials showed that prolonged infusions reduce short-term mortality (RR 0.91; 95% CI, 0.85–0.97, high certainty, which translates to 25 fewer deaths per 1,000 patients, 95% CI, 42 fewer to 8 fewer). In BLING III RCT, prolonged infusion of beta-lactams likely resulted in more days alive out of ICU and out of the hospital than intermittent infusion (bolus) [104]. With **BLING III RCT** data available, the certainty of evidence was assessed as high. This informed a "strong recommendation" in favor of the intervention. This recommendation may pose challenges in low-resource settings with insufficient supply of infusion pumps.

18. Therapeutic Drug Monitoring (TDM) of Antimicrobial Therapy

For adults with sepsis or septic shock, we "suggest" using antimicrobial therapeutic drug monitoring (TDM) on a case-by-case basis in selected patients, based on clinical features, local pathogen- and resistance patterns, drug class, and availability of TDM. (Conditional, Very low evidence)

	Therapeutic Drug Monitoring (TDM) of Antimicrobial Therapy
Strength	**Conditional**
Benefit of Direction	Beneficial. Based on a potential effect of TDM on the assessed desirable outcomes and no indication of harm.
Evidence	**Very low certainty evidence.** SSC 2026, recent systematic review and meta-analysis of 8 RCTs*, consistent with 2021 SSC guidelines and other guidelines**
Remarks	TDM may improve antimicrobial dosing accuracy and possibly reduce short-term mortality in selected patients with conditions that alter drug concentrations. Its use should be reserved for selected patients where PK/PD alterations are expected.

Antimicrobial therapy is subject to changes in pharmacokinetic (PK) and pharmacodynamic (PD) properties in sepsis and septic shock [105], potentially resulting in concentrations that are too low (risking clinical failure) or too high (potentially leading to toxicity) [106]. Multiple conditions can affect antimicrobial concentrations in critically ill patients including augmented renal clearance, acute kidney injury, hypoalbuminemia, renal replacement therapy, and extracorporeal life support.

*The **SSC 2026 panel** identified a **recent systematic review** and **meta- analysis of 8 RCTs** (1,241 participants) [107] with 6 trials assessing TDM of antibacterials and two trials assessing TDM of antifungals. The results of the meta-analysis were uncertain (very low certainty evidence), but point estimates suggested a possible reduction in short-term mortality with the use of TDM as compared with not using TDM [107], whereas the effects for ICU LOS and hospital LOS were considered trivial.
The recommendation is consistent with the **2021 SSC guidelines, which included a best practice statement to use accepted PK/PD principles [25], and **consistent with other guidelines** [108].

19. Antimicrobial Discontinuation, De-escalation and Biomarker Guidance for Antibiotic Discontinuation

19.1 Clinicians should continuously reevaluate patients, search for alternative diagnoses, and discontinue empiric antimicrobial therapy if an alternative cause of illness is demonstrated or strongly suspected in adults with suspected sepsis or septic shock but unconfirmed infection. (GPS)

19.2 For adults with sepsis or septic shock, we "recommend" de-escalation of antimicrobial therapy over no de-escalation when a confirmed microbiological diagnosis and susceptibility profile is available. (Strong, Very low evidence)

19.3 For adults with sepsis or septic shock, we "suggest" de-escalation of antimicrobial therapy over no de-escalation when no pathogens are identified on final culture results. (Conditional, Very low evidence)

19.4 For adults with an initial diagnosis of sepsis or septic shock and adequate source control where optimal duration of therapy is unclear, we "suggest" using procalcitonin AND clinical evaluation to decide when to discontinue antimicrobial therapy over clinical evaluation alone. (Conditional, Low evidence)

	Antimicrobial Discontinuation, De-escalation and Biomarker Guidance for Antibiotic Discontinuation

Strength	**GPS** for suspected sepsis or septic shock but unconfirmed infection. **Strong** for sepsis or septic shock with confirmed microbiological diagnosis **Conditional** when no pathogens are identified on final culture results **Conditional** for procalcitonin AND clinical evaluation to guide discontinuation
Benefit of Direction	Beneficial. De-escalation reduces antimicrobial resistance and is associated with a possible reduction in short-term mortality, without compromising patient outcomes.
Evidence	**Very low certainty evidence** for de-escalation: SSC 2026, Meta-analysis, direct evidence from 26 studies including 2 RCTs*. Other guidelines and prior 2021 SSC guidelines** **Low certainty evidence** for procalcitonin-guided discontinuation: 2025 ADAPT-Sepsis RCT, SSC 2021 meta-analysis of direct evidence from 14 RCTs ***.
Remarks	De-escalation involves discontinuing unnecessary antimicrobial therapy or narrowing the spectrum of agents. In low-resource settings with high MDR rates and limited laboratory services, weigh the risk of undetected MDR pathogens carefully before de-escalating.

***De-escalation:** Antimicrobial exposure is associated with development of antimicrobial resistance, potential toxicities, and risk for *Clostridioides difficile* infection. Reducing both the number and spectrum of antimicrobial agents is a key goal in hospital antimicrobial stewardship. **The SSC 2026 panel** identified **direct evidence from 26 studies**, including **two RCTs** [109,110]. **Meta-analysis** was uncertain (very low certainty evidence). However, point estimates suggested a possible reduction in short-term mortality (26 studies), ICU LOS (5 studies), hospital LOS (4 studies), and antimicrobial resistance (6 studies) with de-escalation of empiric antimicrobial therapy, as compared with no de-escalation. The effects were primarily driven by the 24 observational studies, but effect estimates in the two RCTs were comparable [109,110]. **The recommendations on de-escalation of empiric antimicrobial therapy are consistent with **other guidelines** [111,112], as well as **prior 2021 SSC guidelines** [24,25]. Therefore, the panel issued a strong recommendation for de-escalation of empiric anti-microbial therapy when a confirmed microbiological diagnosis and susceptibility profile is available, and a conditional recommendation for de-escalation in patients who are improving when no pathogens are identified on final culture(s).

***The statement **for use of** biomarker guidance for antibiotic discontinuation was carried over from **2021 SSC guidelines**. Since the 2021 guidelines, the **2025 ADAPT-Sepsis RCT** provided additional evidence that procalcitonin can be used to safely reduce antibiotic duration in patients with sepsis [113]. **SSC 2021 panel** [65,66] identified direct evidence from **14 RCTs** (*n* = 4,499 patients) that assessed use of procalcitonin to guide antimicrobial treatment duration in patients with sepsis (two trials included critically ill patients in general). A **meta-analysis** suggested improved mortality in patients who were managed using procalcitonin versus control, while there was no effect on length of stay in ICU or hospital. The SSC 2026 panel suggests using procalcitonin AND clinical evaluation to decide when to discontinue antimicrobial therapy over clinical evaluation alone if the optimal duration of therapy is unclear.

HEMODYNAMIC MANAGEMENT

20. Blood Pressure Monitoring

For adults with septic shock, we "suggest" using either invasive or noninvasive blood pressure monitoring. (Conditional, Very low evidence)

	Blood Pressure Monitoring
Strength	**Conditional**

Benefit of Direction	Beneficial for timing of vasopressor use.
Evidence	**Very low certainty evidence.** The 2026 SSC guidelines relied on 4 observational studies assessing clinical outcomes and 12 studies evaluating BP concordance*. Multicenter EVERDAC RCT testing**.
Remarks	Invasive blood pressure monitoring is advised in patients with shock who: require intermediate-to-high dose vasopressors, escalating doses of vasopressor, or multiple vasopressors; are receiving frequent arterial blood sampling; or have noninvasive blood pressure measurements which are inconsistent on repeated assessments.

Arterial catheters allow for continuous blood pressure (BP) monitoring and frequent blood sampling, so are commonly used in critically ill patients. However, variability in use exists across ICUs [114]. Potential benefits include continuous and more accurate BP monitoring, ready access to arterial blood for analyses (e.g., blood gases, lactate), and patient comfort; potential downsides include risk (e.g., infection, thrombosis), costs, and clinician time. The **2021 SSC guidelines** [24,25] suggested invasive BP monitoring as soon as practical and if resources are available based on the discordance of invasive and noninvasive measurements.

***The SSC 2026 [1]** relied on **4 observational studies** (28,516 total patients) assessing clinical outcomes and **12 studies** (57,114 total patients) evaluating BP concordance; all evidence was very low certainty. Despite the very low certainty evidence, no difference was observed in mortality. Invasive monitoring was associated with more acute kidney injury and longer lengths of stay ; yet potentially substantial residual confounding likely exists. Concordance of noninvasive with invasive BP measurements (defined as a < 10 mm Hg difference) was 73% for mean pressure (12 studies), 65% for systolic pressure (7 studies) and 85% for diastolic pressure (6 studies). The observed discordance may lead to inappropriate vasopressor use or difficulties maintaining target blood pressure with a noninvasive approach. However, several **SSC 2026** [1] panel members felt strongly that measurement discordance should lead to a suggestion to use invasive monitoring.

****The **multicenter EVERDAC RCT** testing a noninvasive strategy to BP monitoring in circulatory failure (i.e., avoidance of arterial line unless pre-specified safety criteria were met) was published after the 2026 SSC guideline recommendations were finalized [115]. EVERDAC found that, among 1010 patients randomized, 28-day all-cause mortality was noninferior in the noninvasive-strategy group (34.3% mortality vs. 36.9% in the invasive-strategy, $p = 0.006$ for noninferiority) [115].

21. Fluid Type

21.1 For adults with sepsis or septic shock, we "recommend" using crystalloids as first-line fluid for resuscitation. (Strong, Moderate evidence)

21.2 For adults with sepsis or septic shock undergoing initial resuscitation, we "suggest" using balanced crystalloids over 0.9% saline. (Conditional, Moderate evidence)

21.3 For adults with sepsis or septic shock, we "suggest" using crystalloids alone over crystalloids with supplemental albumin for fluid resuscitation. (Conditional, Moderate evidence)

21.4 For adults with sepsis or septic shock, we "recommend against" using starches for resuscitation. (Strong, High evidence)

21.5 For adults with sepsis and septic shock, we "suggest against" using gelatin for resuscitation. (Conditional, Moderate evidence)

	Fluid Type
Strength	**Strong** for crystalloids as first-line, and "against" using starches.

	Conditional for using balanced crystalloids over 0.9% saline, for using crystalloids alone over crystalloids with supplemental albumin, and against using gelatin.
Benefit of Direction	Balanced solutions are beneficial with considerations in some populations (traumatic brain injury, cirrhosis, and patients who received large volumes of crystalloids).
Evidence	**Moderate certainty evidence:** - For crystalloids as first-line: **SSC 2021 & SSC 2026 guidelines***. - For using balanced crystalloids over 0.9% saline: systematic review and meta-analysis (included 11 studies) & individual patient data meta-analysis (IPDMA) derived from 5 high-quality RCTs **. - For using crystalloids alone over crystalloids with supplemental albumin: **SSC 2026** relied on six RCTs*** & 2024 ESICM**** - Against using gelatin: **network meta-analysis & systematic review of RCTs†** **High-certainty evidence.** For "against using starches": meta-analysis of RCTs & network meta-analysis††
Remarks	- For patients with sepsis and traumatic brain injury, we suggest using 0.9% saline. - Use of supplemental albumin may be appropriate for patients who already received large crystalloid volumes or have cirrhosis. Supplemental albumin should be avoided in patients with traumatic brain injury.

*Carried over from the **2021 guidelines [24,25],** the **SSC 2026 panel** [1] recommends **using crystalloids as first-line** for fluid resuscitation and recommends **against using starches (High-certainty evidence)**. **SSC 2026 panel** also **"suggest against" using gelatins (Moderate certainty evidence)** [1].

** The **SSC 2026 panel** considered two recent reviews on **use of balanced solutions** in general critical care patients with sepsis subgroups: one a **systematic review and meta-analysis** that included 11 studies and 35,884 patients [116] and an individual patient data meta-analysis **(IPDMA**) derived from 5 high-quality RCTs and 6,753 patients [117]. The reviews showed that using balanced crystalloids probably reduced mortality compared with 0.9% saline and new RRT and may have had no effect on VFD. The benefit of balanced solutions is greatest when used throughout resuscitation**.** The certainty of evidence has strengthened from the **2021 guidelines** due to **added data.**

***Theoretically, **albumin** maintains intravascular oncotic pressure compared with crystalloids**.** Due to cost and the absence of clear benefit for its use, however, the **2021 guidelines** [24,25] provided a conditional (previously, weak) recommendation for using albumin in patients who had already received large volumes of crystalloids. The current recommendation **SSC 2026** [1] relied on **six RCTs** of 4,383 patients with sepsis or septic shock, or their subgroups in larger trials**.** The panel of **SSC 2026** [1] found probably no effect of albumin on 28-day mortality. There was similarly no effect on 90-day mortality, new-onset organ dysfunction, ventilator or vasopressor-free days, and the requirement for RRT. The panel considered the lack of proven benefit and higher cost of albumin in making this recommendation.

Considerations should be made for **different populations**. For patients with traumatic brain injury, evidence suggests harm with the use of balanced crystalloids [118] or albumin [119], leading the panel to advise using 0.9% saline in this population. For patients with cirrhosis, use of albumin in addition to crystalloids may be preferred [120]. Similarly, evidence suggesting higher blood pressures [121], higher static filling pressures, and lower net fluid balances [121] with albumin led the panel to propose albumin for patients who have already received large volumes of crystalloids. ********These recommendations for the use of balanced solutions and albumin concur with the **2024 ESICM** clinical practice guidelines [122].

† Studies conducted for use of **gelatin** when compared with crystalloids in patients with sepsis, showed inconclusive effect on mortality [123]. Adverse effects of gelatin in **a network meta-analysis** demonstrated higher risk of RRT with gelatin use compared with normal saline and balanced crystalloids. In a **systematic review of RCTs** including patients with hypovolemia, gelatin use increased the risk of anaphylaxis in

comparison with crystalloids use [124]. Furthermore, gelatins may affect hemostasis and the effect on blood transfusions was unclear.

†† A previous **meta-analysis of RCTs** in septic patients showed a higher risk of RRT with the use of **hydroxyethyl starch (HES)** and a higher risk of death in a predefined analysis of low risk of bias trials [125]. A network **meta-analysis** of patients with sepsis or septic shock also demonstrated a higher risk of death and need for RRT [123] with starches in a direct comparison with crystalloids.

22. Liberal Vs. Conservative Approach to Resuscitation

For adults with sepsis or septic shock who have already received fluid resuscitation with 30 mL/kg and have persistent hypoperfusion, we "suggest" using either a liberal or a restrictive fluid resuscitation strategy based on individual patient and health system factors. (Conditional, Low evidence)

	Liberal Vs. Conservative Approach to Resuscitation
Strength	**Conditional**
Benefit of Direction	Beneficial. More personalized approaches to resuscitation.
Evidence	**Low certainty evidence**. SSC 2026 considered four RCTs*. The 2025 ESCIM guidelines made no recommendation**.
Remarks	There was wide variability in the protocols used and the volume of fluids received in the liberal vs. restrictive arms across trials. Patient and health system factors to be considered include patients' current clinical conditions and chronic illnesses (e.g., heart failure) and the availability of monitored beds (i.e., if a restrictive approach necessitates vasopressor use).

*To **inform SSC 2026** [1] updated recommendations, the panel considered four RCTs [50,126-128] that included 3,320 patients with sepsis who had ongoing hypoperfusion or shock after initial fluid resuscitation. The pooled analysis demonstrated that a restrictive (compared with a liberal) approach to ongoing fluid management resulted in probably no difference in mortality. Furthermore, there were probably no differences in VFD, RRT renal replacement-free days and vasopressor-free days.
The **2025 ESCIM clinical practice guidelines made no recommendation regarding liberal vs. restrictive approaches to fluid resuscitation [41]. The panel thought acceptability would vary across patients and clinicians. Taken together, these factors drove the decision to suggest either approach to ongoing fluid resuscitation with advice that patient and health system factors be considered.

23. Fluid Resuscitation Guided by Dynamic Measures, Capillary Refill Time & Cardiac Output Monitoring Devices

23.1 For adults with sepsis or septic shock, we "suggest" using dynamic measures to guide fluid resuscitation over physical examination or static measures alone. (Conditional, Low evidence)

23.2 For adults with sepsis or septic shock, we "suggest" using capillary refill time (CRT) to guide resuscitation as an adjunct to other measures of perfusion. (Conditional, Low evidence)

23.3 For adults with septic shock, there is "insufficient evidence" to make a recommendation on using minimally invasive or noninvasive cardiac output monitoring in addition to usual care. (Insufficient evidence)

	Fluid Resuscitation Guided by Dynamic Measures, Capillary Refill Time (CRT) & Cardiac Output Monitoring Devices
Strength	**Conditional**

Benefit of Direction	Beneficial. Dynamic measures and CRT as guides for fluid resuscitation
Evidence	**For Dynamic measures**: Low certainty evidence. SSC 2026 identified 3 meta-analyses with 18 total RCTs and separate **meta- analysis** done*, Systematic review and meta-analysis of POCUS-guided resuscitation** & ESCIM 2025 clinical practice guideline***. **For CRT:** Low certainty evidence. SSC 2026 2 RCTs & ANDROMEDA-SHOCK trial & ***ANDROMEDA-SHOCK trial-2 RCT. **For CO Monitoring Devices:** Insufficient evidence due to small number studied. SSC 2026 studied 3 RCTs ‡ + another 3 RCTs ‡‡.
Remarks	Dynamic measures include response to a passive leg raise or a fluid bolus using stroke volume (SV), stroke volume variation (SVV), pulse pressure (PP), or pulse pressure variation (PPV). Minimally invasive cardiac output monitoring refers to devices requiring an arterial catheter. Noninvasive cardiac output monitoring refers to devices using bioreactance. Usual care refers to care without a pulmonary artery catheter. The use of critical care ultrasound was not evaluated.

