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GUIDELINES

Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2026

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Introduction

Sepsis, life-threatening acute organ dysfunction due to infection [1], is a global health priority [2, 3] with approximately 49 million cases and 13 million sepsis-related deaths each year [4–6]. Beyond being acutely deadly, sepsis contributes to new and worsened physical, cognitive, and mental health problems in many survivors [7, 8]. Early identification and treatment are critical to improving outcomes.

The Surviving Sepsis Campaign (SSC) guidelines are intended to support clinicians caring for adult patients with sepsis, focusing on management in the hospital, the immediate prehospital setting, and the immediate post-hospital setting. These guidelines incorporate principles of antimicrobial stewardship through responsible antimicrobial use, proper diagnostic strategies, and de-escalation of antimicrobial therapy. The recommendations reflect evidence-based best practice, distilling a large body of research into actionable recommendations. They empower individuals and health systems to make informed choices about care and support improvements in management and outcomes of sepsis (Table 1).

Methods

Details on the guidelines scope, relationship to SSC bundles, history, and sponsorship; committee selection, characteristics, and organization; conflicts of interest management; patient, intervention, comparator, outcome (PICO) question selection; outcomes prioritization;

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Table 1 Table of statements

SYMBOL KEY:

Strength of Recommendation
- ✓✓ Strong Recommendation For
- ✓ Conditional Recommendation For
- ✗ Conditional Recommendation Against
- ✗✗ Strong Recommendation Against

Certainty of Evidence
- ⊕◯◯◯ Very Low
- ⊕⊕◯◯ Low
- ⊕⊕⊕◯ Moderate
- ⊕⊕⊕⊕ High

Type of Recommendation
- Carry Over
- New, Revised, or Revisited but Unchanged Statements

Change in Strength of Recommendation or Change in Certainty of Evidence
- ↖ Upgraded
- ↘ Downgraded

SCREENING AND EARLY MANAGEMENT

1 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.

✓✓ ⊕⊕⊕◯ *Screening*
✓✓ ⊕◯◯◯ *Standard operating procedures*
✓✓ ⊕⊕⊕◯ *Quality improvement strategies*

Remark: Performance improvement programs and quality improvement strategies may vary by setting and in accordance with a hospital/health care system's ability to implement.

2021 STATEMENT
For hospitals and health systems, we **recommend** using a performance improvement program for sepsis, including sepsis screening for acutely ill, high-risk patients and standard operating procedures for treatment.

✓✓ ⊕⊕⊕◯ *Screening*
✓✓ ⊕◯◯◯ *Standard operating procedures*

2 ✓ ⊕⊕◯◯ For hospitals and health systems, we **suggest** using a "code sepsis" or "sepsis huddle" protocol over not using such a protocol.

Remark: "Code sepsis" or "sepsis huddle" protocols involve a multi-disciplinary team huddle at bedside to discuss and expedite sepsis diagnosis and treatment following a positive sepsis screen.

3 ✓ ⊕◯◯◯ 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.

4 ✓✓ ⊕⊕⊕◯ For acutely ill patients in hospital, we **recommend** using NEWS, NEWS2, MEWS, or SIRS over qSOFA as a single tool to screen for sepsis.

5 GOOD PRACTICE STATEMENT Sepsis is a clinical diagnosis and should not be ruled in or ruled out using a single biomarker or diagnostic test.

6 There is **insufficient evidence** to make a recommendation regarding use of novel rapid host response diagnostics.

7 ✓✓ ⊕⊕◯◯ 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.

8 ✓ ⊕⊕◯◯ For adults with possible or probable sepsis or septic shock, we **suggest** measuring blood lactate.

Remark: Fluid administration should be individualized after initial fluid bolus and monitoring of lactate decrement, rather than continuing fluids until lactate normalization is achieved.

9 GOOD PRACTICE STATEMENT Sepsis and septic shock are medical emergencies; treatment and resuscitation should begin immediately.

10 ✓ ⊕⊕◯◯ For adults with sepsis-induced hypoperfusion or septic shock, we **suggest** administering at least 30 ml/kg of intravenous crystalloid in the first 3 hours.

Remark: Consideration should be given to individual patient characteristics and context when selecting initial fluid volume.

Remark: Clinicians prescribing fluids should perform frequent, ongoing reassessment and closely monitor patients to avoid harms of under- or over-resuscitation.

Remark: 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/m².

11 ✓ ⊕◯◯◯ For adults with sepsis-induced hypotension, we **suggest** initial intravenous crystalloid fluid bolus resuscitation followed by vasopressor support if hypotension persists.

Remark: In patients with unstable septic shock, immediate concurrent administration of vasopressors together with intravenous crystalloid fluid may be warranted on a case-by-case basis. Presence of unstable shock should be determined by physical exam. Suggestive clinical features of unstable shock include severely reduced blood pressure, mottled skin, ashen appearance, cyanosis/decreased oxygen saturation, tachycardia, and altered mentation.

12 ✓ ⊕◯◯◯ 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.

Remark: Data are insufficient to recommend a duration of use, dose, or access route (size of peripheral intravenous line or anatomic location). Midline catheters were not considered.

13 ✓✓ ⊕⊕⊕◯ For adults with septic shock, we **recommend** an initial MAP target of 65 mm Hg over higher MAP targets.

Remark: 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.

14 ✓ ⊕⊕◯◯ For adults with septic shock aged 65 years or older, we **suggest** an initial MAP range of 60-65 mm Hg over higher ranges.

15 ✓ ⊕⊕◯◯ For adults with sepsis or septic shock who require ICU admission, we **suggest** admitting the patients to the ICU within 6 hours.

Table 1 (continued)

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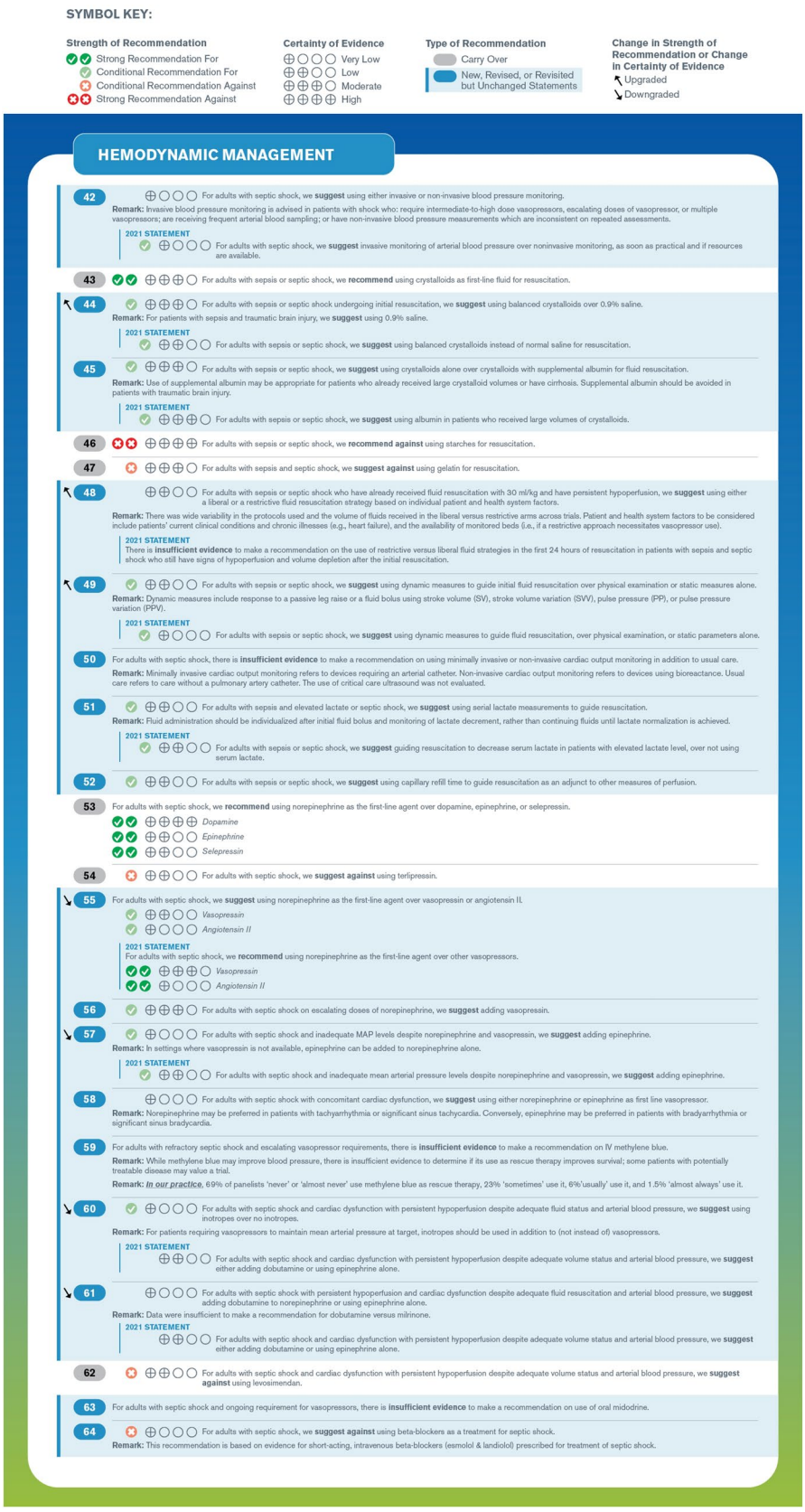

Table 1 (continued)

SYMBOL KEY:

Strength of Recommendation
- Strong Recommendation For
- Conditional Recommendation For
- Conditional Recommendation Against
- Strong Recommendation Against

Certainty of Evidence
- ⊕◯◯◯ Very Low
- ⊕⊕◯◯ Low
- ⊕⊕⊕◯ Moderate
- ⊕⊕⊕⊕ High

Type of Recommendation
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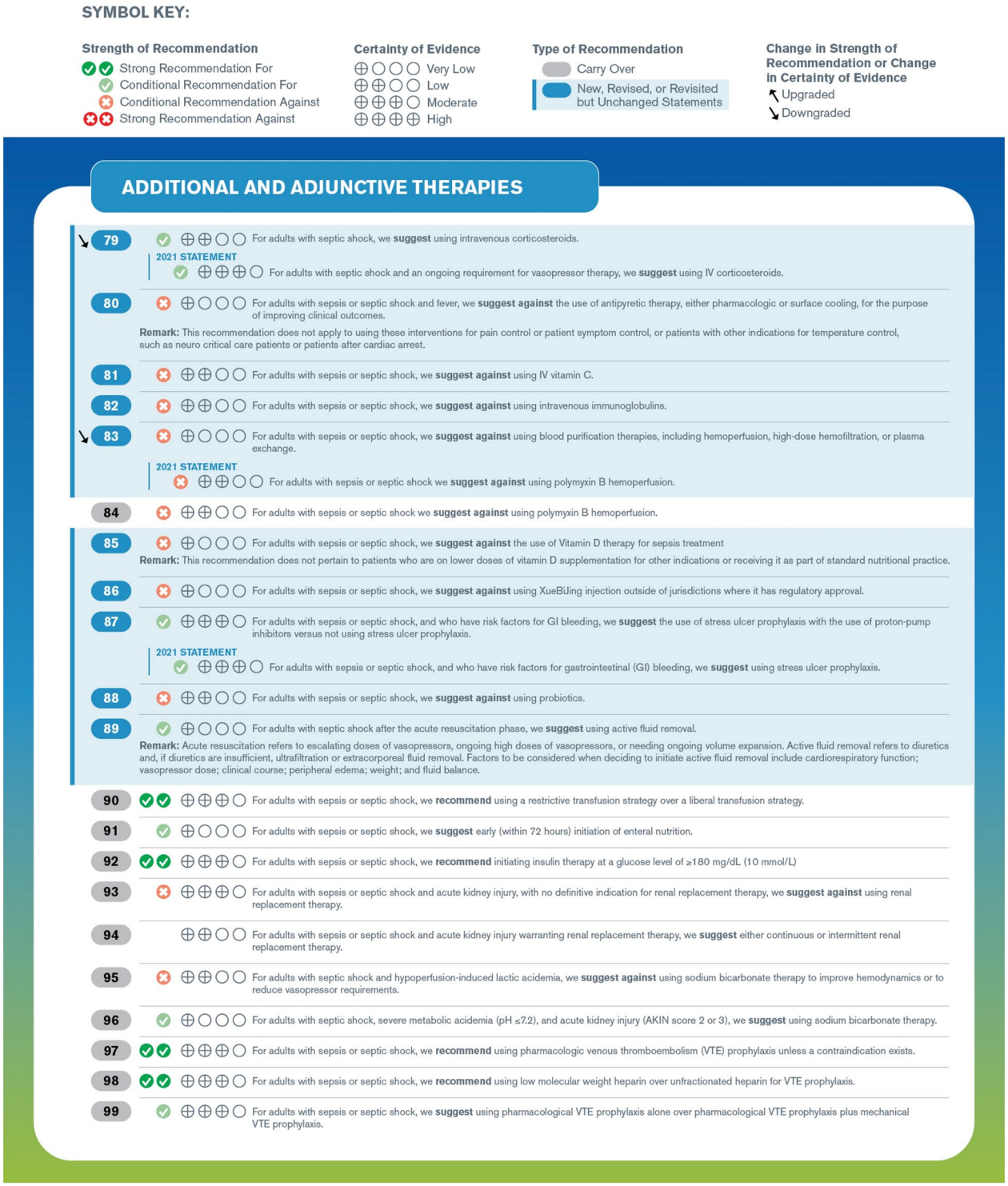
RESPIRATORY SUPPORT