*Dynamic measures better predict fluid responsiveness than static measures [129]. Increases of 10–15% in the chosen parameter (e.g., stroke volume) following a fluid challenge or passive leg raise maneuver are reflective of fluid-responsiveness [129]. The **SSC 2026 panel** identified **3 meta-analyses** [129–131] examining the use of dynamic measures to guide fluid resuscitation, with **18 total RCTs** included across the three analyses. In a separate **meta- analysis** done by the SSC 2026 panel [1] and inclusive of all **18 RCTs,** fluid management guided by dynamic measures likely reduces mortality, likely results in a large reduction in need for RRT and may result in a slight increase in ventilation-free days. Measurements of inferior vena cava diameter or collapsibility principally reflect central venous pressure (CVP) and are subject to the same limitations as CVP measurement. **A **systematic review and meta- analysis** showed that use of **POCUS-guided resuscitation** probably reduces 28-day mortality [132]. Dynamic echocardiographic estimation of SV and changes in this parameter can be useful. Changes in pulse pressure in patients with clinical characteristics that permit valid interpretation (i.e., mechanically ventilated, without spontaneous respiration), although less accurate, may be particularly useful in low resource settings to assess fluid responsiveness. ***The SSC guideline suggestion to use dynamic measures to guide fluid resuscitation is consistent with the **ESCIM 2025 clinical practice guideline** recommendation [41].

† CRT provides distinct hemodynamic information during resuscitation [133]. **SSC 2026** panel identified **2 RCTs** in which 233 total patients were randomized to receive targeted resuscitation using CRT with the goal of normalizing CRT to less than or equal to 3 seconds or targeted resuscitation using lactate measured every 2 hours with a goal of normalization or reduction by 20% [134,135]. The 28-day mortality risk ratio was 0.82 with an absolute mortality reduction of 74 per 1000 deaths. †† The remaining outcomes were assessed from the **ANDROMEDA-SHOCK trial** [134] where there were no statistically significant differences in VFD, RRT-free days, or vasopressor-free days. A subsequent RCT suggested that stopping fluids in patients with CRT less than or equal to 3 seconds appeared safe without compromising tissue perfusion [135]. ††† In the multicenter ANDROMEDA-SHOCK-2 RCT [136] among 1467 patients included in the primary analysis, randomization to a personalized resuscitation protocol targeting CRT was associated with better outcomes compared with usual care. CRT is feasible, reproducible, and may be readily implemented in low resource settings in conjunction with other validated tools of resuscitation.

‡ **SSC 2026** [1] **in 3 RCTs** of 225 patients evaluated the use of minimally invasive cardiac output (CO) monitors in septic shock, with pulse wave analysis used in all three demonstrated an uncertain effect on 28-day mortality, a possible reduction in ICU LOS and invasive mechanical ventilation duration, but no information on potential adverse events related to the peripheral arterial catheters. ‡‡ **SSC 2026** [1] panel studied **another 3 RCTs** of 310 patients to assess the impact of noninvasive cardiac output monitors in septic shock, all of which used bio-reactance, showed an uncertain effect on 28-day mortality, ICU, hospital

LOS, and organ dysfunction. The small number of patients evaluated in both studies led the panel to conclude there was "insufficient evidence" to issue a recommendation addressing their use.

24. Serial Lactate Measurement

For adults with sepsis and elevated lactate or septic shock, we "suggest" using serial lactate measurements to guide resuscitation. (Conditional, Low evidence)

	Serial Lactate Measurement
Strength	**Conditional**
Benefit of Direction	Beneficial. Clinicians consider lactate trends with clinical assessment as a guide.
Evidence	**Low certainty evidence.** Sepsis-3 and Meta-analyses*, SSC 2026 panel conditional recommendation and expert Delphi panel**
Remarks	Fluid administration should be individualized after initial fluid bolus and monitoring of lactate decrement, rather than continuing fluids until lactate normalization is achieved.

*Serum lactate is a critical biomarker for assessing tissue hypoxia and dysfunction, though it does not directly measure tissue perfusion [137]. The **Sepsis-3** definitions explicitly include elevated lactate as a marker of cellular dysfunction alongside refractory hypotension, underscoring its role in identifying patients requiring urgent resuscitation [2]. **Meta-analyses** comparing lactate-guided therapy with traditional approaches, such as early goal-directed therapy or central venous oxygen saturation-guided therapy, consistently show that lactate-guided therapy is associated with improved mortality and reduced organ dysfunction [138].

****SSC 2026 panel** [1] emphasizes that clinicians consider lactate trends with clinical assessment, such as hemodynamics and organ perfusion. Fluid administration should be individualized after initial boluses, as excessive fluids to normalize lactate may cause harm. This conditional recommendation balances lactate's value as a biomarker with the need for personalized, context-driven care, avoiding over-reliance on a single parameter in complex clinical scenarios. In low resource settings without access to lactate measurement, alternative approaches suggested by an **expert Delphi panel** include capillary refill time (CRT) and urinary output as guides to resuscitation [77].

25. Vasopressors

25.1 For adults with septic shock, we "recommend" using norepinephrine as the first-line agent over dopamine, epinephrine, or selepressin. (Strong, High evidence for Dopamine, Low evidence for Epinephrine and Selepressin)

25.2 For adults with septic shock, we "suggest against" using terlipressin. (Conditional, Low evidence)

25.3 For adults with septic shock, we "suggest" using norepinephrine as the first-line agent over vasopressin or angiotensin II. (Conditional, Low evidence for Vasopressin and Very low evidence for Angiotensin II)

25.4 For adults with septic shock on escalating doses of norepinephrine, we "suggest" adding vasopressin. (Conditional, Moderate certainty evidence)

25.5 For adults with septic shock and inadequate MAP levels despite norepinephrine and vasopressin, we "suggest" adding epinephrine. (Conditional, Very low certainty evidence)

25.6 For adults with septic shock with concomitant cardiac dysfunction, we "suggest" using either norepinephrine or epinephrine as first line vasopressor. (Conditional, Very low certainty evidence)

	Vasopressors
Strength	Strong for norepinephrine Conditional for all the other recommendations.
Benefit of Direction	Beneficial to address selection of vasopressor types and benefits of additional vasopressors' use
Evidence	- Norepinephrine over Dopamine: High-certainty evidence. SSC 2026* - Norepinephrine over Epinephrine: Low certainty evidence. SSC 2026* - Norepinephrine over Selepressin: Low certainty evidence. SSC 2026* - Norepinephrine as the first-line agent over vasopressin or angiotensin II: Low certainty evidence. RCTs, Meta-analysis** - Adding vasopressin on escalating doses of norepinephrine: Moderate certainty evidence: 2021 SSC, SSC 2026, meta-analysis of 9 RCTs with 1 multicenter study *** - Adding epinephrine for inadequate MAP levels despite norepinephrine and vasopressin. Low certainty evidence, SSC 2026 and metanalysis †. - Norepinephrine or epinephrine as first line vasopressor with concomitant cardiac dysfunction: Very low certainty evidence. Randomized trial (the CAT Study††
Remarks	In settings where vasopressin is not available, epinephrine can be added to norepinephrine alone. Norepinephrine may be preferred in patients with tachyarrhythmia or significant sinus tachycardia. Conversely, epinephrine may be preferred in patients with bradyarrhythmia or significant sinus bradycardia.

*The **SSC 2026 panel** [1] consistent with the 2021 SSC guidelines **[24,25]**, identified norepinephrine as the first-line vasopressor for treatment of septic shock and comparisons to dopamine, epinephrine, and selepressin were carried over.

** The **SSC 2026** panel identified two **RCTs** of 658 total patients randomized to **vasopressin vs. norepinephrine** as first-line vasopressor [139,140]. **Meta-analysis** found there was possibly no difference in mortality, but probably less use of RRT with vasopressin. Although evidence was low or very low certainty, vasopressin did not appear to result in differences in life-threatening arrhythmia or ischemia (digital, mesenteric, or myocardial). **Two RCTs** of 341 total patients already on norepinephrine who were randomized to the addition of **angiotensin II vs. norepinephrine** along were considered as indirect evidence [141,142]. **Meta-analysis** found that addition of angiotensin II may result in a reduction in mortality but with an uncertain effect on ventricular arrythmias, ischemia (peripheral, intestinal, or myocardial), or deep vein thrombosis (all very low certainty evidence). As the balance of effects did not favor **vasopressin or angiotensin II over norepinephrine**, the panel weighed strongly that vasopressin and angiotensin II tend to be more expensive and less available than norepinephrine, especially in low resource settings [143].

***Consistent with the **2021 SSC guidelines** [24,25], the SSC 206 panel [1] suggests **sequentially adding vasopressin and then epinephrine for patients requiring escalating doses of norepinephrine** to maintain mean arterial BP. To evaluate the addition of vasopressin in this context, **SSC 2026 panel [1]** performed a **meta-analysis of 9 RCTs** (1,439 total patients, including 778 [54.1%] from the only multicenter trial, VASST [144]. Meta-analysis found a probable reduction in mortality with adding vasopressin compared with increasing norepinephrine alone. Compared with norepinephrine mono-therapy, adjunctive vasopressin probably results in less atrial fibrillation but possibly more digital ischemia. Panelists **[1]** using vasopressin initiate it at a median dose of 0.3 μg/kg/min of nor-epinephrine (IQR 0.2–0.5 μg/kg/min).

† Analysis of the results of **addition of epinephrine vs. escalating norepinephrine** found an uncertain effect on mortality of combined epinephrine and norepinephrine over norepinephrine alone [145]. The panel's suggestion was driven by the possible mortality benefits of adding vasopressin and epinephrine, in order, rather than continuing to escalate norepinephrine. Given the widespread availability and safety profile of epinephrine, however, the SSC 2026 panel [1] suggested adding epinephrine to norepinephrine alone in settings where vasopressin is not available. Panelists using epinephrine initiate it at a median dose of 0.8 µg/kg/min of norepinephrine.

†† **The SSC 2026** panel identified no trials evaluating patients with septic shock and concurrent cardiac dysfunction. They identified one **randomized trial** (the CAT Study) [146] of 280 patients, 158 with sepsis, which found epinephrine as compared with norepinephrine had an uncertain effect on mortality [146], consistent with the indirect effect from a network metanalysis. The **SSC 2026** panel [1] did not favor epinephrine over norepinephrine—or vice versa—for adults with septic shock requiring vasopressors in the setting of concomitant cardiac dysfunction.

26. Inotropes

26.1 For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate fluid status and arterial blood pressure, we "suggest" using inotropes over no inotropes.(Conditional, Very low certainty evidence)

26.2 For adults with septic shock with persistent hypoperfusion and cardiac dysfunction despite adequate fluid resuscitation and arterial blood pressure, we "suggest" adding dobutamine to norepinephrine or using epinephrine alone. (Conditional, Very low certainty evidence)

26.3 For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we "suggest against" using levosimendan. (Conditional, Very low certainty evidence)

	Inotropes
Strength	**Conditional**
Benefit of Direction	Beneficial to use inotropes over no inotropes.
Evidence	**Very Low certainty evidence**: Network meta-analysis*, SSC 2026 panel*, 2021 SSC guidelines**
Remarks	For patients requiring vasopressors to maintain mean arterial pressure at target, inotropes should be used in addition to (not instead of) vasopressors. Data were insufficient to make a recommendation for dobutamine vs. milrinone.

Sepsis-induced cardiac dysfunction is common among patients with septic shock and may contribute to worsened clinical outcomes. Cardiac dysfunction should be suspected following evaluation with bed-side echocardiography or cardiac output monitoring devices. *A **network meta-analysis** [147] including 33 trials with 3,470 patients across 16 different comparators suggested that, in an indirect comparison between norepinephrine alone and norepinephrine plus dobutamine, dobutamine had an uncertain effect on mortality. Considering the intuitive physiologic effects, potential benefits from the network meta-analysis, feasibility, acceptability, and negligible cost, with probably no impact on equity, **the SSC 2026 panel** [1] issued a conditional recommendation in favor of using inotropes in patients with septic shock and signs of cardiac dysfunction who are considered, otherwise, adequately resuscitated. However, given the potential harms from vasodilation and hypotension, inotropes such as dobutamine should be used in addition to (not as a replacement for) vasopressors.

Dobutamine and epinephrine are commonly used inotropes, Consistent with the **2021 SSC guidelines [24,25], the **SSC 2026 panel** [1] issued a recommendation to use either agent for patients with septic shock

and cardiac dysfunction with persistent hypoperfusion despite adequate fluid status and arterial blood pressure. The panel judged the current evidence insufficient to issue a recommendation for dobutamine vs. milrinone. The recommendation against using levosimendan is carried over from the 2021 SSC guidelines.

27. Beta-Blockers, Oral Midodrine and Methylene Blue

27.1 For adults with septic shock, we "suggest against" using beta-blockers as a treatment for septic shock. (Conditional, Very low certainty evidence)

27.2 For adults with septic shock and ongoing requirement for vasopressors, there is "insufficient evidence" to make a recommendation on use of oral midodrine.

27.3 For adults with refractory septic shock and escalating vasopressor requirements, there is "insufficient evidence" to make a recommendation on IV methylene blue.

	Beta-Blockers, Oral Midodrine and Methylene Blue
Strength	**Conditional**
Benefit of Direction	Recommendation against the use of beta-blockers was most appropriate.
Evidence	**Very Low certainty evidence:** Meta-analysis* and Systematic review*
Remarks	This recommendation is based on evidence for short-acting, IV beta-blockers (esmolol and landiolol) prescribed for treatment of septic shock. Although methylene blue may improve blood pressure, there is insufficient evidence to determine if its use as rescue therapy improves survival; some patients with potentially treatable disease may value a trial.

Although the use of **beta-blockers** in septic shock may seem counterintuitive, pre-clinical data suggests it may improve outcomes. The exact mechanism remains unclear; however, it may be related to decreased myocardial workload and optimized myocardial energy efficiency. *The SSC 2026 panel considered the most comprehensive **meta-analysis** [148] which was recently published and included 12 RCTs and 1170 patients. Pooled analysis demonstrated an uncertain effect of beta-blockers on mortality, bradycardia, ICU LOS and hospital LOS. Beta-blockers were probably associated with a reduction in new onset tachyarrhythmias, but also probably associated with an increased duration of vasopressor use. The SSC 2026 panel [1] decided a conditional recommendation against the use of beta-blockers was most appropriate.

***Midodrine**, an oral medication with alpha-agonist properties, has some evidence of benefit in orthostatic and intradialytic hypotension and therefore may have utility as a vasopressor-sparing agent. **Meta-analysis** addressing its use in vasodilatory shock was recently published and included **7 small RCTs** [149]. Pooled analysis from those with septic shock demonstrated an uncertain effect of midodrine on mortality, RRT, acute kidney injury, and acute hepatic failure (all very low certainty). Midodrine may increase vasopressor-free days and reduce hospital LOS and ICU LOS. **The SSC 2026 [1]** panel judged desirable effects to be trivial with LOS. Impacts being Important but uncertain, while undesirable effects were unknown given the lack of reporting among included studies.

****Methylene blue** has also been used and studied as a rescue therapy in septic shock due its ability to improve vascular tone through inhibition of endothelial and inducible nitric oxide synthase (iNOS) and down-stream inhibition of soluble guanylate cyclase **[150]. SSC 2026** [1] panel updated an existing **systematic review** of **six RCTs** [150], identifying two additional small RCTs, comparing IV methylene blue to usual care or placebo in patients with septic shock. Although there is very low certainty evidence for its impact upon mortality, methylene blue likely results in a reduction in duration of vasopressors. The panel thus made a conditional recommendation for either using or not using IV methylene blue in refractory septic shock. Lastly, the panel noted that in some low resource settings where other vasopressor treatments

are unavailable (e.g., vasopressin), methylene blue may represent the only viable second-line treatment option for refractory septic shock and thus may be used as a rescue therapy earlier in resuscitation.

RESPIRATORY SUPPORT

28. Monitoring of Hypoxemia

For adults with sepsis, we "suggest" measuring oxygenation by either pulse oximeter (Spo_2) or arterial blood gas (Sao_2) in conjunction with physical examination and clinical acumen. (Conditional, Very low certainty evidence)

	Monitoring of Hypoxemia
Strength	**Conditional**
Benefit of Direction	Beneficial. Prevents hypoxic injury. ABG testing is paramount to mitigate occult hypoxemia.
Evidence	**Very low certainty evidence:** systematic reviews of 45 observational studies, large single-center study, systematic review of 44 studies and the new global consensus definition of ARDS*
Remarks	Arterial blood gas measurements are the gold standard for assessing oxygenation; include other important information such as pH, $Paco_2$, lactate, and bicarbonate; and are preferable when available. Spo_2/Fio_2 (S/F) by pulse oximeter may substitute for Pao_2/Fio_2 (P/F) ratio, but is less accurate in patients in shock, with darker skin tones, and/or with oxygen saturations < 90% or > 97%.

The **SSC 2026** [1] panel issued a conditional recommendation for measuring oxygenation either using pulse oximetry (Spo_2) or arterial blood gas (Sao_2) in conjunction with physical examination and clinical acumen.

However, the panel cautioned against using pulse oximetry for oxygenation measurements in patients in shock, with darker skin tones, and/or oxygen saturations less than 90% or greater than 97 % due to its inaccuracies and emphasized that ABG measurements are the gold standard for assessing oxygenation and are preferred when available.