65		⊕◯◯◯	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.
			Remark: 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 by pulse oximeter may substitute for PaO_2/FiO_2 ratio, but is less accurate in patients in shock, with darker skin tones, and/or with oxygen saturations <90% or >97%.
66		⊕⊕◯◯	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.
			Remark: While there was variability across trials informing this recommendation, most used a lower target of approximately 90-93% SpO_2 and a higher target of $SpO_2 \geq 96$.
			Remark: ***In our practice***, panelists target SpO_2 between 90% (IQR 90-92%) to 96% (IQR 94-98%) for patients with sepsis and acute hypoxemic respiratory failure.
67	✓	⊕◯◯◯	For adults with sepsis and acute hypoxemic respiratory failure, we **suggest** using high flow nasal cannula (HFNC) therapy over conventional oxygen therapy.
			Remark: This recommendation pertains to patients with a PaO_2/FiO_2 ratio <200 or SpO_2/FiO_2 ratio <235.
68	✓	⊕⊕◯◯	For adults with sepsis and acute hypoxemic respiratory failure, we **suggest** using HFNC as the initial therapy over non-invasive positive pressure ventilation.
69	✓	⊕◯◯◯	For adults with sepsis and acute hypoxemic respiratory failure, we **suggest** using HFNC over high flow alternating with non-invasive positive pressure ventilation.
70	✓	⊕◯◯◯	For adults with sepsis and acute hypoxemic respiratory failure who are not intubated, we **suggest** a trial of awake proning.
			Remark: 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.
71	✓✓	⊕⊕⊕⊕	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).
72	✓	⊕⊕◯◯	For adults with sepsis acute hypoxemic respiratory failure without ARDS, we **suggest** using a tidal volume of 6 – 8 ml/kg IBW over a lower (4 to < 6 ml/kg IBW) tidal volume.
			Remark: Patients should be screened regularly for development of ARDS, as ARDS diagnosis is often missed or delayed in clinical practice.
73	✓✓	⊕⊕⊕⊕	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.
74	✓	⊕⊕⊕◯	For adults with sepsis and moderate-severe ARDS, we **suggest** using higher PEEP over lower PEEP.
75	✗✗	⊕⊕⊕◯	For adults with sepsis and moderate-severe ARDS, we **recommend against** using an incremental PEEP titration strategy
76	✓	⊕⊕⊕◯	For adults with sepsis and moderate-severe ARDS, we **suggest** using prone ventilation for greater than 12 hours daily.
77	✓	⊕⊕⊕◯	For adults with sepsis and moderate-severe ARDS, we **suggest** using intermittent NMBA boluses over continuous NMBA infusion.
78	✓	⊕⊕◯◯	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.

Table 1 (continued)



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GOALS OF CARE

100	GOOD PRACTICE STATEMENT	For adults with sepsis or septic shock, clinicians should discuss goals of care and prognosis with patients and/or families.
101	⊕⊕◯◯	For adults with sepsis or septic shock, we **suggest** addressing goals of care early (within 72 hours) over late (72 hours or later).
102		For adults with sepsis or septic shock, there is **insufficient evidence** to issue a recommendation regarding the use of a specific standardized criterion to identify patients for goals of care discussions.
103	GOOD PRACTICE STATEMENT	Health systems should implement strategies to ensure that patients being discharged from hospital after sepsis or septic shock have the opportunity to execute advance directives.
104		For adults with sepsis or septic shock, there is **insufficient evidence** to issue a recommendation on the systematic establishment of advance care directives prior to hospital discharge.
105		For adults with sepsis or septic shock, there is **insufficient evidence** to issue a recommendation regarding formal time-limited trials of critical care. **Remark:** A time-limited trial (TLT) is a collaborative plan to use life-sustaining therapy for a defined duration, after which response to therapy informs the decision as to whether to continue or escalate curative intent ICU care or to instead focus on care with other goals.
106	GOOD PRACTICE STATEMENT	The principles of palliative care (which may include palliative care consultation based on clinician judgment) should be integrated into the treatment plan, when appropriate, to address patient and family symptoms and suffering.
107	⊕⊕◯◯	For adults with sepsis or septic shock, we **suggest against** routine formal palliative care consultation for all patients over palliative care consultation based on clinician judgment.

Table 1 (continued)

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- Strong Recommendation Against

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TRANSITIONS OF CARE

108	✓ ⊕◯◯◯	For adults with sepsis and septic shock admitted to ICU, we **suggest** using a critical care transition program, compared with usual care, upon transfer to the floor.
109	✓ ⊕◯◯◯	For adults with sepsis or septic shock, we **suggest** using a handoff process of critically important information at transitions of care over no such handoff process.
110	GOOD PRACTICE STATEMENT	Hospitals and health systems should screen patients with sepsis or septic shock for economic and social support needs (including housing, nutritional, financial, and spiritual support) and make referrals where available to meet these needs.
111	GOOD PRACTICE STATEMENT	For adults with sepsis or septic shock, comprehensive medication reconciliation should be performed at transitions in care, including at ICU and hospital discharge.
112	✓ ⊕◯◯◯	For adults with sepsis or septic shock, we **suggest** comprehensive medication reconciliation using a pharmacist-based approach at transitions in care.
113	GOOD PRACTICE STATEMENT	Clinical teams should provide adults with sepsis or septic shock and their families the opportunity to participate in shared decision making in post-ICU and hospital discharge planning to ensure discharge plans are acceptable and feasible.
114	GOOD PRACTICE STATEMENT	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.
115	GOOD PRACTICE STATEMENT	For adults with sepsis or septic shock who developed new impairments, hospital discharge plans should include follow-up with clinicians able to support and manage new and long-term sequelae.
116	GOOD PRACTICE STATEMENT	Healthcare systems should implement strategies to ensure that patients, their families, and their primary care providers are provided with adequate information to navigate the transition out of hospital.
117		For adults who survive hospitalization with sepsis or septic shock, there is **insufficient evidence** to issue a recommendation regarding a specific structured multi-component discharge planning process.
118	GOOD PRACTICE STATEMENT	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.
119	✓ ⊕◯◯◯	For adults with sepsis and septic shock and their families, we **suggest** offering written and verbal sepsis education (diagnosis, treatment, post-ICU/sepsis syndrome) prior to hospital discharge and in the follow-up setting.
120	GOOD PRACTICE STATEMENT	Health systems should implement strategies to ensure clinicians have the knowledge and competency to support sepsis survivors and their families during the post-hospital recovery.
121		There is **insufficient evidence** to issue a recommendation regarding providing sepsis-focused educational material to primary care providers as compared to usual care.
122	GOOD PRACTICE STATEMENT	Health systems should implement strategies to support sepsis survivors and their families during the post-hospital recovery.
123		There is **insufficient evidence** to make a recommendation on early post-hospital discharge follow-up versus routine post-hospital discharge follow-up.

Table 1 (continued)

evidence synthesis; certainty of evidence assessment; recommendation formulation; consensus voting; and implications of strong vs. conditional recommendations are presented in Supplemental Digital Content 1. We highlight key aspects of the methodology here.

The SSC guidelines were fully funded by the 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. Sponsoring professional societies supported the participation of their representatives. There was no industry support. The 69-person guidelines committee had broad geographic diversity, representing 23 countries, with 38% of panelists currently or previously practicing in a low- or middle-income country (LMIC). The guidelines committee also had broad diversity of clinical professions and disciplines, as detailed in Supplemental Digital Content 1. We convened a patient and family advisory panel who worked with the committee throughout the guidelines development process to ensure incorporation of patients' values and preferences.

The guidelines committee was organized into six subgroups based on clinical domain: screening and early management; infection; hemodynamics; respiratory support; adjunctive and additional therapies; and goals of care, transitions of care, and long-term outcomes, as well as a usability workgroup that developed material to support the dissemination and uptake of the guidelines. Each subgroup had at least one panelist currently practicing in a LMIC.

Evidence synthesis

The process for selecting PICO questions and completing evidence synthesis is detailed in Supplemental Digital Content 1. Prioritized patient-centered outcomes were selected a priori for each question. PICO questions addressed in this guideline update are presented in Supplemental Digital Content 2.

Evidence synthesis followed the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology. Evidence profiles for each PICO question are presented in Supplemental Digital Content 3, Supplemental Digital Content 4, Supplemental Digital Content 5, Supplemental Digital Content 6, Supplemental Digital Content 7 and Supplemental Digital Content 8. The certainty of evidence was graded as high, medium, low, or very low according to GRADE methodology. We used the Evidence to Decision (EtD) framework [9] to support consistent, transparent, and structured formulation of statements across the guideline. The EtD

framework considers the balance of effects, the certainty of evidence, as well as patient values, resource intensity, equity, and cost-effectiveness [9]. The EtD summary of judgements for each PICO question is presented in Supplemental Digital Content 3, Supplemental Digital Content 4, Supplemental Digital Content 5, Supplemental Digital Content 6, Supplemental Digital Content 7 and Supplemental Digital Content 8. We used standardized language to summarize the findings of evidence syntheses based on effect size (i.e., point estimate) and certainty of the evidence, as recommended by GRADE methodology [10].

Process for determining the type of statement

Figure 1 summarizes the stepwise process we used to determine the type of statement for each PICO question. In contrast to many other guidelines, we always provided a graded recommendation when there was at least low certainty evidence to inform a recommendation. For most PICO questions, we relied most heavily on the balance of desirable and undesirable effects to inform recommendations. However, when the balance of effects was equivalent, we relied on other domains in the EtD framework to determine the type of recommendation and used "either/or" statements when the balance of all EtD domains for two different approaches or therapies was equivalent. However, for PICOs where the comparator was usual care alone, we used the language of "we make no recommendation due to equal balance of effects" since suggestions to use or not use a particular therapy were viewed as potentially confusing and unhelpful.

Types of graded recommendations

Using the GRADE approach, we classified each graded recommendation as either "strong" or "conditional" (referred to as "weak" recommendations in prior SSC guidelines). We used the language "we recommend" for strong recommendations and "we suggest" for conditional recommendations, consistent with GRADE guidance.

Implications of graded recommendations

A strong recommendation indicates that most, if not all, individuals in the relevant clinical situation should receive, or avoid, the intervention. In contrast, a conditional recommendation acknowledges that the balance between desirable and undesirable may vary depending on patient values, clinical circumstances, or resource availability. Conditional recommendations may not be universally implementable and are less likely to be suitable for rigid performance metrics or enforcement. Flexibility and local context should guide their adaptation into

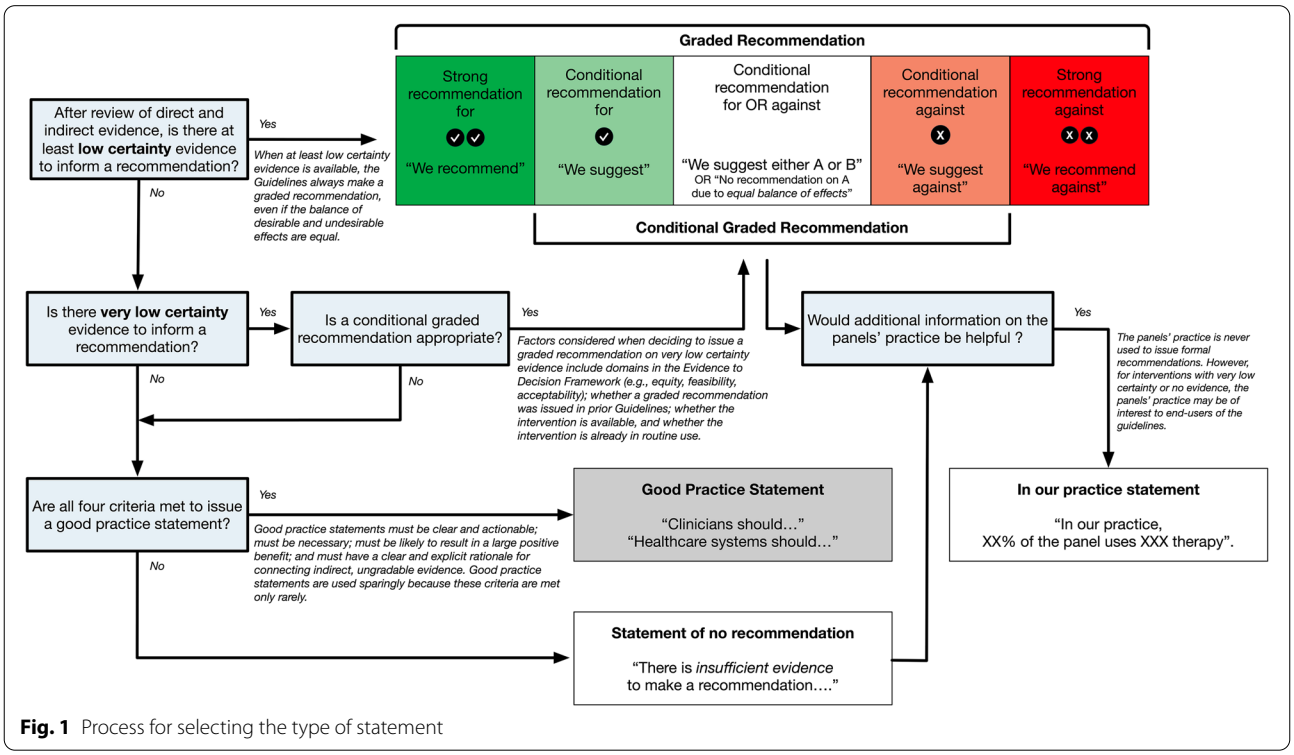

Fig. 1 Process for selecting the type of statement

policy. Further details on implication of strong vs. conditional recommendations are presented in Table 2 and Supplemental Digital Content 1.