***The SSC 2026** [1] recommendation is in part based on a **systematic review** of **45 observational** studies, 30 of which were in adult patients with acute respiratory failure, that examined the accuracy of substituting a SpO2/FiO2 ratio for a PaO2/FiO2 ratio and found that the Spearman correlation coefficient ranged between 0.5 and 0.8 [151]. **A **large single-center study** in adult patients in the United States comparing 48,097 paired oxygenation values by pulse oximetry and ABG, showed that Black patients had nearly three times the frequency of occult hypoxemia compared with White patients, which was not detected by pulse oximetry [152]. ***A **systematic review** that examined the accuracy of arterial oxygenation by pulse oximetry, including **44 studies**, reported an overestimation of arterial oxygen saturation (SaO2) by pulse oximetry in patients with darker skin tones [153]. †**Also, the new global consensus definition of ARDS** allows for the use of pulse oximetry-based measurements for the diagnosis of ARDS. The use of SpO2/FiO2 < 315 (if SpO2 < 97%) has been suggested for use **in low-resource settings** when an ABG is unavailable, as an alternative to PaO2/FiO2 for the diagnosis of ARDS (mild) in non-intubated patients with ARDS, and to categorize the severity in intubated patients with ARDS [154].

29. Oxygen Targets

For adults with sepsis and acute hypoxemic respiratory failure, we "suggest" titrating Fio_2 to target either higher, more liberal oxygen levels or lower, conservative oxygen levels depending on patient factors and resource limitations. (Conditional, Low certainty evidence)

	Oxygen Targets
Strength	**Conditional**
Benefit of Direction	Beneficial. Prevents hypoxic injury.
Evidence	**Low certainty evidence:** SSC 2026 Meta-analysis of 10 RCTs*, Cochrane meta-analysis**
Remarks	Although there was variability across trials informing this recommendation, most used a lower target of approximately 90–93% Spo_2 and a higher target of Spo_2 ≥96. Panelists target Spo_2 between 90% to 96% for patients with sepsis and acute hypoxemic respiratory failure.

*According to the **SSC 2026** [1] panelists, for adults with sepsis and acute hypoxemic respiratory failure, they "suggest" titrating Fio_2 to target either higher, more liberal oxygen levels or lower, conservative oxygen levels depending on patient factors and resource limitations. This recommendation is based on **10 RCTs** (24,022 patients) reporting 28-day or 90-day mortality. The **SCC 2026** [1] **Meta-analysis** of **these trials** demonstrated that lower, conservative oxygen targets may result in little to no difference in short-term mortality. There may also be little to no difference in duration of mechanical ventilation or mechanical ventilation free days, but these estimates were each based on one trial**.** Although the higher, liberal oxygen targets in included trials were similar (generally Spo_2 ≥96%), the lower, conservative oxygen targets varied considerably. Intermediate oxygen targets (Spo_2 94–95%) were not addressed with this analysis, since few trials targeted this range. However, the SSC 2026 panel determined that it is reasonable to target the lower end of the liberal oxygen target range (Spo_2 96–97%) or intermediate oxygen targets (Spo_2 94–95%) even when resources are not limited.

A further analysis done to support this guideline, updating a previous **Cochrane meta-analysis [155], revealed no effect on mortality when including all trials regardless of focus on sepsis or not. **The SSC 2026 panel** acknowledged some patients may benefit from lower oxygen targets while others may benefit from higher oxygen targets. Indeed, possible heterogeneity of treatment effect was identified in an individualized treatment effect analysis, where sepsis was associated with benefit from higher oxygen targets [156]. "In their practice", the SSC 2026 panelists target Spo_2 between 90% (IQR 90–92%) and 96% (IQR 94–98%) for patients with sepsis and acute hypoxemic respiratory failure.

30. Noninvasive Respiratory Support & Awake Proning

30.1 For adults with sepsis and acute hypoxemic respiratory failure, we "suggest" using high flow nasal cannula (HFNC) therapy over conventional oxygen therapy. (Conditional, Very low certainty evidence)

30.2 For adults with sepsis and acute hypoxemic respiratory failure, we "suggest" using HFNC as the initial therapy over noninvasive positive pressure ventilation (NIPPV). (Conditional, Very low certainty evidence)

30.3 For adults with sepsis and acute hypoxemic respiratory failure, we "suggest" using HFNC over high flow alternating with noninvasive positive pressure ventilation. (Conditional, Very low certainty evidence)

30.4 For adults with sepsis and acute hypoxemic respiratory failure who are not intubated, we "suggest" a trial of awake proning. (Conditional, Very low certainty evidence)

	Noninvasive Respiratory Support & Awake Proning

Strength	**Conditional**
Benefit of Direction	Beneficial, avoids invasive ventilation
Evidence	**Very low certainty evidence.** Meta-analysis of evidence collected by SSC 2026 panel was based on 11 RCTs for HFNC over conventional oxygen therapy, 7 RCTs for HFNC over NIPPV and 2 RCTs for HFNC over alternating HFNC and NIPPV + the FLORALI trial *. Meta-analysis of SSC 2026 panel of 17 RCTs to inform about trials of awake proning**
Remarks	The recommendation of using high flow nasal cannula (HFNC) therapy over conventional oxygen therapy pertains to patients with a Pao_2/Fio_2 ratio <200 or Spo_2/Fio_2 ratio <235. The duration and frequency of proning will depend on patient tolerance. Sedation should not be used for the purposes of promoting tolerance of proning in non-intubated patients.

*The evidence collected by the **SSC 2026** panel for suggesting HFNC over conventional oxygen therapy is based on **11 RCTs** (3546 patients) and applies to patients with a Pao_2/Fio_2 ratio less than 200 or an Spo_2/Fio_2 ratio less than 235**.** The evidence for suggesting HFNC over NIPPV is based on **7 RCTs** (2465 patients). The evidence for suggesting HFNC over alternating HFNC and NIPPV is based on **two RCTs** (515 patients). In **meta-analysis**, **HFNC therapy** resulted in an uncertain but potential reduction in mortality; trivial reduction in hospital LOS [157-159]; and uncertain but potential increase in VFDs, as compared with **conventional oxygen therapy** [157, 159]. HFNC had an uncertain but possible reduction in need for intubation. Subgroup analysis in two studies indicated that the incidence of intubation was lower in patients with a Pao_2/Fio_2 less than or equal to 200mm Hg or Fio_2 greater than 0.6 [158]. In **meta-analysis**, **HFNC** was associated with a possible decrease in mortality [158, 160, 161] and shorter duration of mechanical ventilation, as compared with **NIPPV** [158]. There was no effect on hospital LOS [158, 160, 161], an uncertain effect on ventilation-free days at 28 d [160, 161], and probably no important effect on the rate of adverse events (7 more per 1000 patients for pneumonia (varied definitions), 95% CI, 4 fewer to 25 more, moderate certainty) [161] and 2 more per 1000 patients for cardiac arrest (9 fewer to 23 more, moderate certainty) [161]. In **meta-analysis**, **HFNC** had an uncertain effect on mortality [162], as compared with **alternating HFNC and NIPPV**. HFNC was associated with shorter hospital LOS [162] and more ventilator free days as compared with alternating therapy [162]. The impact on mortality and duration of mechanical ventilation drove the suggestion of HFNC over conventional oxygen and NIPPV. Furthermore, HFNC appears safe and may be better tolerated than NIPPV. Indeed, in the **FLORALI trial**, respiratory discomfort (as measured by visual analog scale) was lower with HFNC, as compared with NIPPV alternating with HFNC [163]. In low resource settings without HFNC, NIPPV has been suggested as reason- able alternative by an expert Delphi panel [77].

Awake self-proning has been proposed as a method to improve oxygenation, reduce work of breathing, optimize ventilation perfusion matching, and potentially reduce risk of further lung injury among patients with acute hypoxic respiratory failure [164]. As per **the SSC 2026 panel [1] who identified **17 RCTs** (3537 patients) to inform about the recommendation that "for adults with sepsis and acute hypoxemic respiratory failure who are not intubated, we "suggest" a trial of awake proning". Awake proning may result in a slight reduction in the requirement for intubation. **Meta-analysis** yielded uncertain results for most other outcomes due to indirectness (as all trials focused on patients with COVID-19) and imprecision. However, point estimates suggested that awake proning may result in reduced mortality at 14 days, increased hospital-free days [165], and increased VFD [165], but with wide CIs that could not exclude the possibility of harm. Furthermore, point estimates suggested that awake proning may result in increased serious adverse events [165]. The **SSC 2026 panel** [1] were unable to make a recommendation on the duration of awake proning.

31. Invasive Mechanical Ventilation

31.1 For adults with sepsis and ARDS, we "recommend" using a low tidal volume ventilation strategy (6 mL/kg) over a high tidal volume strategy (> 10 mL/kg). (Strong, High certainty evidence)

31.2 For adults with sepsis-associated hypoxemic respiratory failure without ARDS, we "suggest" using a tidal volume of 6—8 mL/kg ideal body weight (IBW) over a lower (4 to < 6 mL/kg IBW) tidal volume. (Conditional, Low certainty evidence)

31.3 For adults with sepsis and ARDS, we "recommend" using an upper limited goal for plateau pressure of 30 cm H_2o) over higher plateau pressures. (Strong, High certainty evidence)

31.4 For adults with sepsis and moderate-severe ARDS, we "suggest" using higher positive end-expiratory pressure (PEEP) over lower PEEP. (Conditional, Moderate certainty evidence)

31.5 For adults with sepsis and moderate-severe ARDS, we "recommend against" using an incremental PEEP titration strategy. (Strong, Moderate certainty evidence)

31.6 For adults with sepsis and moderate-severe ARDS, we "suggest" using prone ventilation for greater than 12 hr daily. (Conditional, Moderate certainty evidence)

31.7 For adults with sepsis and moderate-severe ARDS, we "suggest" using intermittent NMBA boluses over continuous NMBA infusion. (Conditional, Moderate certainty evidence)

	Invasive Mechanical Ventilation
Strength	**Strong** for 31.1, 31.3, 31.5 **Conditional** for 31.2, 31.4, 31.6, 31.7
Benefit of Direction	Beneficial. Improved survival, improved oxygenation, prevention of volume-induced lung injuries, and more ventilator-free days.
Evidence	**31.1 High certainty of evidence.** Several meta-analyses, the largest trial of a volume- and pressure-limited strategy, retrospective study, patient-level mediation analysis* **31.2 Low certainty evidence**. SSC 2026 meta-analysis of 2 RCTs** **31.3 High certainty of evidence**. 2021 SSC, 3 RCTS, systematic review included 5 RCTs, LUNGSAFE study, and secondary analysis of 5 observational studies*** **31.4 Moderate certainty evidence.** SSC 2021 panel, 3 multicenter RCTs, a patient-level analysis of 2 of the randomized PEEP trials†. **31.5 Moderate certainty evidence.** 2021 SSC recommendation, two RCTs †† **31.6 Moderate certainty evidence.** 2021 SSC carried over to SSC 2026, Repeated meta-analysis of a previous one with PROSEVA trial added‡ **31.7 Moderate certainty evidence.** 2021 SSC carried over to SSC 2026. Several RCTs, the largest ROSE Trial, meta-analysis of all trials was not appropriate‡‡
Remarks	Patients should be screened regularly for development of ARDS, as ARDS diagnosis is often missed or delayed in clinical practice.

Most statements on invasive mechanical ventilation were carried over from 2021 SSC guidelines [24,25]. For their document the **2021 SSC panel** [1] used the 2012 Berlin definition and the terms mild, moderate, and severe ARDS (PaO2 /FiO2 ≤ 300, ≤ 200, and ≤ 100mm Hg, respectively).

*The use of lung-protective strategies for patients with ARDS is supported by clinical trials and has been widely accepted. **Several meta-analyses** suggest decreased mortality in patients with a pressure- and

volume-limited strategy for established ARDS [166, 167]. **The largest trial** of a volume- and pressure-limited strategy showed 9% absolute decrease in mortality in ARDS patients ventilated with **tidal volumes of 6mL/kg** compared with 12mL/kg predicted body weight (PBW) and aiming for plateau pressure ≤ 30 cm H2O [168]. **A retrospective study** suggested that tidal volumes should be lowered even with plateau pressures ≤ 30 cm H2O [169] because lower plateau pressures were associated with reduced hospital mortality [170]. A **patient-level mediation analysis** suggested that a tidal volume that results in a driving pressure (plateau pressure minus set PEEP) below 12–15cm H_2O may be advantageous in patients without spontaneous breathing efforts [171]. Tidal volumes > 6 cc/kg coupled with plateau pressures > 30cm H_2O should be avoided in ARDS. Respiratory rate should be increased to a maximum of 35 breaths/min during tidal volume reduction to maintain minute ventilation.

Due to the lack of guidance regarding the optimal tidal volume for mechanically ventilated patients without ARDS, the **SSC 2026 meta-analysis of **two RCTs** [172,173] revealed possibly no difference in mortality at 90 days, no important difference between low and moderate tidal volumes in hospital LOS, duration of mechanical ventilation, VFD at day 28, and in incidence of ARDS and pneumonia within 7 days of ICU admission. One of the 2 trials [173] suggested that there may be an increased risk for delirium in the lower tidal volume group. Given the balance of effects and pragmatic concerns that ARDS is often under-recognized the panel felt that recommending lower tidal volumes of **6–8 mL/kg IBW** in adults who are mechanically ventilated for sepsis-induced hypoxemic respiratory failure **without ARDS** was the safest approach to prevent volume-induced lung injuries in those patients who may have early evolving or unrecognized ARDS.

***Three RCTS** [168, 174, 175] compared a strategy of low tidal volume and **limited plateau pressure** with a strategy using higher tidal volume and plateau pressure; pooled data suggest reduced mortality and more ventilator-free days in patients managed with low plateau pressures. A **systematic review** which included **five RCTs** also identified a strong relationship between plateau pressure and mortality [176]. The recommendation is also supported by large international observational study, LUNGSAFE [177]. A **secondary analysis of five observational** studies identified a plateau pressure cut-off value of 29 cm H_2O, above which an ordinal increment was accompanied by an increment of risk of death [178]. The **2021 SSC** panel therefore recommend that the upper limit goal for plateau pressure should be less than 30 cm H_2O.

† **SSC 2021 panel** included **3 multicenter RCTs** [179–181] investigating use of **higher PEEP versus lower PEEP strategies** *in conjunction with low tidal volumes* for the management of patients with ARDS. Among patients with ARDS receiving lower VTs, they did not identify a significant benefit for use of a higher PEEP versus lower PEEP strategy for improving mortality, days on mechanical ventilation, or ventilator-free days; and there was no increase in the risk of barotrauma. Patients with moderate or severe ARDS (PaO2/FiO2 ≤ 200 mm Hg) had decreased mortality with the use of higher **PEEP**, whereas those with mild ARDS did not [182]. A **patient-level analysis** of **two of the randomized PEEP trials** [180,181] suggested that patients with ARDS who respond to increased PEEP with improved oxygenation have a lower risk of death; this association was stronger in patients with more severe ARDS (P/F < 150 mm Hg) compared with patients with less severe ARDS.

†† **Two important RCTs** were published both of which utilized a "non-traditional" approach to recruitment maneuvers. Both trials conducted lung recruitment with incremental PEEP levels, followed by a decremental PEEP titration according to either best respiratory- system static compliance [183] or oxygen saturation. When the incremental PEEP recruitment studies are analyzed separately from studies utilizing traditional recruitment maneuvers, recruitment with incremental PEEP is associated with increased 28-day mortality, which justifies the "strong recommendation against" using incremental PEEP titration for recruitment. The **2021 SSC** panel focused their recommendations to patients with moderate-to-severe ARDS.

‡ A meta-analysis evaluating the use of **prone ventilation** in sepsis induced severe ARDS was published [184] that was updated from a previous meta-analysis published before, to which only one study, the **PROSEVA trial** [185], was added. This **repeated meta-analysis** confirmed the results from the previous published work: In patients with ARDS and a PaO_2/FiO_2 ratio < 200, the use of prone compared with supine position within the first 36 hours of intubation, when performed for > 12 hours a day, showed improved survival. **Meta-analysis** including this study demonstrated reduced mortality in severe ARDS patients treated with prone compared with supine position as well as improved oxygenation as measured by change in PaO_2/FiO_2 ratio [184]. This **2021 SSC** recommendation was carried over to **SSC 2026**.

‡‡ As regards the recommendation for using NMBA, **several RCTs** have been published, the largest of which is the **ROSE Trial** [186]. Because of the presence of significant statistical and clinical heterogeneity, a **meta-analysis** of all trials was not appropriate. Given the uncertainty that still exists pertaining to these important outcomes and the balance between benefits and potential harms, the **2021 SSC** panel [1] issued a weak recommendation favoring intermittent NMBA boluses over a continuous infusion. This recommendation was carried over to **SSC 2026**.

32. Venovenous ECMO

For adults with severe ARDS due to sepsis, we "suggest" using veno-venous ECMO when conventional mechanical ventilation fails in experienced centers with infrastructure to support its use. (Conditional, Low certainty evidence)

	Venovenous ECMO
Strength	**Conditional**
Benefit of Direction	Beneficial: Life-saving in refractory hypoxemia, improves oxygenation when conventional ventilation fails, but cost is a substantial issue.
Evidence	**Low certainty of evidence.** Carried over from 2021 guidelines to SSC 2026 recommendation. Two RCTs, and one systematic review *.
Remarks	In clinical practice, patient selection is important and usually discussed prior to initiation of ECMO at an ECMO center.

*This statement regarding the use of Venovenous ECMO in patients with severe acute respiratory failure to facilitate gas exchange in the setting of refractory hypoxemia or hypercapnic respiratory acidosis was **carried over from 2021 guidelines to SSC 2026**. The evidence for the use of VV-ECMO in sepsis-induced ARDS is limited, with **two RCTs** completed to assess the potential efficacy of VV-ECMO for severe ARDS [187, 188]. However, **one recent systematic review** found that VV-ECMO delivered at expert centers reduced mortality for patients with severe ARDS [189].