Good practice statements

We followed the GRADE guidance to identify statements that were better classified as good practice statements (previously referred to as "best practice statements" in prior SSC guidelines) [11, 12]. These statements represented guidance that did not rely on a formal evidence profile. We used this classification in situations where generating high-certainty evidence was infeasible. To qualify as a good practice statement, a recommendation had to meet all of the following criteria: (1) it was clear and actionable, (2) it addressed a necessary practice, (3) the net benefit (or harm) was unequivocal, (4) the evidence was difficult or inappropriate to summarize quantitatively, (5) the rationale was explicit, and (6) GRADE methods were not suitable to formally assess certainty of evidence.

Remarks

Formal remarks were included to provide additional context when the statement alone could not fully capture the important considerations influencing the recommendation. Remarks were used to clarify or qualify recommendations—often in situations where the evidence was weak, conflicting, or incomplete.

In our practice statements

We decided a priori to include "In Our Practice" statements describing the panel's practice in areas where evidence was insufficient to support a formal recommendation or where evidence was assessed as low or very low certainty and the panel determined that an "in our practice" statement would be helpful to end-users of the guideline. In-our-practice statements are not guidance or endorsement of a specific intervention. Instead, they document how panelists currently approach situations characterized by uncertainty, absence of data, or context-specific clinical variability. The goal of these statements is to provide some information on current practice even when rigorous evidence is lacking.

Carryover statements

We retained several statements from the 2021 SSC guidelines that remain clinically relevant, accurate, and essential to comprehensive sepsis care. These statements typically addressed topics without significant new evidence or where further research was unlikely to alter the prior SSC guidance. These carryover statements did not undergo updated evidence synthesis, as they were deemed unlikely to have sufficient new evidence to warrant a change in guidance based on the panels' knowledge of the literature. However, the panel reviewed and voted for each carryover statement for continued relevance and accuracy.

Consensus voting

We required a minimum 75% response rate and at least 80% agreement among eligible panelists to finalize a recommendation (and associated formal remarks). For new or updated statements that did not meet the consensus threshold on the first vote, we allowed two additional rounds of voting to reach consensus. Between rounds, statements were refined based on panel feedback before revoting. Carryover statements were allowed just one round of voting. We achieved a greater than 98% response rate for each round of voting.

Sepsis terminology

These 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) [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 SSC guidelines are intended to be applied pragmatically to patients diagnosed with

Table 2 Implications of strong vs. conditional recommendations

Stakeholder	Strong recommendation	Conditional recommendation
Patients and families	All or most would want the intervention	Most would want the intervention, but a substantial proportion would not
Clinicians	The intervention should be given to all or most patients. There is little need for shared decision-making for tailoring to context	The intervention should be done for most patients, but clinicians should consider shared decision-making, clinical context, and resources
Policy makers	Often more appropriate for policy or performance measure	May be less appropriate for policy or performance measure
Researchers	Research resources are better spent on other topics	Additional research may be warranted and may change future recommendations

sepsis and septic shock according to local practice. Furthermore, we did not restrict literature searches or evidence syntheses to studies using the Sepsis-3 definition, as studies using prior sepsis definitions are still informative to current practice.

Because the diagnosis of sepsis may be uncertain in clinical practice, we developed standardized language for definite, probable, possible, and unlikely sepsis, which are used throughout the SSC guidelines (Table 3).

Screening and early management

Performance improvement programs

1. 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 recommendation, moderate certainty evidence for screening) (strong recommendation, very low certainty evidence for standard operating procedures) (strong recommendation, moderate certainty evidence for quality improvement strategies) ***Remarks***: Performance improvement programs and quality improvement strategies may vary by setting and in accordance with a hospital/healthcare system's ability to implement	**New** (sepsis quality improvement); carried over (performance improvement program with screening and standard operating procedures)

The recommendations for sepsis screening and standard operating procedures were carried over, so did not undergo formal updated evidence synthesis. However, several relevant randomized-controlled trials (RCTs) have been published since the 2021 SSC guidelines, further supporting these recommendations. One 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 (73 min sooner; 95% CI, 93–53 min sooner) and an uncertain effect on mortality with a point estimate suggesting a possible large decrease (adjusted risk ratio [aRR] 0.81; 95% CI, 0.48–1.39) [13]. Second, 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 (aRR 0.85; 95% CI, 0.77–0.93) [14].

The recommendation for using quality improvement (QI) strategies was newly added. QI is a systematic and ongoing effort to improve evidence-based care processes, such as timely antibiotic administration, with the aim of improving clinical outcomes. 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 (odds ratio [OR] 0.66; 95% CI, 0.61–0.72) [15]. 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 [16–18]. Although most studies evaluating the impact of QI initiatives are observational, we 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 [19]. Patients randomized to this QI intervention had shorter time to antimicrobial therapy (2.3 vs. 3.0 h, $p = 0.04$) and increased days alive and out of hospital at 28 days (median, 24.1 vs. 22.5 d, $p = 0.01$) [19].

The panel considered the balance of effects, costs, and feasibility, and judged that the desirable effects of QI interventions to probably outweigh undesirable

Table 3 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

effects in most settings. Our recommendation for using a performance improvement program for sepsis incorporating screening, standard operating procedures, and QI strategies is consistent with the U.S. Centers' for Disease Control and Prevention's Hospital Sepsis Program Core Elements guidance [20, 21]. The Core Elements summarize key features of effective hospital or health system performance improvement programs for sepsis [20, 21]. Recent surveys suggest opportunities for improvement in hospital sepsis programs, to support delivery of evidence-based management [22–24]. Most studies were conducted in high-resource settings, but QI initiatives—particularly those focused on sepsis bundle element adherence and data feedback—may be applicable in resource-limited settings with appropriate contextual adaptation. However, it is important to start with an understanding of the system and the particular constraints that limit the quality of sepsis care. Furthermore, future research should clarify which QI elements drive observed effects and how best to sustain improvements.

In conclusion, QI initiatives likely improve sepsis processes of care and may have small effects on mortality. They are recommended as part of a systems-based approach to improving sepsis management. Further, the integration of a performance improvement program for sepsis, including screening of high-risk patients and standardized treatment protocols, within existing antibiotic stewardship programs can enhance overall patient outcomes and optimize antimicrobial use [25].

Implementation strategies

2. For hospitals and health systems, we "suggest" using a "code sepsis" or "sepsis huddle" protocol over not using such a protocol **New**

(conditional recommendation, low certainty evidence)

Remark: "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

"Code sepsis" is a multidisciplinary-driven process of care that aims to expedite the diagnosis and treatment of sepsis. While code sepsis protocols vary, common elements include a screening tool for tracking clinical indicators of sepsis, a trigger mechanism for alert activation for suspected sepsis by either a bedside clinician or an automated algorithm, and a response team that will provide immediate bedside evaluation and treatment [26–29]. Composition of the response teams varies widely. For example, the response team may be a dedicated multidisciplinary sepsis response team, a general rapid response team with expertise in sepsis, or an ad hoc team of individuals already involved in the patient's care (e.g., nurse, physician, pharmacist, unit manager). Likewise, the process of screening for sepsis and activating a code sepsis response varies, and may involve manual screening, automating screening, or proactive rounding. Finally, the implementation of sepsis evaluation and treatment varies and may include fast-track protocols, algorithms, or checklists. As with rapid response systems, code sepsis implementation requires an institutional commitment and designated leadership to oversee its performance and effectiveness [26].

Multiple interventional and observational studies with global representation investigating "code sepsis" were identified with mixed results in qualitative review. Several studies reported improved processes and outcome of care with the intervention, including lower mortality [26–28, 30–34], reduced odds of mechanical ventilation [26, 28], shorter time to administration of antibiotics [29, 32, 35–42] and fluids [37, 40, 42–44], lower proportion of patients receiving vasopressors [43], and earlier escalation of care [33, 37, 45]. Furthermore, 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 (aRR 0.85; 95% CI, 0.77–0.93) [14]. Meanwhile, some studies showed no difference in time-to-sepsis recognition [41, 46], administration of antibiotics [19, 31, 43–45, 47, 48], fluid resuscitation [41], escalation of care [19, 27, 42, 48, 49], use of vasopressors [26], and mortality [19, 29, 36–39, 42, 43, 48, 49].

Overall, the panel assessed that the balance of evidence favored the implementation of a multidisciplinary "code sepsis" response to improve outcomes in patients with sepsis. The benefit also extends to patients not found to have sepsis by mitigating morbidity and mortality through early identification of patients at risk for clinical deterioration and worse outcomes. Implementing a "code sepsis" protocol may be possible in most settings, by leveraging existing staff and existing rapid response systems. A recent study on sepsis management in 66 hospitals in 24 LMICs identified nearly one-third (28%) used an ICU outreach service [50], which could potentially be used for a code sepsis response team. Therefore, the panel issued a conditional recommendation for the use of a multidisciplinary "code sepsis" response for sepsis care. The benefit of implementing a code sepsis protocol likely varies across hospitals and health systems depending on the quality of usual care; it may provide more benefit in

settings with less robust infrastructure for sepsis recognition and treatment, but relatively less incremental benefit in settings that already have robust systems in place to rapidly identify and treat sepsis.

Screening for sepsis en route to hospital

3. 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 **New**
(conditional recommendation, very low certainty evidence)

Sepsis treatment is time-sensitive, and for the one-half of sepsis patients transported to hospitals by ambulance, the prehospital period is opportune to identify sepsis and initiate hospital notification and treatment [51–53]. Using prehospital sepsis screening tools to identify patients at high risk for sepsis and sepsis-related death could shorten time-to-treatment and improve clinical outcomes. Prehospital notification has improved timeliness of care in other acute care conditions, and diagnostic momentum initiated through ambulance screening and pre-arrival notification can improve sepsis performance [54, 55].

In a scoping review and a separate systematic review of prehospital sepsis screening tools, all had moderate ability to identify patients with sepsis in the prehospital environment [56–58]. 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 (sensitivity 73.1%; 95% CI, 71.8–74.4%; area under receiver operating curve [AUC] 0.77; 95% CI, 0.71–0.83) of studied screening tools. However, due to the lower specificity (81.6%, 95% CI, 80.4–82.7%), high rate of false-positive screens (positive predictive value 6.5%, 95% CI, 5.8–7.3%), and perceived difficulty of use in the prehospital environment, the panel refrained from recommending a specific screening tool [59]. qSOFA score had the lowest prehospital sepsis sensitivity (23.1%, 95% CI, 21.8–24.3%) [59]. These findings largely align with the test characteristics of these tools in the emergency department, suggesting that standardized screening can improve early sepsis recognition [60].

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 [44, 61–63].

Based on available evidence, the 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. Screening is likely most effective when it is combined with standard hospital pre-notification pathways and emergency department-based procedures to facilitate rapid evaluation, risk stratification, and treatment.

The use of a prehospital screening tool is likely feasible and adaptable in all geographic settings and should be a research priority in low-resource settings.

Screening for sepsis in hospital

4. For acutely ill patients in hospital, we "recommend" using NEWS, NEW2, MEWS, or SIRS over qSOFA as a single tool to screen for sepsis **Revisited**
(strong recommendation, moderate certainty evidence)

The Third International Consensus Conference on the Definitions of Sepsis (Sepsis-3) identified qSOFA as a predictor of death or prolonged ICU stay in patients with known or suspected infection, but no analysis had been performed at that time to support its use as a screening tool [1, 64]. The 2021 SSC guidelines recommended against qSOFA as a sole sepsis screening tool [65, 66]. Since then, numerous studies have investigated its use as a screening tool, with consistent findings [67–69]. 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 [70–73]. Similar findings have been reported in an LMIC [74].

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 [59]. EWS were designed to identify patients at risk of clinical deterioration from a variety of causes, and as such, they perform well in assisting with the identification of sepsis.

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 [14]. This benefit extended to non-septic patients as well [14]. This shows that qSOFA, while having a lower sensitivity for sepsis than other tools, is still useful for detecting clinical deterioration.

The use of artificial intelligence (AI) is receiving increasing attention as a tool for early screening and prediction of sepsis [75, 76]. Future research may inform practice in this area and should involve comparative studies.

Biomarkers and rapid diagnostic tests for sepsis

5. Sepsis is a clinical diagnosis and should not be ruled in or ruled out using a single biomarker or diagnostic test (good practice statement)	**New**
6. There is "insufficient evidence" to make a recommendation regarding use of novel rapid host response diagnostics	**New**

Several novel host response diagnostic tests are approved by regulatory bodies and available as diagnostic aids for sepsis. Sepsis can be straightforward to diagnose when infection is obvious and organ dysfunction is clearly related; however, diagnosis can be difficult when infection is unconfirmed and there may be alternative causes for acute organ dysfunction. Newer sepsis diagnostic tests aim to categorize patients with suspected sepsis into risk categories: for example, low, medium, and high.