ADJUNCTIVE THERAPIES FOR THE MANAGEMENT OF SEPSIS

33. Adjunctive Therapies for the Management of Sepsis

33.1 IV Corticosteroids: For adults with septic shock, we "suggest" using IV corticosteroids. (Conditional, Low certainty evidence)

33.2 Antipyretics: For adults with sepsis or septic shock, we "suggest against" the use of antipyretic therapy, either pharmacologic or surface cooling, for the purpose of improving clinical outcomes. (Conditional, Very low certainty evidence)

33.3 IV Vitamin C: For adults with sepsis or septic shock, we "suggest against" using IV vitamin C in patients with sepsis or septic shock. (Conditional, Low certainty evidence)

33.4 <u>IV Immunoglobulin (IVIG)</u>: For adults with sepsis or septic shock, we "suggest against" using IV immunoglobulins. (Conditional, Low certainty evidence)

33.5 <u>Vitamin D</u>: For adults with sepsis and septic shock, we "suggest against" using Vitamin D therapy for sepsis treatment. (Conditional, Very low certainty evidence)

33.6 <u>IV XueBiJing</u>: For adults with sepsis or septic shock, we "suggest against" using XueBiJing injection outside of jurisdictions where it has regulatory approval. (Conditional, Very low certainty evidence)

33.7 <u>Blood Purification</u>:

33.7.1 For adults with sepsis or septic shock, we "suggest against" using blood purification techniques, including hemoperfusion, high-dose hemofiltration, or plasma exchange. (Conditional, Very low certainty evidence)

33.7.2 For adults with sepsis or septic shock we "suggest against" using polymyxin B hemoperfusion. (Conditional, Low certainty evidence)

	Adjunctive Therapies for the Management of Sepsis
Strength	**Conditional**
Benefit of Direction	Corticosteroids beneficial. Other therapies: no enough evidence for validation
Evidence	**Low or very low certainty of evidence. According to SSC 2026 panel:** **Corticosteroids:** meta-analysis of 45 RCTs + SCCM guideline*. **Anti-pyretics:** systematic review of 13 RCTs + 3 trials**. **IV vitamin C:** SSC 2026 panel updated 2 systematic reviews + 6 trials***. **IVIG:** 2021 SSC updated meta-analyses of 2 RCTs and 3 meta-analyses†. **Vitamin D:** Updated systematic review of 11 RCTs & the VIOLET trial †† **IV XueBiJing:** The SSC 2026 panel updated two systematic reviews††† **Blood Purification:** updated existing systematic reviews including 71 RCTs‡
Remarks	The recommendation of using antipyretic therapy does not apply to using antipyretic therapy for pain control, patient symptom control, or for patients with other indications for temperature control, such as neuro critical care patients or patients after cardiac arrest. The recommendation of using vitamin D does not pertain to patients who are on lower doses of Vitamin D supplement for other indication or receiving it as part of standard nutritional practice.

***Corticosteroids** have been studied extensively. In a recent **meta-analysis** identifying **45 RCTs** including 9543 patients [190], corticosteroids may result in a small reduction in 28-day mortality and long-term mortality at 60 days or later, although these results are limited by imprecision and inconsistency. Corticosteroids result in a greater incidence of shock reversal at 7 days, increases in hyperglycemia and hypernatremia and have an uncertain effect on neuromuscular weakness. The **SSC 2026 panel** [1] made a conditional recommendation favoring IV corticosteroids in patients with septic shock, which is consistent with a recent Society of Critical Care Medicine (**SCCM) guideline** on the use of steroids in sepsis, ARDS, and pneumonia [191].

****Anti-pyretic therapy:** The **SSC 2026** [1] used a **systematic review of 13 RCTs** [192], including a total 3333 adults with infection, to evaluate the use of pharmacologic agents (acetaminophen or non-steroidal anti- inflammatory agents) and/or surface cooling. No difference in mortality at 28–90 days, with very low certainty due to imprecision. **Three trials** reported an uncertain effect on shock reversal at a variety of time points. Similarly, there was an uncertain effect on LOS. The panel made a conditional recommendation against the use of anti-pyretic therapy for the purposes of temperature control.

*****IV vitamin C:** The **SSC 2026** panel updated two previous **systematic reviews** [193,194] and identified **6 additional trials** for a total of 55 RCTs evaluating IV vitamin C as monotherapy or in combination with thiamin and corticosteroids. Although the included studies demonstrated a low risk of adverse events, IV vitamin C can result in factitious hyperglycemia, and largest trial **(LOVIT)** proactively modified glucose monitoring strategies to avoid this risk [195]. Given the lack of an impact on mortality seen in the low risk of bias trials, the panel made a conditional recommendation against the use of IV vitamin C in sepsis.

† **IV Immunoglobulin (IVIG):** The **SSC 2026 panel** did not identify any new **large RCTs** evaluating IV immunoglobulin (IVIG) in sepsis or septic shock since the 2021 guidelines [196]. In addition to IgM-enriched vs. non-enriched IgM, the panel also evaluated subgroups of high vs. low dose IVIG. The 2021 SSC [24,25] updated meta-analyses of 2 RCTs and 3 meta-analyses demonstrated reduced mortality with IVIG and IVIGM, however the quality of evidence is low with many of the included studies at high risks of bias. Overall, the balance of effects (beneficial and undesirable) remains uncertain.

†† **Vitamin D:** The **SSC 2026 panel** updated an existing **systematic review** of vitamin D therapy in sepsis, including **11 RCTs** [197]. There are uncertain effects of vitamin D therapy on mortality, duration of mechanical ventilation and ICU LOS in patients with sepsis. Vitamin D therapy may have little to no impact on adverse events including hypercalcemia and renal stones. In the **VIOLET trial** [198], the subgroup of patients with sepsis (350 patients) had a higher 90 mortality risk with high-dose (540,000 international units) enteral vitamin D supplementation. Given the very low certainty of evidence, the balance of undesirable and desirable effects, and the subgroup analysis in the VIOLET trial of patients with sepsis suggesting possible harm, the panel made a conditional recommendation against the vitamin D therapy for sepsis.

††† **IV XueBiJing:** XueBiJing is a mixed herbal product that was licensed in 2004 for treatment of sepsis in China [199] that has antagonistic effects on endotoxin and inflammatory mediators [199]. The **SSC 2026** panel **updated two systematic reviews** [200, 201] of XueBiJing in severe infection. The evidence suggests that XueBiJing injection may result in a large reduction in mortality at 28–30 days, as well as moderate-to-large improvements in important outcomes, such as ICU LOS. The high-quality RCTs demonstrate high control group mortality rates despite recruiting relatively non-sick populations. How the medication would interact with other therapies commonly used in other healthcare systems (e.g., corticosteroids), is unclear. More research is required to provide adequate validation before a recommendation could be made.

‡ **Blood Purification:** The rationale for this therapy is to modulate the host immune response by removing excess inflammatory mediators and/or restoring deficient plasma proteins, thereby improving clinical outcomes by mitigating the manifestations of a dysfunctional immune response [202,203]. The **SSC 2026** panel **updated existing systematic reviews** of blood purification techniques, which included RCTs of hemoperfusion/hemadsorption (**41 RCTs**), hemofiltration (**26 RCTs**), and plasmapheresis (**4 RCTs**) [202, 203]. Although there is a signal for a reduction in short-term mortality (28–30 d) with all three techniques the certainty of evidence is low due to varying factors for each technique. There are inconsistent findings suggestive of benefit in non-mortality outcomes. The panel did not find sufficient evidence to provide a separate recommendation.

ADDITIONAL SUPPORTIVE THERAPIES IN PATIENTS WITH SEPSIS

34. Insulin Therapy

For adults with sepsis or septic shock, we "recommend" initiating insulin therapy at a glucose level of ≥180 mg/dL (10 mmol/L). (Strong, Moderate certainty evidence)

	Insulin Therapy
Strength	**Strong**
Benefit of Direction	Beneficial to avoid the risk of hypoglycemia.

Evidence	**Moderate certainty of evidence.** The American Diabetes Association* & Network meta-analysis of 35 RCTs of the 2021 SSC guidelines**.
Remarks	Hyperglycemia (> 180mg/dL), hypoglycemia and increased glycemic variability are associated with increased mortality in critically ill patients.

***The American Diabetes Association**, in its most recent recommendations for glycemic control of critically ill patients, recommended the initiation of insulin therapy for persistent hyperglycemia > 180 mg/dL and thereafter a target glucose range of 140−180 mg/dL [204].

****2021 SSC guidelines** [24,25] identified a network **meta-analysis of 35 RCTs** [205]. The analysis compared four different blood glucose targets. No significant difference in the risk of hospital mortality was observed between the four blood glucose ranges. Target concentrations of < 110 and 110−144mg/dL were associated with a four- to nine-fold increase in the risk of hypoglycemia compared with 144−180 and > 180mg/dL. Overall, the balance of effects favored initiation of insulin therapy at a glucose level of > 180mg/dl. After considering the resources required, cost, health equity issues, and applicability to low- and middle-income economies, the panel made a strong recommendation for the initiation of insulin therapy at a glucose level of ≥ 180mg/ dL (10 mmol/L).

35. Blood Transfusion

For adults with sepsis or septic shock, we "recommend" using a restrictive transfusion strategy over a liberal transfusion strategy. (Strong, Moderate certainty evidence)

	Blood Transfusion
Strength	Strong
Benefit of Direction	A restrictive strategy is feasible in low- and middle-income countries.
Evidence	**Moderate certainty of evidence.** Meta-analysis of RCTs + TRICOP trial*
Remarks	A restrictive transfusion strategy typically includes a hemoglobin concentration transfusion trigger of 70g/L; however, RBC transfusion should not be guided by hemoglobin concentration alone. Assessment of a patient's overall clinical status and consideration of extenuating circumstances such as acute myocardial ischemia, severe hypoxemia or acute hemorrhage is required.

*The literature search of **2021 SSC panel** [24,25] identified a recent **systematic review** and meta-analysis of RCTs **[206]** and one new RCT: The Transfusion Requirements in Critically Ill Oncologic Patients **(TRICOP) trial** [207]. Their update of the meta-analysis showed no difference in 28-day mortality. This is due to the inclusion of the TRICOP study where lower 28 mortality was observed with a liberal strategy. Overall, the quality of evidence was judged moderate. The overall balance of effects is uncertain and does not favor either the intervention or comparator. However, a restrictive strategy was determined likely beneficial with regards to resources required, cost effectiveness, and health equity considerations.

36. Stress Ulcer Prophylaxis

For adults with sepsis or septic shock, and who have risk factors for GI bleeding, we "suggest" using stress ulcer prophylaxis with proton-pump inhibitors over not using stress ulcer prophylaxis. (Conditional, Moderate certainty evidence)

	Stress Ulcer Prophylaxis
Strength	**Conditional**
Benefit of Direction	Beneficial to prevent stress ulcers.

Evidence	**Moderate certainty of evidence.** SSC 2026 updated systematic review (12 RCTs including the 2024 REVISE trial) + Systematic review*. The 2024 SCCM & American Society of Health- System Pharmacists Guideline**
Remarks	Since stress ulcer prophylaxis is widespread available and requires few resources, this recommendation is applicable to low resource settings. In the absence of PPIs, H2 receptor antagonists are a reasonable alternative.

***SSC 2026** panel **[1] updated an existing systematic review** [208] with **12 RCTs**, including the **2024 REVISE trial** [209]. The panel suggested the use of proton-pump inhibitors (PPIs) for stress ulcer prophylaxis in adults with sepsis and septic shock at risk for clinically important bleeding. A **systematic review** suggests that the most important risk factors for clinically important bleeding include acute kidney injury, male gender, coagulopathy, shock, and chronic liver failure [210]. **The **2024 SCCM and American Society of Health- System Pharmacists Guideline** for the Prevention of Stress-Related Gastrointestinal Bleeding in Critically Ill Adults suggests use of stress ulcer prophylaxis to prevent clinically important bleeding [211]. However, in contrast to this guideline, it suggests use of PPIs of H2 receptor antagonists as first-line.

37. Renal Replacement Therapy

37.1 For adults with sepsis or septic shock and acute kidney injury, with no definitive indication for renal replacement therapy, we "suggest against" using renal replacement therapy. (Conditional, Moderate certainty evidence)

37.2 For adults with sepsis or septic shock and acute kidney injury warranting renal replacement therapy, we "suggest" either continuous or intermittent renal replacement therapy. (Conditional, Low certainty evidence)

	Renal Replacement Therapy
Strength	**Conditional**
Benefit of Direction	It was acknowledged that the resources required for the interventions vary.
Evidence	**Moderate certainty of evidence** for patients with no definitive indication for renal replacement therapy. The 2021 panel* STARRTAKI trial** **Low certainty of evidence** for patients with acute kidney injury warranting renal replacement therapy: 2021 updated literature with 2 meta-analysis***
Remarks	Recommendations were made after considering of the resources required, cost and health equity issues.

*The **2021 panel** [24,25] issued a weak recommendation against the use of RRT in patients with sepsis and AKI for increases in creatinine or oliguria alone, and without other absolute indications for dialysis (uremic complications, refractory academia, refractory fluid overload or hyperkalemia).

The results of the **STARRT-AKI trial which randomized 3,000 participants, demonstrated no difference in mortality in those allocated to an accelerated strategy of RRT compared with those allocated to a "standard" strategy. No differential effect was observed in the a priori sepsis subgroup of 1,689 patients [212]. The results of this trial were included in an **updated meta-analysis**. No effect of the timing of initiation of renal replacement therapy on mortality and renal recovery was observed.

***The 2021 updated literature** search identified **two meta-analysis** comparing continuous and intermittent renal replacement therapies [213, 214]. The quality of evidence was judged as low. The balance of effects favored neither Intermittent Hemodialysis (IHD) nor Continuous Renal Replacement Therapy (CRRT).

38. Enteral Nutrition

For adults with sepsis or septic shock, we "suggest" early (within 72 h) initiation of enteral nutrition. (Conditional, Very low certainty evidence)

	Enteral Nutrition
Strength	**Conditional**
Benefit of Direction	Neither intervention was considered more beneficial when considering resources utilization, cost effectiveness, and equity issues.
Evidence	**Very low certainty of evidence**. 2021 guidelines, one multicenter RCT trial conducted in 44 French ICUs *
Remarks	Given the plausible possibility of benefit when considering the available physiological data, and the absence of any apparent harm, the conditional recommendation to start feeding early in patients with sepsis and septic shock was made.

*This statement was carried over from 2021 SSC guidelines. The literature search of **2021 guidelines** [24,25] identified **one multicenter RCT** [215], a trial conducted in **44 French ICUs** randomized 2,410 invasively mechanically ventilated patients with shock to early enteral nutrition vs early parenteral nutrition. Of those participants, 1,504 (62%) had sepsis. No significant effect favoring early enteral nutrition was observed for all outcomes evaluated. The overall balance of effects did not favor either early enteral feeding (within 72 hours) compared with enteral feeding commenced after that time.

39. Sodium Bicarbonate

39.1 For adults with septic shock and hypoperfusion-induced lactic acidemia, we "suggest against" using sodium bicarbonate therapy to improve hemodynamics or to reduce vasopressor requirements. (Conditional, Low certainty evidence)

39.2 For adults with septic shock, severe metabolic acidemia (pH ≤7.2), and acute kidney injury (AKIN score 2 or 3), we "suggest" using sodium bicarbonate therapy. (Conditional, Very low certainty evidence)

	Sodium Bicarbonate
Strength	**Conditional**
Benefit of Direction	Beneficial for patients with septic shock, severe metabolic acidosis (pH ≤7.2) and AKI (AKIN score 2 or 3).
Evidence	**Low and Very low certainty of evidence**. 2021 guidelines, one multicenter RCT trial of 400 patients*
Remarks	When considering the subset of patients with septic shock, severe metabolic acidosis and AKI, the balance of effects probably favors IV bicarbonate

* These statements were carried over from the 2021 SSC guidelines [24,25]. The literature search of **2021 guidelines** panel identified **one multicenter RCT** trial [216], in which 400 patients with severe metabolic acidemia (pH ≤ 7.20) were randomly allocated to receive IV 4.2% sodium bicarbonate with the aim of achieving an arterial pH of 7.3, or control (no bicarbonate). No between-group difference was observed in the primary outcome of a composite of 28-day mortality and organ failure at day 7. However, hypernatremia, hypocalcemia, and metabolic alkalosis were observed more frequently in those randomized to bicarbonate. In the subgroup of patients with AKI defined as AKI Network (AKIN) stage 2 or 3 at randomization (182/389−47%), lower mortality was observed with bicarbonate therapy. There was a significant differential effect between patients with an AKIN score of 2 or 3 compared with those with a score of 0-1.

40. Active Fluid Removal

For adults with septic shock after the acute resuscitation phase, we "suggest" using active fluid removal. (Conditional, Very low certainty evidence)

	Active Fluid Removal
Strength	**Conditional**
Benefit of Direction	Active fluid removal may be beneficial after the acute resuscitation phase.
Evidence	**Very low certainty of evidence.** SSC 2026 recent meta-analysis consisting of 13 RCTs*, ESICM Clinical Practice Guideline**
Remarks	Acute resuscitation refers to escalating doses of vasopressors, ongoing high doses of vasopressors, or needing ongoing volume expansion. Active fluid removal refers to diuretics and, if diuretics are insufficient, ultrafiltration or extracorporeal fluid removal. Factors to be considered when deciding to initiate active fluid removal include cardiorespiratory function; vasopressor dose; clinical course; peripheral edema; weight; and fluid balance.

*The management of fluid balance appears to be important, particularly in the "evacuation" or "de-escalation" phase of resuscitation. **SSC 2026 panel** considered a **recent meta-analysis** [217] consisting of 13 RCTs, of which 10 RCTs (2,239 patients) assessed de-resuscitation strategies with diuretics only, 3 RCTs assessed de-resuscitation strategies with diuretics plus ultrafiltration; 3 RCTs (184 patients) focused specifically on patients' sepsis. Across all critically ill patients, the pooled analysis demonstrated an uncertain effect of active fluid removal on mortality, with the use of diuretics only having a potentially more favorable effect than the use of diuretics with or without RRT. The pooled effects on receipt of RRT, ICU LOS, vasopressor free-days, and health-related quality of life were likewise uncertain, and the effect on ischemic complications could not be estimated. Mortality among the subgroup of sepsis patients was also uncertain. ****The SSC 2026** panel suggestion to use active fluid removal after the acute resuscitation phase in septic shock is consistent with the **ESICM Clinical Practice Guideline** [217] on fluid therapy in adult critically ill patients which suggests protocolized fluid removal by diuretics but against the *routine* use of ultrafiltration or extracorporeal fluid removal without other indication for RRT in a general critically ill population.