Sepsis diagnostic tests use several approaches to assess the likelihood of sepsis. Some tests use WBC characteristics, for example, monocyte distribution width (MDW) and IntelliSep, which evaluate size characteristics of circulating monocytes and deformability of neutrophils, respectively [77–80]. SeptiCyte Rapid and TriVerity assess messenger RNA transcripts that are associated with infection and sepsis [81, 82]. TriVerity also seeks to distinguish viral vs. bacterial infection [82]. Sepsis ImmunoScore uses AI to combine electronic health record data with specific biomarker and cytokine measurements [83]. Additional tests assess individual serum biomarkers such as pancreatic stone protein to assess risk of sepsis [84].

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, and clinicians should familiarize themselves with an individual test's characteristics before using it. None of the tests should be considered definitive; all should be used in combination with a full clinical evaluation. 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 re-assess for sepsis. Finally, in patients with clear sepsis at presentation, for example, those with greater than 90% probability of sepsis after initial evaluation, the tests add little diagnostic or confirmatory value.

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. Improved diagnostic accuracy may result in better patient outcomes; however, no studies have assessed the clinical outcomes of a diagnostic strategy incorporating these tests. Due to the costs of these diagnostic aids, and lack of evidence that they improve patient-centered outcomes or resource utilization, the panel did not recommend the use of any specific sepsis diagnostic aids. Studies evaluating the impact of diagnostic aids on patient outcomes and resource utilization are a research priority. Thus, it is reasonable for health systems and clinicians to make use of these novel host response diagnostics when feasible, rather than studying their impact on patient outcomes and resource utilization.

Most of these novel host response biomarkers are not yet available in resource-limited settings [85, 86].

Blood cultures

7. 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 recommendation, low certainty evidence)	**New**

Identifying the causative organism in sepsis helps to optimize antimicrobial therapy, ensure that the causative pathogen is treated, support antimicrobial stewardship,

and improve patient outcomes. A pathogen is identified in approximately 60–70% of patients with sepsis, although blood cultures are positive in only approximately 10–20% of patients [87]. There is limited direct evidence evaluating the clinical benefit of blood culture testing. However, given the high mortality and morbidity associated with sepsis and the importance of appropriate antimicrobial coverage, the 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.

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 [88, 89]. The panel examined multiple guidelines and a recent scoping review stratifying the probability of bacteremia based on presenting illness, with septic shock having a greater than or equal to 50% yield [90–94]. Blood cultures are generally obtained from two different sites [91], using 10-mL blood volume per tube [95]. Multi-site collection is often recommended based on (a) the ability to distinguish pathogens from contaminants when using different venipunctures sites and (b) potential increased sensitivity for pathogen detection with two sets of cultures (e.g., one study showed sensitivity for detecting bacteremia increased from 91.5 to 99.3% when two sets of blood cultures were collected vs. one [89, 96]). However, 2025 German National Guidelines [93] recommend collecting blood cultures from a single site based on a 2025 systematic review of 7 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 10 mL, improved pathogen detection, less contamination, and require less venipuncture [89].

The number of blood cultures and the use of anaerobic bottles should be individualized, especially in low-resource settings. A small percentage (approximately 15% of blood cultures with positive growth) show growth in only anaerobic bottles [97, 98]. In most cases, however, this result does not require a change from empiric antibiotic therapy, as true anaerobic bloodstream infections usually occur in clinical situations where empiric treatment already includes anaerobic coverage [92, 99, 100]. Thus, the use of aerobic bottles alone can be justified since anaerobic cultures may not confer substantial additional benefit unless anaerobic pathogens are highly suspected. In low-resource settings, collection of a single set of blood cultures can be justified based on the 2025 systematic review showing similar yield between single vs. multiple blood culture sets [89].

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 multicenter study of 325 patients presenting to the emergency department with sepsis-induced hypotension or hypoperfusion (systolic blood pressure [SBP] < 90 mmHg or lactate ≥ 4 mmol/L), blood culture positivity decreased from 31.4% pre-antimicrobial to 19.4% at a median 70 min (interquartile range [IQR], 50–110 min) post-antimicrobial, a 12.0% absolute reduction and 38.2% relative reduction in blood culture sensitivity [101]. Wherever possible, blood cultures should be collected before administration of antimicrobial, but should not delay the initiation antimicrobial therapy, particularly in patients with hypotension.

Repeat cultures are recommended to confirm clearance of bacteremia or fungemia for *Staphylococcus aureus*, *Staphylococcus lugdunensis*, and *Candida* species [92, 102, 103].

Although the PICO question focused specifically on blood cultures, additional cultures to elucidate the source of infection should be considered (e.g., peritoneal fluid culture) depending on the suspected site of infection.

Blood lactate measurement

8. For adults with possible, probable, or definite sepsis or septic shock, we "suggest" measuring blood lactate (conditional recommendation, low certainty evidence)	**Carryover**

This statement on performance was carried over, please see the 2021 SSC guidelines for rationale [65, 66].

Initial fluid resuscitation

9. Sepsis and septic shock are medical emergencies; treatment and resuscitation should begin immediately (good practice statement)	**Carryover**
10. For adults with sepsis-induced hypoperfusion or septic shock, we "suggest" administering at least 30 mL/kg of IV crystalloid in the first 3 h (conditional recommendation, low certainty evidence) ***Remark***: Consideration should be given to individual patient characteristics and context when selecting initial fluid volume ***Remark***: Clinicians prescribing fluids should perform frequent, ongoing reassessment and closely monitor patients to avoid harms of under- or over-resuscitation ***Remark***: Weight-based fluid volume should be calculated based on actual body weight, or by adjusted or ideal body weight in patients with body mass index > 30 kg/m^2 (Table 4)	**Revisited**

Timely, effective fluid resuscitation is crucial for the stabilization of sepsis-induced tissue hypoperfusion in sepsis and septic shock. As recommended in previous SSC guidelines, 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 [65, 66, 104, 105]. Although evidence in support of 30 mL/kg stems from observational studies and include studies evaluating 30 mL/kg as part of a bundle of care practices, there are no new data suggesting a change is needed from prior SSC guidelines.