41. Probiotics

For adults with sepsis or septic shock, we "suggest against" using probiotics. (Conditional, Very low certainty evidence)

	Probiotics
Strength	**Conditional**
Benefit of Direction	Uncertain potential benefit.
Evidence	**Very low certainty of evidence.** 41 RCTs* & the Large PROSPECT trial**
Remarks	Future trials of different organisms, in sepsis-specific populations, and in the recovery phase of sepsis may help to inform future recommendations.

There are over 65 RCTs evaluating probiotics or symbiotics in the ICU, including over 20 different bacterial species alone or in combination [218]. *The SSC 2026 identified **41 RCTs** that evaluated mortality, finding probiotics may have little to no impact on mortality. The effects of probiotics on VAP and duration of invasive mechanical ventilation were uncertain but point estimates suggested potential benefit. **When restricted to trials at low risk of bias, including the **large PROSPECT trial** [219], the potential benefits or improvements were no longer observed. Compounding this uncertainty is the indirectness of the populations studied (only a minority of studies were patients with sepsis, most were general ICU

populations), and wide variety of potential probiotic/ symbiotic regimens to choose from. Overall, the **SSC 2026 [1] panel** was uncertain as to the effect of probiotics in sepsis; given the lack of benefit seen in the low risk of bias trials, the panel made a conditional recommendation against the use of probiotics.

42. Venous Thromboembolism Prophylaxis

42.1 For adults with sepsis or septic shock, we "recommend" using pharmacologic venous thromboembolism (VTE) prophylaxis unless a contraindication exists. (Strong, Moderate certainty evidence))

42.2 For adults with sepsis or septic shock, we "recommend" using low molecular weight heparin (LMWH) over unfractionated heparin (UFH) for VTE prophylaxis. (Strong, Moderate certainty evidence)

42.3 For adults with sepsis or septic shock, we "suggest" using pharmacological VTE prophylaxis alone over pharmacological VTE prophylaxis plus mechanical VTE prophylaxis. (Conditional, Moderate certainty evidence)

	Venous Thromboembolism Prophylaxis
Strength	**Strong:** for using pharmacologic VTE prophylaxis & for using LMWH over UFH for Deep Vein Thrombosis (DVT) prophylaxis. **Conditional:** for using pharmacological VTE prophylaxis alone over pharmacological VTE prophylaxis plus mechanical VTE prophylaxis.
Benefit of Direction	Beneficial. For prevention and getting lower rates of DVT
Evidence	**Moderate certainty of evidence:** Unchanged from 2016, carried over from 2021 to SSC 2026, prior meta-analysis, no new RCT evidence*. The PREVENT study**
Remarks	Critically ill patients are at risk for DVT (may be as high as 10%) as well as PE (may be 2%–4%) acquired in the ICU. In some patients with sepsis and septic shock pharmacologic prophylaxis may be contraindicated. These patients may benefit from mechanical VTE prophylaxis. No data for this population exist. Further research is indicated.

*The recommendation of **SSC 2026 [1]** for the use of LMWH over UFH for VTE prophylaxis in patients with sepsis or septic shock is **unchanged from the 2016 guidelines** and were **carried over from 2021 SSC guidelines** [24,25]. The literature review of SSC 2026 panel found **no new RCT evidence**. The **prior meta-analysis** demonstrated significantly lower rates of DVT following the administration of LMWH compared to UFH. No difference in the rates of clinically significant bleeding, mortality or PE was observed. It was determined that the balance of overall effects favored LMWH over UFH. Further, LMWH may have greater consumer acceptance as it requires only one subcutaneous injection daily.

The **PREVENT study randomized 2003 critically ill patients to intermittent pneumatic calf compression alone or in combination with pharmacological prophylaxis [220]. No difference in mortality, or the rates of DVT and PE were observed. No difference in lower extremity ischemia was demonstrated. Resource implications and costs associated with the use of mechanical VTE prophylaxis, together with the lack of any effect on a patient centered outcome support a weak recommendation against the use of the combination of mechanical and pharmacologic prophylaxis.

Implementation Considerations

- **Be aware about the continuously changing issues** of patient heterogeneity, variable control care, and lack of understanding about ideal configuration of interventions.
- **The variation in both ICU and post ICU management** of critically ill patients increases the complexity of understanding and defining best practice.
- **We recommend discussing goals of care and prognosis** with patients and families over no such discussion for adults with sepsis or septic shock.
- **Patient and family goals of care** is matched to ways both to promote recovery/avoid complications/recurrence and to ensure care.
- **Not all patients are the same** and understanding which patients ought to receive which interventions should be considered .
- **Not all healthcare delivery systems are the same**– even within one system, some patients may be very well supported while others may not–really complicating what 'control' care looks like.
- **Lack of understanding about dosing and intensity** of many of the proposed interventions, and when and whether they should be combined in packages is generally missing.
- **The principles of palliative care** (which may include palliative care consultation based on clinician judgement) should be integrated into the treatment plan, when appropriate, to address patient and family symptoms and suffering.
- **For adult survivors who had received invasive mechanical ventilation >48 hr** during hospitalization for sepsis or septic shock, we "suggest" offering physical rehabilitation services after hospital discharge.
- **Comprehensive medication reconciliation should be performed at transitions** in care, including at ICU and hospital discharge for adults with sepsis or septic shock.
- **The healthcare system should be aware of what optimal care during the recovery period** might look like for this patient population.
- **For adult survivors** of sepsis or septic shock and their families, clinicians should provide information about the hospital stay, sepsis and related diagnoses, treatments, and common impairments after sepsis in the written and verbal **discharge summary**.
- **Health systems should implement strategies to execute advanced directives** to patients being **discharged** from hospital after sepsis or septic shock.
- **After hospital discharge health systems should facilitate assessment and follow-up** for physical, cognitive, and emotional problems for sepsis or septic shock.
- **Patients who survive a protracted period of ICU care for sepsis require physical rehabilitation challenges and a way to organize and coordinate care** as they typically face a long and complicated road to recovery and also great uncertainty to overcome.
- **We suggest offering services that support mental health** for adult survivors of hospitalized patients with sepsis or septic shock. after hospital discharge.

Research Gaps

Literature review shows insufficient research data that need further studies for:

- The use of artificial intelligence (AI) as a tool for early screening and prediction of sepsis.
- The efficacy, safety and cost-effectiveness of the newer modalities e.g.; ultrasound for cardiac output monitoring.

- Research to identify sepsis phenotypes which may benefit from blood purification treatments.
- Fluid resuscitation guided by dynamic measures in low-resource settings.
- Further studies to inform about vasopressor selection and titration.
- Studies to address the benefits of multimodal vasopressor strategies.
- Studies to address the timing of adjunctive vasopressor initiation.
- Studies needed for optimal timing for vasopressor initiation in sepsis-induced hypotension.
- Studies to inform the optimal safety protocols for using peripheral vasopressors, including safe duration, maximal doses, peripheral IV access size, and peripheral IV anatomic location.
- Trials needed to assess the impact of inotropes in sepsis, define which patients benefit, and determine optimal timing, dosing, and weaning strategies.
- The use of active fluid removal and the use of ultrafiltration or extracorporeal fluid removal after the acute resuscitation phase in septic shock.

Clinical Indicators for Monitoring

- **Incidence of ARDS and pneumonia within 7 days of ICU admission**
  Numerator: Number of patients with sepsis or septic shock who had ARDS and pneumonia within 7 days of ICU admission.
  Denominator: Total number of patients admitted to ICU with sepsis or septic shock.

- **Incidence of Ventilator-free days of patients with sepsis or septic shock during ICU stay**
  Numerator: Number of Ventilator-free days during ICU stay from day of ICU admission.
  Denominator: Total number of days of stay in ICU of patients with sepsis or septic shock.

- **Percentage of patients with sepsis or septic shock who had received Venous thromboembolism (VTE) prophylaxis**
  Numerator: Number of patients who had received thromboembolism (VTE) prophylaxis.
  Denominator: Total number of patients admitted to ICU with sepsis or septic shock.

- **Percentage of patients with sepsis or septic shock, who received early (within 72 h) initiation of enteral nutrition.**
  Numerator: Number of patients who received early (within 72 h) enteral nutrition.
  Denominator: Total number of patients admitted to ICU with sepsis or septic shock.

- **Rate of 28-days mortality in patients with sepsis or septic shock**
  Numerator: Number of patients with sepsis or septic shock who died within 28 days from the day of admission to ICU (28-day mortality)
  Denominator: Total number of patients admitted to ICU with sepsis or septic shock

Update of the Guideline

The Guidelines of this current version (Year 2026) are subject to revision, and the updated versions will be published when needed, as warranted by the evolution of new-evidenced medical knowledge, new technology, and new practice trends.

Guidelines Development Contributors and Participants

Contributors and Participants:
The Guidelines Development Group (GDG) of the Egyptian Board of Anesthesia, Surgical Intensive Care, and Pain Management.

Annexes

Annex 1:

Evidence-to-Decision Tables

1. Screening and Early Management

1.1 Performance Improvement Programs

Criterion	Details
Problem	High sepsis mortality in Egypt; delayed recognition in many hospitals.
Benefit	Early detection, standardized treatment, improved survival.
Risk/Harm	Minimal; requires training and resources.
Certainty of Evidence	High.
Values & Preferences	Patients value rapid diagnosis and treatment.
Resource Use	Moderate; requires staff training and monitoring systems.
Equity	Improves care across diverse hospitals.
Acceptability	High among clinicians and administrators.
Feasibility	Feasible with phased implementation.
Recommendation	Strong: Implement sepsis performance improvement programs, including screening and SOPs.

2. Infection Management

2.1 Antimicrobial Therapy Timing

Criterion	Details
Problem	Delayed antibiotics linked to higher mortality.
Benefit	Early antibiotics reduce mortality in septic shock.
Risk/Harm	Overuse may drive resistance.
Certainty of Evidence	High for septic shock; moderate for sepsis without shock.
Values & Preferences	Patients prioritize survival over resistance concerns.
Resource Use	Moderate; requires rapid access to antimicrobials.
Equity	Critical in rural/low-resource hospitals.
Acceptability	High among clinicians.
Feasibility	Feasible with stock management and protocols.
Recommendation	Strong: Administer antimicrobials within 1 hour for septic shock; within 3 hours for possible sepsis without shock.

2.2 Source Control

Criterion	Details
Problem	Delayed source control worsens outcomes.
Benefit	Early intervention reduces mortality.
Risk/Harm	Procedural risks (surgery, drainage).
Certainty of Evidence	Moderate.
Values & Preferences	Patients value rapid relief of the infection source.
Resource Use	High; requires surgical/IR availability.
Equity	Limited in rural hospitals.
Acceptability	High among clinicians.
Feasibility	Feasible in tertiary centers; challenging in district hospitals.
Recommendation	Conditional: Early source control within 6 hours.

2.3 De-escalation

Criterion	Details
Problem	Overuse of broad-spectrum antimicrobials.
Benefit	Reduces resistance, improves stewardship.
Risk/Harm	Risk of undertreatment if misapplied.
Certainty of Evidence	Moderate.
Values & Preferences	Patients value safety and survival.
Resource Use	Low; requires culture facilities.
Equity	Limited in hospitals without microbiology labs.
Acceptability	High among stewardship advocates.
Feasibility	Feasible with daily review.
Recommendation	Strong: De-escalate antimicrobials when culture results available.

3. Hemodynamic Management

3.1 Initial Fluid Resuscitation

Criterion	Details
Problem	Hypoperfusion and shock are common in Egyptian ICUs.
Benefit	30 ml/kg crystalloid improves perfusion.
Risk/Harm	Risk of fluid overload, especially in elderly/CHF patients.
Certainty of Evidence	Moderate.
Values & Preferences	Patients value survival; clinicians cautious about overload.
Resource Use	Low; crystalloids widely available.
Equity	Accessible in most hospitals.
Acceptability	High.
Feasibility	Feasible with monitoring.
Recommendation	Conditional: Administer 30 ml/kg crystalloid within 3 hours, with reassessment.

3.2 Vasopressor Use

Criterion	Details
Problem	Persistent hypotension after fluids.
Benefit	Restores MAP, reduces mortality.
Risk/Harm	Peripheral administration risks extravasation.
Certainty of Evidence	Moderate.
Values & Preferences	Patients value stabilization.
Resource Use	Moderate; requires vasopressor availability.
Equity	Limited in rural hospitals.
Acceptability	High.
Feasibility	Feasible with training.
Recommendation	Conditional: Start vasopressors peripherally if central access delayed; target MAP 65 mmHg.

3.3. Balanced Crystalloids vs. Saline

Criterion	Details
Problem	Choice of resuscitation fluid impacts renal outcomes and mortality.
Benefit	Balanced crystalloids reduce risk of hyperchloremic acidosis and renal injury.
Risk/Harm	Saline may worsen acidosis; balanced solutions may be contraindicated in TBI.
Certainty of Evidence	Moderate.
Values & Preferences	Patients value survival and renal protection.
Resource Use	Balanced crystalloids slightly more costly but widely available.
Equity	Accessible in tertiary hospitals; limited in rural centers.
Acceptability	High among intensivists.
Feasibility	Feasible with procurement planning.
Recommendation	Conditional: Use balanced crystalloids over saline, except in TBI

3.4. Albumin Supplementation

Criterion	Details
Problem	Fluid overload risk after large crystalloid volumes.
Benefit	Albumin may improve oncotic pressure in cirrhosis or hypoalbuminemia.
Risk/Harm	Expensive; avoid in TBI.
Certainty of Evidence	Low.
Values & Preferences	Patients value reduced edema and improved perfusion.
Resource Use	High cost; limited availability in Egypt.
Equity	May widen gap between tertiary and district hospitals.
Acceptability	Moderate among clinicians.
Feasibility	Limited in resource-constrained settings.
Recommendation	Conditional: Consider albumin in selected patients after large crystalloid volumes or cirrhosis.

3.5. Dynamic Measures for Fluid Responsiveness

Criterion	Details
Problem	Static measures (CVP) unreliable for guiding fluids.
Benefit	Dynamic measures improve the precision of resuscitation.
Risk/Harm	Requires monitoring equipment and training.
Certainty of Evidence	Moderate.
Values & Preferences	Patients value tailored resuscitation.
Resource Use	Moderate; requires monitors.
Equity	Limited in rural hospitals.
Acceptability	High among critical care teams.
Feasibility	Feasible in ICUs with monitoring capacity.
Recommendation	Conditional: Use dynamic measures (passive leg raise, SVV, PPV) over static measures.

4. Respiratory Support

4.1. Oxygen Therapy

Criterion	Details
Problem	Hypoxemia common in sepsis.
Benefit	Supplemental oxygen improves tissue oxygenation.
Risk/Harm	Hyperoxia may increase oxidative stress.
Certainty of Evidence	Moderate.
Values & Preferences	Patients value relief of dyspnea and survival.
Resource Use	Low; oxygen widely available.
Equity	Accessible in most Egyptian hospitals.
Acceptability	High.
Feasibility	Feasible with standard oxygen delivery systems.
Recommendation	Strong: Provide supplemental oxygen to maintain SPO2 ≥ 90%.

4.2. High-Flow Nasal Oxygen (HFNO) vs. Standard Oxygen

Criterion	Details
Problem	Patients with hypoxemic respiratory failure may deteriorate.
Benefit	HFNO reduces the need for intubation in selected patients.
Risk/Harm	Requires equipment; may delay intubation if misused.
Certainty of Evidence	Moderate.
Values & Preferences	Patients value comfort and avoidance of intubation.
Resource Use	Higher cost; limited availability in Egypt.
Equity	Available in tertiary centers; limited in district hospitals.
Acceptability	High among intensivists.
Feasibility	Feasible in ICUs with HFNO devices.
Recommendation	Conditional: Use HFNO in hypoxemic respiratory failure when available.

4.3. Non-Invasive Ventilation (NIV)

Criterion	Details
Problem	NIV may prevent intubation in selected patients.
Benefit	Reduces complications of invasive ventilation.
Risk/Harm	Risk of delayed intubation and aspiration.
Certainty of Evidence	Low.
Values & Preferences	Patients value the avoidance of intubation.
Resource Use	Moderate; requires trained staff.
Equity	Limited in rural hospitals.
Acceptability	Moderate among clinicians.
Feasibility	Feasible in ICUs with NIV capability.
Recommendation	Conditional: Consider NIV in selected patients with sepsis-related respiratory failure, with close monitoring.

4.4. Invasive Mechanical Ventilation

Criterion	Details
Problem	Severe sepsis often requires intubation.
Benefit	Ensures oxygenation and ventilation.
Risk/Harm	Ventilator-associated complications.
Certainty of Evidence	High.
Values & Preferences	Patients value survival despite risks.
Resource Use	High; requires ICU infrastructure.
Equity	Limited in district hospitals.
Acceptability	High among intensivists.
Feasibility	Feasible in tertiary ICUs.
Recommendation	Strong: Provide invasive mechanical ventilation when indicated, with lung-protective strategies.

4.5. VV-ECMO

Criterion	Details
Problem	Refractory hypoxemia despite optimal mechanical ventilation.
Benefit	Provides extracorporeal oxygenation and CO2 removal, bridging patients through severe ARDS or septic respiratory failure.
Risk/Harm	High risk of bleeding, thrombosis, infection; requires specialized expertise.
Certainty of Evidence	Low (benefit in selected patients).
Values & Preferences	Patients and families value survival in otherwise fatal scenarios.
Resource Use	Very high; requires ECMO circuits, perfusionists, and specialized ICU teams.
Equity	Limited to tertiary centers in Egypt; not feasible in most hospitals.
Acceptability	High among ECMO-capable centers.
Feasibility	Feasible only in specialized ICUs with ECMO programs.
Recommendation	Conditional: Consider VV-ECMO in refractory hypoxemia unresponsive to optimal mechanical ventilation, in centers with expertise.

5. Additional Supportive Therapies

5.1 Corticosteroids (for refractory septic shock)

Criterion	Details
Problem	Persistent hypotension despite fluids and vasopressors.
Benefit	Shortens duration of shock, may reduce vasopressor requirement.
Benefit Direction	Positive – stabilizes circulation, improves shock resolution.
Risk/Harm	Hyperglycemia, secondary infections, and muscle weakness.
Certainty of Evidence	Moderate.
Values & Preferences	Patients value stabilization and survival.
Resource Use	Low; widely available.
Equity	Accessible in most Egyptian hospitals.
Acceptability	High among intensivists.
Feasibility	Feasible with monitoring.
Recommendation	Conditional: Consider IV corticosteroids in refractory septic shock.

5.2. IV Vitamin C

Criterion	Details
Problem	Oxidative stress and endothelial dysfunction in sepsis.
Benefit	Proposed antioxidant and vasopressor-sparing effects.
Benefit Direction	Neutral/uncertain – evidence inconsistent, no proven survival benefit.
Risk/Harm	Risk of oxalate nephropathy at high doses.
Certainty of Evidence	Low.
Values & Preferences	Patients value innovative therapies.
Resource Use	Moderate cost.
Equity	Limited availability.
Acceptability	Moderate.
Feasibility	Feasible in tertiary centers.
Recommendation	Conditional: No routine use; consider only in research settings.

5.3. Stress Ulcer Prophylaxis

Criterion	Details
Problem	Critically ill patients at risk of GI bleeding.
Benefit	Reduces the incidence of stress-related mucosal bleeding.
Benefit Direction	Positive – prevents GI bleeding in high-risk patients.
Risk/Harm	Increased risk of pneumonia, C. difficile.
Certainty of Evidence	Moderate.
Values & Preferences	Patients value the prevention of bleeding.
Resource Use	Low.
Equity	Widely available.
Acceptability	High.
Feasibility	Feasible with standard ICU protocols.
Recommendation	Conditional: Use prophylaxis in patients with risk factors (mechanical ventilation >48h, coagulopathy).

5.4. Active Fluid Removal (Diuretics/Ultrafiltration)

Criterion	Details
Problem	Fluid overload after resuscitation.
Benefit	Improves oxygenation, reduces edema.
Benefit Direction	Positive – improves organ function by reducing overload.
Risk/Harm	Risk of hypoperfusion, electrolyte imbalance.
Certainty of Evidence	Low.
Values & Preferences	Patients value comfort and reduced edema.
Resource Use	Moderate.
Equity	Limited in rural hospitals.
Acceptability	Moderate.
Feasibility	Feasible in tertiary ICUs.
Recommendation	Conditional: Consider active fluid removal in fluid-overloaded patients.

5.5. Enteral Nutrition

Criterion	Details
Problem	Malnutrition worsens outcomes in sepsis.
Benefit	Maintains gut integrity, reduces infection risk.
Benefit Direction	Positive – improves recovery and reduces complications.
Risk/Harm	Aspiration risk if not monitored.
Certainty of Evidence	Moderate.
Values & Preferences	Patients value nutrition and recovery.
Resource Use	Moderate.
Equity	Widely available in Egyptian ICUs.
Acceptability	High.
Feasibility	Feasible with trained staff.
Recommendation	Strong: Initiate early enteral nutrition when feasible.

5.6. Insulin Therapy

Criterion	Details
Problem	Hyperglycemia common in sepsis.
Benefit	Tight glucose control reduces complications.
Benefit Direction	Positive – reduces morbidity when glucose maintained <180 mg/dL.
Risk/Harm	Hypoglycemia risk with tight control.
Certainty of Evidence	Moderate.
Values & Preferences	Patients value safety.
Resource Use	Low.
Equity	Widely available.
Acceptability	High.
Feasibility	Feasible with monitoring.
Recommendation	Strong: Maintain glucose <180 mg/dL; avoid tight control <110 mg/dL.

5.7. Renal Replacement Therapy (RRT)

Criterion	Details
Problem	Acute kidney injury common in septic shock.
Benefit	Supports renal function, removes toxins.
Benefit Direction	Positive – improves metabolic control and survival in severe AKI.
Risk/Harm	Hypotension, resource-intensive.
Certainty of Evidence	Moderate.
Values & Preferences	Patients value survival.
Resource Use	High.
Equity	Limited in rural hospitals.
Acceptability	High in tertiary centers.
Feasibility	Feasible in specialized ICUs.
Recommendation	Conditional: Initiate RRT for severe AKI or metabolic derangements.

5.8. Sodium Bicarbonate

Criterion	Details
Problem	Severe metabolic acidosis in sepsis.
Benefit	May improve pH and hemodynamics.
Benefit Direction	Neutral/uncertain – benefit limited to severe acidosis (pH <7.2).
Risk/Harm	Sodium overload, paradoxical intracellular acidosis.
Certainty of Evidence	Low.
Values & Preferences	Patients value stabilization.
Resource Use	Low.
Equity	Widely available.
Acceptability	Moderate.
Feasibility	Feasible with monitoring.
Recommendation	Conditional: Consider in severe acidosis (pH <7.2).

5.9. RBC Transfusion

Criterion	Details
Problem	Anemia common in sepsis.
Benefit	Improves oxygen delivery.
Benefit Direction	Positive – improves oxygenation when Hb <7 g/dL.
Risk/Harm	Transfusion reactions, infection risk.
Certainty of Evidence	Moderate.
Values & Preferences	Patients value survival.
Resource Use	High; requires blood bank.
Equity	Limited in rural hospitals.
Acceptability	High.
Feasibility	Feasible in tertiary centers.
Recommendation	Strong: Transfuse when Hb <7 g/dL; avoid liberal transfusion.

5.10. VTE Prophylaxis

Criterion	Details
Problem	Sepsis patients at high risk of venous thromboembolism.
Benefit	Reduces the incidence of DVT/PE.
Benefit Direction	Positive – prevents VTE, improves survival.
Risk/Harm	Bleeding risk.
Certainty of Evidence	High.
Values & Preferences	Patients value the prevention of complications.
Resource Use	Low.
Equity	Widely available.
Acceptability	High.
Feasibility	Feasible with standard ICU protocols.
Recommendation	Strong: Provide pharmacologic VTE prophylaxis unless contraindicated.

Annex 2:

Table 1: Sepsis Terminology in This Guideline.

Definite sepsis	Sepsis is confirmed based on history, clinical examination, and diagnostic testing. An alternative diagnosis is very unlikely.
Probable sepsis	High suspicion for sepsis. Sepsis is the most likely diagnosis based on history, clinical examination, and diagnostic testing. An alternative diagnosis is less likely.
Possible sepsis	Moderate suspicion for sepsis. Sepsis is a possible diagnosis; however, an alternative diagnosis is also likely based on history, clinical examination, and diagnostic testing.
Unlikely sepsis	Low suspicion for sepsis. Clinical assessment is not consistent with sepsis, or an alternate diagnosis is more likely based on history, clinical examination, and diagnostic testing.

Annex 3:

Table 2: 30 mL/kg in Liters, by Weight and Height

	Height (m) (feet, inches)		
Weigh (kg) (lb.)	**1.5 m (4′11″)**	**1.7 m (5′7″)**	**1.9 m (6′3″)**
50 (110)	1.5	1.5	1.5
60 (132)	1.8	1.8	1.8
70 (154)	2.1	2.1	2.1
80 (176)	*1.9*	2.4	2.4
90 (200)	*2.0*	*2.4*	2.7
100 (220)	*2.1*	*2.5*	*3.0*
110 (242)	*2.2*	*2.6*	*3.3*
120 (264)	*2.3*	*2.7*	*3.0*
130 (287)	*2.5*	*2.8*	*3.1*
140 (309)	*2.6*	*3.0*	*3.2*
150 (331)	*2.7*	*3.1*	*3.3*
160 (353)	*2.8*	*3.2*	*3.4*

REFERENCES

1. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic shock 2026. Critical Care Medicine April 2026; 54 (4): 715-812

2. Singer M, Deutschman CS, Seymour CW, et al: The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016; 315:801–810

3. Arabi YM, Alsaawi A, Alzahrani M, et al; SCREEN Trial Group and the Saudi Critical Care Trials Group: Electronic sepsis screening among patients admitted to hospital wards: A stepped-wedge cluster randomized trial. *JAMA* 2025; 333:763–773

4. Freund Y, Cancella de Abreu M, Lebal S, et al: Effect of the 1-h bundle on mortality in patients with suspected sepsis in the emergency department: A stepped wedge cluster randomized clinical trial. *Intensive Care Med* 2024; 50:1086–1095

5. Damiani E, Donati A, Serafini G, et al: Effect of performance improvement programs on compliance with sepsis bundles and mortality: A systematic review and meta-analysis of observational studies. *PLoS One* 2015; 10:e0125827

6. Tarabichi Y, Cheng A, Bar-Shain D, et al: Improving timeliness of antibiotic administration using a provider and pharmacist facing sepsis early warning system in the emergency department setting: A randomized controlled quality improvement initiative. *Crit Care Med* 2022; 50:418–427

7. CDC: Hospital Sepsis Program Core Elements. 2023. Available at: https://www.cdc.gov/sepsis/media/pdfs/sepsis- core-elements-H.pdf Accessed August 14, 2025

8. Guirgis FW, Jones L, Esma R, et al: Managing sepsis: Electronic recognition, rapid response teams, and standardized care save lives. *J Crit Care* 2017; 40:296–302

9. Patocka C, Turner J, Xue X, et al: Evaluation of an emergency department triage screening tool for suspected severe sepsis and septic shock. *J Healthc Qual* 2014; 36:52–61; quiz 59

10. Williams G, Alberto L, Taha M, et al: The challenges of compliance with sepsis management protocols in low and low-middle income countries - A cross-sectional study. *Intensive Crit Care Nurs* 2025; 90:104032

11. Piedmont S, Goldhahn L, Swart E, et al: Sepsis incidence, suspicion, prediction and mortality in emergency medical services: A cohort study related to the current international sepsis guideline. *Infection* 2024; 52:1325–1335

12. Troncoso R Jr, Garfinkel EM, Hinson JS, et al: Do prehospital sepsis alerts decrease time to complete CMS sepsis measures? *Am J Emerg Med* 2023; 71:81–85

13. Hunter CL, Silvestri S, Stone A, et al: Prehospital sepsis alert notification decreases time to initiation of CMS sepsis core measures. *Am J Emerg Med* 2019; 37:114–117

14. Guerra WF, Mayfield TR, Meyers MS, et al: Early detection and treatment of patients with severe sepsis by prehospital personnel. *J Emerg Med* 2013; 44:1116–1125

15. Mixon M, Dietrich S, Floren M, et al: Time to antibiotic administration: Sepsis alerts called in emergency department versus in the field via emergency medical services. *Am J Emerg Med* 2021; 44:291–295

16. Adegbite BR, Edoa JR, Ndzebe Ndoumba WF, 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. *E Clinical Medicine* 2021; 42:101184

17. Chua WL, Rusli KDB, Aitken LM: Early warning scores for sepsis identification and prediction of in-hospital mortality in adults with sepsis: A systematic review and meta-analysis. *J Clin Nurs* 2024; 33:2005–2018

18. Elperin J, Van Perre K, Bryant NH: 1193: Sepsis: Is it time to leave sirs behind? A systematic review and meta-analysis of sepsis definitions. *Crit Care Med* 2023; 51:59

19. Qiu X, Lei Y, Zhou RX: SIRS, SOFA, qSOFA, and NEWS in the diagnosis of sepsis and prediction of adverse outcomes: A systematic review and meta-analysis. *Expert Rev Anti Infect Ther* 2023; 21:891–900

20. Crouser ED, Parrillo JE, Seymour CW, et al: Monocyte distribution width: A novel indicator of sepsis-2 and sepsis-3 in high- risk emergency department patients. *Crit Care Med* 2019; 47:1018–1025

21. Vashti A, Mullan PJ, Nitzberg M: Single-site sampling strategy versus multi-site sampling strategy in blood culture collection within the hospital setting: A systematic review. *Am J Infect Control* 2025; 53:1113–1120

22. S3-Leitlinie: Sepsis – Prävention, Diagnose, Therapie und Nachsorge – Update 2025. Available at: https://register.awmf.org/assets/guidelines/079-001l_S3_Sepsis-Praevention-Diagnose-Therapie-Nachsorge_2025-07.pdf Accessed August 12, 2025

23. Cheng MP, Stenstrom R, Paquette K, et al; FABLED Investigators: Blood culture results before and after antimicrobial administration in patients with severe manifestations of sepsis: A diagnostic study. *Ann Intern Med* 2019; 171:547–554

24. Evans L, Rhodes A, Alhazzani W, et al: Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock 2021. *Intensive Care Med* 2021; 47:1181–1247

25. Evans L, Rhodes A, Alhazzani W, et al: Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock 2021. *Crit Care Med* 2021; 49:e1063–e1143

26. Borthwick HA, Brunt LK, Mitchem KL, et al: Does lactate measurement performed on admission predict clinical outcome on the intensive care unit? A concise **systematic review**. Ann Clin Biochem 2012; 49:391–394

27. Liu G, An Y, Yi X, et al: Early lactate levels for prediction of mortality in patients with sepsis or septic shock: **A meta-analysis**. Int J Exp Med 2017; 10:37–47

28. Levy MM, Evans LE, Rhodes A: The surviving sepsis campaign bundle: 2018 update. Crit Care Med 2018; 46:997–1000

29. Shankar-Hari M, Phillips GS, Levy ML, et al; Sepsis Definitions Task Force: Developing a new definition and assessing new clinical criteria for septic shock: For the third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016; 315:775–787

30. Ljungström L, Pernestig AK, Jacobsson G, et al: Diagnostic accuracy of procalcitonin, neutrophil-lymphocyte count ratio, C-reactive protein, and lactate in patients with suspected bacterial sepsis. PLoS One 2017; 12:e0181704

31. Morris E, McCartney D, Lasserson D, et al: Point-of-care lactate testing for sepsis at presentation to health care: A systematic review of patient outcomes. Br J Gen Pract 2017; 67:e859–e870

32. Rhodes A, Evans LE, Alhazzani W, et al: Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med* 2017; 45:486–552

33. Shankar-Hari M, Phillips GS, Levy ML, et al; Sepsis Definitions Task Force: Developing a new definition and assessing new clinical criteria for septic shock: For the third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016; 315:775–787

34. Kuttab HI, Lykins JD, Hughes MD, et al: Evaluation and predictors of fluid resuscitation in patients with severe sepsis and septic shock. *Crit Care Med* 2019; 47:1582–1590

35. Corl KA, Levy MM, Holder AL, et al: Moderate IV fluid resuscitation is associated with decreased sepsis mortality. *Crit Care Med* 2024; 52:e557–e567

36. Peake SL, Delaney A, Bellomo R; ARISE Investigators: Goal- directed resuscitation in septic shock. *N Engl J Med* 2015; 372:190–191

37. Pro CI, et al.: A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014; 370:1683–1693

38. Mouncey PR, Osborn TM, Power GS, et al; ProMISe Trial Investigators: Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med* 2015; 372:1301–1311

39. Ward MA, Kuttab HI, Badgett RG: The effect of early fluid resuscitation on mortality in sepsis: A systematic review and meta-analysis. *Crit Care Med* 2025; 53:e1790–e1802

40. Taylor SP, Karvetski CH, Templin MA, et al: Initial fluid resus- citation following adjusted body weight dosing is associated with improved mortality in obese patients with suspected septic shock. *J Crit Care* 2018; 43:7–12

41. Mekontso Dessap A, AlShamsi F, Belletti A, et al; European Society of Intensive Care Medicine: European Society of Intensive Care Medicine (ESICM) 2025 clinical practice guideline on fluid therapy in adult critically ill patients: Part 2-the volume of resuscitation fluids. *Intensive Care Med* 2025; 51:461–477

42. Ahn C, Yu G, Shin TG, et al: Comparison of early and late norepinephrine administration in patients with septic shock: A systematic review and meta-analysis. Chest 2024; 166:1417–1430

43. Permpikul C, Tongyoo S, Viarasilpa T, et al: Early use of norepinephrine in septic shock resuscitation (CENSER). A randomized trial. Am J Respir Crit Care Med2019; 199:1097–1105

44. Shi R, Braïk R, Monnet X, et al: Early norepinephrine for patients with septic shock: An updated systematic review and meta-analysis with trial sequential analysis. Crit Care2025; 29:182

45. Li Y, Li H, Zhang D: Timing of norepinephrine initiation in patients with septic shock: A systematic review and meta-analysis. Crit Care2020; 24:488

46. Zhou HX, Yang C-F, Wang H-Y, et al: Should we initiate vasopressors earlier in patients with septic shock: A mini systemic review. World J Crit Care Med2023; 12:204–216

47. Elbouhy MA, Soliman M, Gaber A, et al: Early use of norepinephrine improves survival in septic shock: Earlier than early. Arch Med Res2019; 50:325–332

48. Bai X, Yu W, Ji W, et al: Early versus delayed administration of norepinephrine in patients with septic shock. Crit Care2014; 18:532

49. Colon Hidalgo D, Patel J, Masic D, et al: Delayed vasopressor initiation is associated with increased mortality in patients with septic shock. J Crit Care2020; 55:145–148

50. National Heart L, et al.: Early restrictive or liberal fluid management for sepsis-induced hypotension. The multicenter CLOVERS RCT. N Engl J Med2023; 388:499–510

51. Owen VS, Rosgen BK, Cherak SJ, et al: Adverse events associated with administration of vasopressor medications through a peripheral intravenous catheter: A systematic review and meta-analysis. Crit Care2021; 25:146

52. Tian DH, Smyth C, Keijzers G, et al: Safety of peripheral administration of vasopressor medications: A systematic review. Emerg Med Australas2020; 32:220–227

53. Ricard JD, Salomon L, Boyer A, et al: Central or peripheral catheters for initial venous access of ICU patients: A randomized controlled trial. Crit Care Med2013; 41:2108–2115

54. Stolz A, Efendy R, Apte Y, et al: Safety and efficacy of peripheral versus centrally administered vasopressor infusion: A single-center retrospective observational study. Aust Crit Care2022; 35:506–511

55. Delaney A, Finnis M, Bellomo R, et al: Initiation of vasopressor infusions via peripheral versus central access in patients with early septic shock: A retrospective cohort study. Emerg Med Australas2020; 32:210–219

56. Munroe ES, Heath ME, Eteer M, et al: Use and outcomes of peripheral vasopressors in early sepsis-induced hypotension across Michigan hospitals: A retrospective cohort study. Chest2024; 165:847–857

57. Munroe ES, Co IN, Douglas I, et al; NHLBI PETAL Network: Peripheral vasopressor use in early sepsis-induced hypotension. JAMA Netw Open2025; 8:e2529148

58. Asher E, Karameh H, Nassar H, et al; Jerusalem Platelets Thrombosis and Intervention in Cardiology (JUPITER-16) Study Group: Safety and outcomes of peripherally administered vasopressor infusion in patients admitted with shock to an intensive cardiac care unit-A single-center prospective study. J Clin Med2023; 12:5734

59. Groetzinger LM, Williams J, Svec S, et al: Peripherally infused norepinephrine to avoid central venous catheter placement in a medical intensive care unit: A pilot study. Ann Pharmacother2022; 56:773–781

60. Medlej K, Kazzi AA, El Hajj Chehade A, et al: Complications from administration of vasopressors through peripheral ve-nous catheters: An observational study. J Emerg Med2018; 54:47–53

61. Meng L, Wang Y, Zhang L, et al: Heterogeneity and variability in pressure autoregulation of organ blood flow: lessons learned over 100+ years. Crit Care Med2019; 47:436–448

62. Asfar P, Meziani F, Hamel J-F, et al; SEPSISPAM Investigators: High versus low blood-pressure target in patients with septic shock. N Engl J Med2014; 370:1583–1593

63. Hylands M, Moller MH, Asfar P, et al: A systematic review of vasopressor blood pressure targets in critically ill adults with hypotension. Can J Anaesth2017; 64:703–715

64. Lamontagne F, Richards-Belle A, Thomas K, et al; 65 trial investigators: Effect of reduced exposure to vasopressors on 90-day mortality in older critically ill patients with vasodilatory hypotension: A randomized clinical trial. JAMA2020; 323:938–949

65. Angriman F, Momenzade N, Adhikari NKJ, et al: Blood pressure targets for adults with vasodilatory shock - An individual patient data meta-analysis. NEJM Evid2025;4:EVIDoa 2400359

66. Endo A, Yamakawa K, Tagami T, et al; OPTPRESS trial investigators: Efficacy of targeting high mean arterial pressure for older patients with septic shock (OPTPRESS): A multicenter , pragmatic, open-label, randomized controlled trial. Intensive Care Med2025; 51:883–892

67. Cardoso LT, Grion CM, Matsuo T, et al: Impact of delayed admission to intensive care units on mortality of critically ill patients: A cohort study. Crit Care 2011; 15:R28

68. Groenland CNL, Termorshuizen F, Rietdijk WJR, et al: Emergency department to ICU time is associated with hospital mortality: A registry analysis of 14,788 patients from Six University Hospitals in The Netherlands. Crit Care Med 2019; 47:1564–1571

69. Chalfin DB, Trzeciak S, Likourezos A, et al; DELAY-ED study group: Impact of delayed transfer of critically ill patients from the emergency department to the intensive care unit. Crit Care Med 2007; 35:1477–1483

70. Harris S, Singer M, Sanderson C, et al: Impact on mortality of prompt admission to critical care for deteriorating ward patients: An instrumental variable analysis using critical care bed strain. Intensive Care Med 2018; 44:606–615

71. Kalil AC, Johnson DW, Lisco SJ, et al: Early goal-directed therapy for sepsis: A novel solution for discordant survival outcomes in clinical trials. Crit Care Med 2017; 45:607–614

72. Klompas M, Calandra T, Singer M: Antibiotics for sepsis-finding the equilibrium. JAMA2018; 320:1433–1434

73. Leung LY, Huang H-L, Hung KK, et al: Door-to-antibiotic time and mortality in patients with sepsis: Systematic review and meta-analysis. Eur J Intern Med2024; 129:48–61

74. Pak TR, Young J, McKenna CS, et al: Risk of misleading conclusions in observational studies of time-to-antibiotics and mortality in suspected sepsis. Clin Infect Dis2023; 77:1534–1543

75. Hechtman RK, Kipnis P, Cano J, et al: Heterogeneity of benefit from earlier time-to-antibiotics for sepsis. Am J Respir Crit Care Med2024; 209:852–860

76. Alam N, Oskam E, Stassen PM, et al; PHANTASi Trial Investigators and the ORCA (Onderzoeks Consortium Acute Geneeskunde) Research Consortium the Netherlands: Prehospital antibiotics in the ambulance for sepsis: A multicenter, open label, randomized trial. Lancet Respir Med2018; 6:40–50

77. Thwaites L, Nasa P, Abbenbroek B, et al: Management of adult sepsis in resource-limited settings: Global expert consensus statements using a Delphi method. *Intensive Care Med* 2025; 51:21–38

78. Lane D, Ichelson RI, Drennan IR, et al: Prehospital management and identification of sepsis by emergency medical serv- ices: A systematic review. *Emerg Med J* 2016; 33:408–413

79. Varney J, Motawea KR, Kandil OA, et al: Prehospital administration of broad-spectrum antibiotics for sepsis patients: A systematic review and meta-analysis. *Health Sci Rep* 2022; 5:e582

80. Poynter MJ, Farrugia A, Kelly E, et al: Prehospital administration of antibiotics in addition to usual care versus usual care alone for patients with suspected sepsis – a systematic review. *Paramedicine* 2023; 21:52–65

81. Peng F, Chang W, Xie JF, et al: Ineffectiveness of procalcitonin-guided antibiotic therapy in severely critically ill patients: A meta-analysis. Int J Infect Dis 2019; 85:158–166

82. Wacker C, Prkno A, Brunkhorst FM, et al: Procalcitonin as a diagnostic marker for sepsis: A systematic review and meta-analysis. Lancet Infect Dis 2013; 13:426–435

83. Jensen JU, Hein L, Lundgren B, et al; Procalcitonin And Survival Study (PASS) Group: Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: A randomized trial. Crit Care Med 2011; 39:2048–2058

84. Layios N, Lambermont B, Canivet JL, et al: Procalcitonin usefulness for the initiation of antibiotic treatment in intensive care unit patients. Crit Care Med 2012; 40:2304–2309

85. Najafi A, Khodadadian A, Sanatkar M, et al: The comparison of procalcitonin guidance administer antibiotics with empiric antibiotic therapy in critically ill patients admitted in intensive care unit. Acta Med Iran 2015; 53:562–567

86. Metlay JP, Waterer GW, Long AC, et al: Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med 2019; 200:e45–e67

87. Huston JM, Barie PS, Dellinger EP, et al: Surgical infection society guidelines on management of intra-abdominal infection: 2024 update. *Surg Infect (Larchmt)* 2024; 25:419–435

88. Coccolini F, Sartelli M, Sawyer R, et al: Source control in emergency general surgery: WSES, GAIS, SIS-E, SIS-A guidelines. *World J Emerg Surg* 2023; 18:41

89. Paul M, Carrara E, Retamar P, et al: European society of clinical microbiology and infectious diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). *Clin Microbiol Infect* 2022; 28:521–547

90. Carey GB, Holleck JL, Ein Alshaeba S, et al: Estimated mortality with early empirical MRSA coverage in hospitalized patients: Systematic review and meta-analysis. *J Antimicrob Chemother* 2023; 78:1150–1159

91. Cortegiani A, Russotto V, Maggiore A, et al: Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients. *Cochrane Database Syst Rev* 2016; 2016:CD004920

92. Timsit JF, Azoulay E, Schwebel C, et al; EMPIRICUS Trial Group: Empirical micafungin treatment and survival without invasive fungal infection in adults with ICU-acquired sepsis (EMPIRICUS). *JAMA* 2016; 316:1555–1564

93. Petersen MW, Perner A, Jonsson AB, et al: Empirical metronidazole for patients with severe bacterial infection: Systematic review with meta-analysis and trial sequential analysis. *Acta Anaesthesiol Scand* 2019; 63:802–813

94. Chanderraj R, Baker JM, Kay SG, et al: In critically ill patients, anti-anaerobic antibiotics increase risk of adverse clinical outcomes. *Eur Respir J* 2023; 61:2200910

95. Metlay JP, Waterer GW, Long AC, et al: Diagnosis and treatment of adults with community-acquired pneumonia. ATS/IDSA guideline. *Am J Respir Crit Care Med* 2019; 200:e45–e67

96. Mazuski JE, Tessier JM, May AK, et al: Surgical Infection Society revised guidelines on management of intra-abdominal infection. *Surg Infect (Larchmt)* 2017; 18:1–76

97. Kullberg RFJ, Haak BW, Chanderraj R, et al: Empirical antibiotic therapy for sepsis: Save the anaerobic microbiota. *Lancet Respir Med* 2025; 13:92–100

98. Anton-Vazquez V, Hine P, Krishna S, et al: Rapid versus standard antimicrobial susceptibility testing to guide treatment of bloodstream infection. *Cochrane Database Syst Rev* 2021; 5:CD013235

99. Caspar Y, Deves A, Richarme C, et al: Clinical impact and cost-consequence analysis of ePlex® blood culture identification panels for rapid diagnosis of bloodstream infections. *Eur J Clin Microbiol Infect Dis* 2024; 43:1193–1203

100. Timbrook TT, Morton JB, McConeghy KW, et al: The effect of molecular rapid diagnostic testing on clinical outcomes in bloodstream infections: Systematic review and meta-analysis. *Clin Infect Dis* 2017; 64:15–23

101. Mohd Hafiz AA, Staatz CE, Kirkpatrick CMJ, et al: Continuous infusion vs. bolus dosing: Implications for beta-lactam antibiotics. *Minerva Anesthesiol* 2012; 78:94–104

102. Abdul-Aziz MH, Lipman J, Akova M, et al; DALI Study Group: Is prolonged infusion of piperacillin/tazobactam and meropenem associated with improved pharmacokinetic/pharmacodynamic and patient outcomes? (DALI cohort). *J Antimicrob Chemother* 2016; 71:196–207

103. Abdul-Aziz MH, Hammond NE, Brett SJ, et al: Prolonged vs intermittent infusions of beta-lactam antibiotics in adults with sepsis or septic shock: A systematic review and meta-analysis. *JAMA* 2024; 332:638–648

104. Dulhunty JM, Brett SJ, De Waele JJ, et al; BLING III Study Investigators: Continuous vs intermittent beta-lactam antibiotic infusions in critically ill patients with sepsis: The BLING III randomized clinical trial. *JAMA* 2024; 332:629–637

105. Roberts JA, Abdul-Aziz MH, Lipman J, et al: Individualized antibiotic dosing for patients who are critically ill: Challenges and potential solutions. *Lancet Infect Dis* 2014; 14:498–509

106. Veiga R, Paiva JA: Pharmacokinetics-pharmacodynamics issues relevant for the clinical use of beta-lactam antibiotics in critically ill patients. *Crit Care* 2018; 22:233

107. Sanz-Codina M, Bozkir HO, Jorda A, et al: Individualized antimicrobial dose optimization: A systematic review and meta-analysis of randomized controlled trials. *Clin Microbiol Infect* 2023; 29:845–857

108. Abdul-Aziz MH, Alffenaar JC, Bassetti M, et al; ESICM Infection Section: Antimicrobial therapeutic drug monitoring in critically ill adult patients: A Position Paper. *Intensive Care Med* 2020; 46:1127–1153

109. Leone M, Bechis C, Baumstarck K, et al; AZUREA Network Investigators: De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: A multicenter non-blinded randomized noninferiority trial. *Intensive Care Med* 2014; 40:1399–1408

110. Lopez-Cortes LE, Delgado-Valverde M, Moreno-Mellado E, et al; SIMPLIFY study group: Efficacy and safety of a structured de-escalation from antipseudomonal beta-lactams in bloodstream infections due to Enterobacterales. *Lancet Infect Dis* 2024; 24:375–385

111. Tabah A, Bassetti M, Kollef MH, et al: Antimicrobial de- escalation in critically ill patients: A position statement from a task force of the European society of intensive care medicine (ESICM) and European society of clinical microbiology and infectious diseases (ESCMID) critically ill patients study group (ESGCIP). *Intensive Care Med* 2020; 46:245–265

112. NICE organization. Surveillance report 2018 – Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) NICE guideline NG15. Available at: https://www.nice.org.uk/guidance/ng15/resources/ surveillance-report-2018-antimicrobial-stewardship-systems-and-processes-for-effective-antimicrobial-medicine- use-2015-nice-guideline-ng15-pdf-6119358364357 Accessed July 18, 2025.

113. Dark P, Hossain A, McAuley DF, et al; ADAPT-Sepsis Collaborators: Biomarker-guided antibiotic duration for hospitalized patients with suspected sepsis: The ADAPT-sepsis randomized clinical trial. *JAMA* 2025; 333:682–693

114. Gershengorn HB, Garland A, Kramer A, et al: Variation of arterial and central venous catheter use in United States in- tensive care units. *Anesthesiology* 2014; 120:650–664

115. Muller G, Contou D, Ehrmann S, et al: Deferring arterial catheterization in critically ill patients with shock. *N Engl J Med* 2025; 393:1875–1888

116. Hammond NE, Zampieri FG, Di Tanna GL, et al: Balanced crystalloids versus saline in critically ill adults - A systematic review with meta-analysis. *NEJM Evid* 2022; 1:EVIDoa2100010

117. Zampieri FG, Cavalcanti AB, Di Tanna GL, et al: Balanced crystalloids versus saline for critically ill patients (BEST-Living): A systematic review and individual patient data meta- analysis. *Lancet Respir Med* 2024; 12:237–246

118. Diz JC, Luna-Rojas P, Díaz-Vidal P, et al: Effect of treatment with balanced crystalloids versus normal saline on the mortality of critically ill patients with and without traumatic brain injury: A systematic review and meta-analysis. *Anesth Analg* 2025; 141:152–161

119. Investigators SS, et al: Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med* 2007; 357:874–884

120. Philips CA, Maiwall R, Sharma MK, et al: Comparison of 5% human albumin and normal saline for fluid resuscitation in sepsis induced hypotension among patients with cirrhosis (FRISC study): A randomized controlled trial. *Hepatol Int* 2021; 15:983–994

121. Caironi P, Tognoni G, Masson S, et al; ALBIOS Study Investigators: Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med* 2014; 370:1412–1421

122. Arabi YM, Belley-Cote E, Carsetti A, et al; European Society of Intensive Care Medicine: European society of intensive care medicine clinical practice guideline on fluid therapy in adult critically ill patients. Part 1: The choice of resuscitation fluids. *Intensive Care Med* 2024; 50:813–831

123. Rochwerg B, Alhazzani W, Sindi A, et al; Fluids in Sepsis and Septic Shock Group: Fluid resuscitation in sepsis: A systematic review and network meta-analysis. Ann Intern Med 2014; 161:347–355

124. Moeller C, Fleischmann C, Thomas-Rueddel D, et al: How safe is gelatin? A systematic review and meta-analysis of gelatin-containing plasma expanders vs crystalloids and albumin. J Crit Care 2016; 35:75–83

125. Haase N, Perner A, Hennings LI, et al: Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: Systematic review with meta-analysis and trial sequential analysis. BMJ 2013; 346:f839

126. Macdonald SPJ, Keijzers G, Taylor DM, et al; REFRESH trial investigators: Restricted fluid resuscitation in suspected sepsis associated hypotension (REFRESH): A pilot randomized controlled trial. *Intensive Care Med* 2018; 44:2070–2078

127. Jessen MK, Andersen LW, Thomsen MH, et al: Restrictive fluids versus standard care in adults with sepsis in the emergency department (REFACED): A multicenter, randomized feasibility trial. *Acad Emerg Med* 2022; 29:1172–1184

128. Meyhoff TS, Hjortrup PB, Wetterslev J, et al; CLASSIC Trial Group: Restriction of intravenous fluid in ICU patients with septic shock. *N Engl J Med* 2022; 386:2459–2470

129. Bednarczyk JM, Fridfinnson JA, Kumar A, et al: Incorporating dynamic assessment of fluid responsiveness into goal- directed therapy: A systematic review and meta-analysis. *Crit Care Med* 2017; 45:1538–1545

130. Ehrman RR, Gallien JZ, Smith RK, et al: Resuscitation guided by volume responsiveness does not reduce mortality in sepsis: A meta-analysis. *Crit Care Explor* 2019; 1:e0015

131. Azadian M, Win S, Abdipour A, et al: Mortality benefit from the passive leg raise maneuver in guiding resuscitation of septic shock patients: A systematic review and meta-analysis of randomized trials. *J Intensive Care Med* 2022; 37:611–617

132. Basmaji J, Arntfield R, Desai K, et al: The impact of point-of- care ultrasound-guided resuscitation on clinical outcomes in patients with shock: A systematic review and meta-analysis. *Crit Care Med* 2024; 52:1661–1673

133. Putowski Z, Gołdyn M, Pluta MP, et al: Correlation between mean arterial pressure and capillary refill time in patients with septic shock: A systematic review and meta-analysis. *J Intensive Care Med* 2023; 38:838–846

134. Hernandez G, Ospina-Tascón GA, Damiani LP, et al; The ANDROMEDA SHOCK Investigators and the Latin America Intensive Care Network (LIVEN): 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; 321:654–664

135. Castro R, Kattan E, Ferri G, et al: Effects of capillary refill time-vs. lactate-targeted fluid resuscitation on regional, microcirculatory and hypoxia-related perfusion parameters in septic shock: A randomized controlled trial. *Ann Intensive Care* 2020; 10:150

136. Kattan E, Bakker J, Estenssoro E, et al: Hemodynamic phenotype-based, capillary refill time-targeted resuscitation in early septic shock: The ANDROMEDA-SHOCK-2 randomized clinical trial study protocol. *Rev Bras Ter Intensiva* 2022; 34:96–106

137. Levy B: Lactate and shock state: The metabolic view. *Curr Opin Crit Care* 2006; 12:315–321

138. Pan J, Peng M, Liao C, et al: Relative efficacy and safety of early lactate clearance-guided therapy resuscitation in patients with sepsis: A meta-analysis. *Medicine (Baltim)* 2019; 98:e14453

139. Gordon AC, Mason AJ, Thirunavukkarasu N, et al; VANISH Investigators: Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: The VANISH randomized clinical trial. *JAMA* 2016; 316:509–518

140. Hajjar LA, Zambolim C, Belletti A, et al: Vasopressin versus norepinephrine for the management of septic shock in cancer patients: The VANCS II randomized clinical trial. *Crit Care Med* 2019; 47:1743–1750

141. Khanna A, English SW, Wang XS, et al; ATHOS-3 Investigators: Angiotensin II for the treatment of vasodilatory shock. *N Engl J Med* 2017; 377:419–430

142. Chawla LS, Busse L, Brasha-Mitchell E, et al: Intravenous angiotensin II for the treatment of high-output shock (ATHOS trial): a pilot study. *Crit Care* 2014; 18:534

143. Drugs.com. Comparing Levophed vs Vasopressin. Available at: https://www.drugs.com/compare/levophed-vs-vasopres- sin Accessed July 22, 2025

144. Russell JA, Walley KR, Singer J, et al; VASST Investigators: Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008; 358:877–887

145. Chen C, Pang L, Wang Y, et al: Combination era, using combined vasopressors showed benefits in treating septic shock patients: A network meta-analysis of randomized controlled trials. *Ann Transl Med* 2019; 7:535

146. Myburgh JA, Higgins A, Jovanovska A, et al; CAT Study investigators: A comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Med* 2008; 34:2226–2234

147. Belletti A, Benedetto U, Biondi-Zoccai G, et al: The effect of vasoactive drugs on mortality in patients with severe sepsis and septic shock. A network meta-analysis of randomized trials. *J Crit Care* 2017; 37:91–98

148. McChesney C, Orozco N, Fiorini K, et al: Impact of short-acting beta-blockers on the outcomes of patients with septic shock: A systematic review and meta-analysis. *Crit Care Med* 2025; 53:e1125–e1139

149. Kilcommons SJ, Hammal F, Kamaleldin M, et al: Adjunctive midodrine therapy for vasopressor-dependent shock in the ICU: A systematic review and meta-analysis. *Crit Care Med* 2025; 53:e384–e399

150. Fernando SM, Tran A, Soliman K, et al: Methylene blue in septic shock: A systematic review and meta-analysis. *Crit Care Explor* 2024; 6:e1110

151. Chaudhuri D, Lazarte J, Shah K, et al. Approaches to converting Spo2/FIO2 ratio to PaO2/FIO2 ratio for assessment of respiratory failure in critically ill patients: A systematic review. *Crit Care Med* 2026 Jan 6. [online first]

152. Sjoding MW, Dickson RP, Iwashyna TJ, et al: Racial bias in pulse oximetry measurement. *N Engl J Med* 2020; 383:2477–2478

153. Martin D, Johns C, Sorrell L, et al: Effect of skin tone on the accuracy of the estimation of arterial oxygen saturation by pulse oximetry: A systematic review. *Br J Anaesth* 2024; 132:945–956

154. Alipanah-Lechner N, Cavalcanti AB, Diaz J, et al: From Berlin to global: The need for syndromic definitions of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2024; 209:21–23

155. Klitgaard TL, Schjørring OL, Nielsen FM, et al: Higher versus lower fractions of inspired oxygen or targets of arterial oxygenation for adults admitted to the intensive care unit. *Cochrane Database Syst Rev* 2023; 9:CD012631

156. Buell KG, Spicer AB, Casey JD, et al: Individualized treatment effects of oxygen targets in mechanically ventilated critically ill adults. *JAMA* 2024; 331:1195–1204

157. Frat JP, Quenot J-P, Badie J, et al; SOHO-COVID Study Group and the REVA Network: Effect of high-flow nasal cannula oxygen vs standard oxygen therapy on mortality in patients with respiratory failure due to COVID-19: The SOHO-COVID randomized clinical trial. *JAMA* 2022; 328:1212–1222

158. Perkins GD, Ji C, Connolly BA, et al; RECOVERY-RS Collaborators: Effect of noninvasive respiratory strategies on intubation or mortality among patients with acute hypoxemic respiratory failure and COVID-19: The RECOVERY-RS randomized clinical trial. *JAMA* 2022; 327:546–558

159. Crimi C, Noto A, Madotto F, et al; COVID-HIGH Investigators: High-flow nasal oxygen versus conventional oxygen therapy in patients with COVID-19 pneumonia and mild hypoxemia: A randomized controlled trial. *Thorax* 2023; 78:354–361

160. Nagata K, Yokoyama T, Tsugitomi R, et al; JaNP-Hi Study Investigators: Continuous positive airway pressure versus high-flow nasal cannula oxygen therapy for acute hypoxemic respiratory failure: A randomized controlled trial. *Respirology* 2024; 29:36–45

161. Investigators R, et al.: High-flow nasal oxygen vs noninvasive ventilation in patients with acute respiratory failure: The RENOVATE randomized clinical trial. *JAMA* 2025; 333:875–890

162. Coudroy R, Frat J-P, Ehrmann S, et al; FLORALI-IM study group and the REVA Research Network: High-flow nasal oxygen alone or alternating with non-invasive ventilation in critically ill immunocompromised patients with acute respiratory failure: A randomized controlled trial. *Lancet Respir Med* 2022; 10:641–649

163. Frat JP, Thille AW, Mercat A, et al; FLORALI Study Group: High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015; 372:2185–2196

164. Luo J, Pavlov I, Tavernier E, et al; Awake Prone Positioning Meta-Analysis Group: Awake prone positioning in adults with COVID-19: An individual participant data meta-analysis. *JAMA Intern Med* 2025; 185:572–581

165. Alhazzani W, Parhar KKS, Weatherald J, et al; COVI- PRONE Trial Investigators and the Saudi Critical Care Trials Group: Effect of awake prone positioning on endo- tracheal intubation in patients with COVID-19 and acute respiratory failure: A randomized clinical trial. *JAMA* 2022; 327:2104–2113

166. Landry DW, Levin HR, Gallant EM, et al: Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation 1997; 95:1122–1125 354.

167. Gordon AC, Mason AJ, Thirunavukkarasu N, et al; VANISH Investigators: Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: The VANISH randomized clinical trial. JAMA 2016; 316:509–518

168. Brower RG, Matthay MA, Morris A, et al; Acute Respiratory Distress Syndrome Network: 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; 342:1301–1308

169. Hager DN, Krishnan JA, Hayden DL, et al; ARDS Clinical Trials Network: Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. *Am J Respir Crit Care Med* 2005; 172:1241–1245

170. Checkley W, Brower R, Korpak A, et al; Acute Respiratory Distress Syndrome Network Investigators: Effects of a clinical trial on mechanical ventilation practices in patients with acute lung injury. *Am J Respir Crit Care Med* 2008; 177:1215–1222

171. Amato MB, Meade MO, Slutsky AS, et al: Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015; 372:747–755

172. de Haro C, Neto AS, Gomà G, et al: Effect of a low versus intermediate tidal volume strategy on pulmonary complications in patients at risk of acute respiratory distress syndrome- a randomized clinical trial. *Front Med (Lausanne)* 2023; 10:1172434

173. Writing Group for the PI, et al.: Effect of a low vs intermediate tidal volume strategy on ventilator-free days in intensive care unit patients without ARDS: A randomized clinical trial. *JAMA* 2018; 320:1872–1880

174. Brochard L, Roudot-Thoraval F, Roupie E, et al: Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. *Am J Respir Crit Care Med* 1998; 158:1831–1838

175. Brower RG, Shanholtz CB, Fessler HE, et al: Prospective, ran- domized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. *Crit Care Med* 1999; 27:1492–1498

176. Papazian L, Aubron C, Brochard L, et al: Formal guidelines: Management of acute respiratory distress syndrome. *Ann Intensive Care* 2019; 9:69

177. Laffey JG, Bellani G, Pham T, et al; LUNG SAFE Investigators and the ESICM Trials Group: Potentially modifiable factors contributing to outcome from acute respiratory distress syn- drome: The LUNG SAFE study. *Intensive Care Med* 2016; 42:1865–1876

178. Villar J, Martín-Rodríguez C, Domínguez-Berrot AM, et al; Spanish Initiative for Epidemiology, Stratification and Therapies for ARDS (SIESTA) Investigators Network: A quantile analysis of plateau and driving pressures: Effects on mortality in patients with acute respiratory distress syn- drome receiving lung-protective ventilation. *Crit Care Med* 2017; 45:843–850

179. Brower RG, Lanken PN, MacIntyre N, et al; National Heart, Lung, and Blood Institute ARDS Clinical Trials Network: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004; 351:327–336

180. Meade MO, Cook DJ, Guyatt GH, et al; Lung Open Ventilation Study Investigators: Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2008; 299:637–645

181. Mercat A, Richard JC, Vielle B, et al: Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2008; 299:646–655

182. Briel M, Meade M, Mercat A, et al: Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: Systematic review and meta-analysis. *JAMA* 2010; 303:865–873

183. Cavalcanti AB, Suzumura ÉA, Laranjeira LN, et al: Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: A randomized clinical trial. *JAMA* 2017; 318:1335–1345

184. Munshi L, Del Sorbo L, Adhikari NKJ, et al: Prone position for acute respiratory distress syndrome. A systematic review and meta-analysis. *Ann Am Thorac Soc* 2017; 14(Suppl 4):S280–S288

185. Guérin C, Reignier J, Richard JC, et al; PROSEVA Study Group: Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013; 368:2159–2168

186. National Heart, Lung, and Blood Institute PETAL Clinical Trials Network; Moss M, Huang DT, Brower RG, et al: Early neuromuscular blockade in the acute respiratory distress syndrome. *N Engl J Med* 2019; 380:1997–2008

187. Combes A, Hajage D, Capellier G, et al; EOLIA Trial Group, REVA, and ECMONet: Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018; 378:1965–1975

188. Peek GJ, Mugford M, Tiruvoipati R, et al; CESAR trial collaboration: Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): A multicenter randomized controlled trial. *Lancet* 2009; 374:1351–1363

189. Munshi L, Walkey A, Goligher E, et al: Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: A systematic review and meta-analysis. *Lancet Respir Med* 2019; 7:163–172

190. Pitre T, Drover K, Chaudhuri D, et al: Corticosteroids in sepsis and septic shock: A systematic review, pairwise, and dose-response meta-analysis. *Crit Care Explor* 2024; 6:e1000

191. Diaz-Gomez JL, Sharif S, Ablordeppey E, et al: Society of critical care medicine guidelines on adult critical care ultrasonography: Focused update 2024. *Crit Care Med* 2025; 53:e447–e458

192. Sakkat A, Alquraini M, Aljazeeri J, et al: Temperature control in critically ill patients with fever: A meta-analysis of randomized controlled trials. *J Crit Care* 2021; 61:89–95

193. Reintam Blaser A, Alhazzani W, Belley-Cote E, et al: Intravenous vitamin C therapy in adult patients with sepsis: A rapid practice guideline. *Acta Anaesthesiol Scand* 2023; 67:1423–1431

194. Agarwal A, Basmaji J, Fernando SM, et al: Parenteral Vitamin C in patients with severe infection: A systematic review. *NEJM Evid* 2022; 1:EVIDoa2200105

195. Lamontagne F, Masse M-H, Menard J, et al; LOVIT Investigators and the Canadian Critical Care Trials Group: Intravenous Vitamin C in adults with sepsis in the intensive care unit. *N Engl J Med* 2022; 386:2387–2398

196. Pan B, Sun P, Pei R, et al: Efficacy of IVIG therapy for patients with sepsis: A systematic review and meta-analysis. *J Transl Med* 2023; 21:765

197. Kaur M, Soni KD, Trikha A: Does vitamin D improve all-cause mortality in critically ill adults? An updated systematic review and meta-analysis of randomized controlled trials. *Indian J Crit Care Med* 2022; 26:853–862

198. National Heart L, et al.: Early high-dose Vitamin D(3) for critically ill, Vitamin D-deficient patients. *N Engl J Med* 2019; 381:2529–2540

199. Liu S, Yao C, Xie J, et al; EXIT-SEP Investigators: Effect of an herbal-based injection on 28-Day mortality in patients with sepsis: The EXIT-SEP randomized clinical trial. *JAMA Intern Med* 2023; 183:647–655

200. Li C, Wang P, Zhang Li, et al: Efficacy and safety of Xuebijing injection (a Chinese patent) for sepsis: A meta-analysis of randomized controlled trials. *J Ethnopharmacol* 2018; 224:512–521

201. Wang J, Zhu J, Guo J, et al: Could xuebijing injection reduce the mortality of severe pneumonia patients? A systematic review and meta-analysis. *Evid Based Complement Alternat Med* 2020; 2020:9605793

202. Chen JJ, Lai P-C, Lee T-H, et al: Blood purification for adult patients with severe infection or sepsis/septic shock: A net- work meta-analysis of randomized controlled trials. *Crit Care Med* 2023; 51:1777–1789

203. Rimmer E, Houston BL, Kumar A, 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; 18:699

204. American Diabetes Association: 14. Diabetes care in the hospital: Standards of medical care in diabetes—2018. Diabetes Care 2018; 41(Suppl 1):S144–S151

205. Yatabe T, Inoue S, Sakaguchi M, et al: The optimal target for acute glycemic control in critically ill patients: A network meta-analysis. Intensive Care Med 2017; 43:16–28

206. Hirano Y, Miyoshi Y, Kondo Y, et al: 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; 23:262

207. Bergamin FS, Almeida JP, Landoni G, et al: Liberal versus restrictive transfusion strategy in critically ill oncologic patients: The transfusion requirements in critically ill oncologic patients randomized controlled trial. Crit Care Med 2017; 45:766–773

208. Wang Y, Parpia S, Ge L, et al: Proton-pump inhibitors to pre- vent gastrointestinal bleeding - an updated meta-analysis. *NEJM Evid* 2024; 3:EVIDoa2400134

209. Cook D, Deane A, Lauzier F, et al; REVISE Investigators: Stress ulcer prophylaxis during Invasive mechanical ventilation. *N Engl J Med* 2024; 391:9–20

210. Granholm A, Zeng L, Dionne JC, et al; GUIDE Group: Predictors of gastrointestinal bleeding in adult ICU patients: a systematic review and meta-analysis. *Intensive Care Med* 2019; 45:1347–1359

211. MacLaren R, Dionne JC, Granholm A, et al: Society of Critical Care Medicine and American Society of Health-System Pharmacists Guideline for the Prevention of Stress-Related Gastrointestinal Bleeding in Critically Ill Adults. *Crit Care Med* 2024; 52:e421–e430

212. 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; Irish Critical Care Trials Group; Bagshaw SM, Wald R, Adhikari NKJ; et al: Timing of initiation of renal-replacement therapy in acute kidney injury. N Engl J Med 2020; 383:240–251

213. Zha J, Li C, Cheng G, et al: The efficacy of renal replacement therapy strategies for septic-acute kidney injury: A PRISMAcompliant network meta-analysis. Medicine (Baltimore) 2019; 98:e15257

214. Zhao Y, Chen Y: Effect of renal replacement therapy modalities on renal recovery and mortality for acute kidney injury: A PRISMA-compliant systematic review and meta-analysis. Semin Dial 2020; 33:127–132

215. Reignier J, Boisramé-Helms J, Brisard L, et al; NUTRIREA-2 Trial Investigators; Clinical Research in Intensive Care and Sepsis (CRICS) group: Enteral versus parenteral early nutrition in ventilated adults with shock: A randomized, controlled, multicenter, open-label, parallel-group study (NUTRIREA-2). Lancet 2018; 391:133–143

216. Jaber S, Paugam C, Futier E, et al; BICAR-ICU Study Group: Sodium bicarbonate therapy for patients with severe metabolic acidemia in the intensive care unit (BICAR-ICU): A multicenter, open-label, randomized controlled, phase 3 trial. Lancet 2018; 392:31–40

217. Ostermann M, Alshamsi F, Artigas Raventos A, et al: European society of intensive care medicine clinical practice guideline on fluid therapy in adult critically ill patients: Part 3-fluid removal at de-escalation phase. *Intensive Care Med* 2025; 51:1749–1763

218. Sharif S, Greer A, Skorupski C, et al: Probiotics in critical ill- ness: A systematic review and meta-analysis of randomized controlled trials. *Crit Care Med* 2022; 50:1175–1186

219. Johnstone J, Meade M, Lauzier F, et al; Prevention of Severe Pneumonia and Endotracheal Colonization Trial (PROSPECT) Investigators and the Canadian Critical Care Trials Group: Effect of probiotics on incident ventilator- associated pneumonia in critically ill patients: A randomized clinical trial. *JAMA* 2021; 326:1024–1033

220. Arabi YM, Al-Hameed F, Burns KEA, et al; Saudi Critical Care Trials Group: Adjunctive intermittent pneumatic compression for venous thromboprophylaxis. N Engl J Med 2019; 380:1305–1315