Consistent with 2016 and 2021 SSC guidelines, we suggest administering at least 30 mL/kg of IV crystalloids for initial fluid resuscitation in patients with sepsis-induced hypoperfusion or septic shock [65, 66, 104, 105]. Sepsis-induced hypoperfusion may be identified by hypotension (e.g., MAP < 65 mmHg, SBP < 90 mmHg, relative hypotension (e.g., SBP markedly below known baseline), or elevated lactate. Although lactate greater than or equal to 4 mmol/L has historically been the threshold for fluid resuscitation, intermediate lactate elevation (> 2 to < 4 mmol/L) is common in patients with sepsis [106], associated with increased mortality [106, 107], consistent with lactate threshold for the Sepsis-3 definitions of septic shock (> 2 mmol/L) [1, 107], and may also benefit from fluid resuscitation to avoid progression to overt hypoperfusion or shock [108]. Clinicians should, thus, consider fluid resuscitation in patients presenting with intermediate lactate elevation, particularly if there are no contraindications to fluid administration.

The fixed volume of 30 mL/kg is based on observational evidence [16–18, 108], with most studies using actual body weight. There are no prospective interventional studies comparing different volumes for initial resuscitation in sepsis or septic shock. 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 h 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 [109]. 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) $p < 0.01$ [110]. In the ARISE [111], ProCESS [112], and PROMISE [113] 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 [114]. 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 30 mL/kg was completed within 3 h (low certainty) [115].

Due to potential concerns of administering very large volumes of crystalloid fluid in obese patients, the panel determined that fluid volumes may be calculated using adjusted or ideal body weight in patients with high body mass index [116–118]. In low-resource settings where the availability of respiratory support may be limited, the risks of fluid overload are more pronounced, so the clinical context should be considered when ordering fluid resuscitation [119, 120]. However, prior trials suggesting harm from fluid resuscitation in low-resource settings have generally used volumes far exceeding 30 mL/kg. For example, in the SSSP-2 trial, patients randomized to the resuscitation protocol received a median 3.5 L fluid in the first 6 h (≥ 70 mL/kg based on weigh inferred from arm circumference) vs. 2.0L (~ 50 mL/kg) in the usual care arm [121]. It is important that fluid resuscitation be tailored to actual body weight in cachectic or underweight patients to avoid over-resuscitation [122]. The panel emphasized the need for clinical reassessment during and following initial fluid resuscitation to reduce the risk of either under or over-resuscitation.

Table 4 displays 30 mL/kg in liters for patients of varying heights and weights.

The SSC 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/

Table 4 30 mL/kg in liters, by weight and height

Weigh (kg) (lb.)	Height (m) (feet, inches)		
	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*

White cells, for patients with body mass index (BMI) ≤ 30 kg/m^2, display 30 mL/kg using actual body weight. Italicized values, for patients with BMI > 30 kg/m^2, display 30 mL/kg using adjusted body weight. Adjusted body weight was calculated as ideal body weight + 0.4 × (actual body weight–adjusted body weight), where ideal body weight was calculated using the Devine formula (as presented in Devine BJ, 1974 Gentamicin therapy. Drug Intell Clin Pharm 8:650) for males

kg of IV crystalloids in the initial phase" [123]. The SSC 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).

Timing of vasopressor initiation relative to fluid resuscitation

11. For adults with sepsis-induced hypotension, we "suggest" initial IV crystalloid fluid bolus resuscitation followed by vasopressor support if hypotension persists **New**
(conditional recommendation, very low certainty evidence)
Remark: 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—either immediately, concomitantly with, or after fluid resuscitation—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 [124, 125]. Persistent hypotension is associated with worse outcomes in observational studies [126].

Recent studies provide mixed evidence on the timing of vasopressor administration in sepsis-induced hypotension. Four relevant systematic reviews and meta-analyses were identified [124, 127–129]. 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 [125, 130]. However, these trials were limited by a prolonged time to shock resolution, several hours in both arms [125, 130]. Nonetheless, the findings of these trials were similar to observational studies suggesting that early vasopressor use may be associated with lower mortality [131, 132]. 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 [133]. Recent observational studies have indicated that peripheral administration of vasopressors is both feasible and safe [134, 135], so early vasopressor administration is adaptable to all settings.

The 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.

It is important to note that studies often exclude patients with severe comorbidities or in critical states, which may limit the generalizability of available evidence. Furthermore, most studies did not account for local variations in sepsis care practices, which may affect outcomes.

Further multicenter RCTs with larger sample sizes are needed to confirm the optimal timing for vasopressor initiation in sepsis-induced hypotension. There are currently five geographically diverse RCTs underway, the results of which are likely to provide further evidence on the subject: NCT05179499, NCT04569942, NCT06709573, NCT05836272, NCT05931601.

Route of vasopressor administration

12. 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 **Revisited**
(conditional recommendation, very low certainty evidence)
Remark: 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 [136]. Recent data suggest that clinicians [137] and hospital policies [138] are more comfortable with peripheral vasopressor administration than with delayed initiation of vasopressors if no central access is present.

The panel considered 1 RCT [139] 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 (hazard ratio [HR] 1.30; 95% CI, 0.84–2.01, very low certainty evidence). We

also considered observational studies which, when evaluated via meta-analysis, found an uncertain effect on mortality with peripheral vasopressor administration (2 studies [139, 140] with 611 patients, 28-day mortality aRR: 0.85; 95% CI, 0.63–1.14; 3 studies [141–143] with 1868 patients, 90-day mortality aRR: 0.89; 95% CI, 0.73–1.08; both very low certainty). Across 7 studies [139, 141–146] (1657 patients), the pooled complication rate for peripheral vasopressor administration was 5.97% (95% CI, 1.17–14.09%, very low certainty).

The panel determined that balance of effects and resource use probably favors initial peripheral vasopressor administration; however, evidence certainty was very low. Thus, we 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 [65, 66]. Existing studies demonstrating safety of peripheral vasopressor administration generally occurred in the setting of a safety protocol to ensure the peripheral IV was high quality, monitor frequently for extravasation, and treat extravasation when present, but the specific details of safety protocols vary [147]. In low-resource settings where frequent monitoring for adequacy of peripheral IVs and presence of extravasation is not feasible, peripheral vasopressors should be used with caution.

Future studies are needed to inform the optimal safety protocols for using peripheral vasopressors, including the safe duration of peripheral vasopressor use, specific vasopressor medications and maximal doses, peripheral IV access size, and peripheral IV anatomic location. Further, understanding the efficacy and safety of midline catheters [148] to administer vasopressors in adult septic shock is a research priority.

"In our practice," 86.6% of panel members use peripheral vasopressors on at least some occasions. Of these panel members, 12.1% do so only until central access can be placed. Nearly one-half (46.6%) use peripheral vasopressors for up to 6 h, 13.8% use them for up to 24 h, and 27.6% do not have a set duration for use. Vasopressor dose (79.3% of panel members), peripheral access site (70.7%), and specific vasopressor (48.3%) are common factors influencing panel members' decision to switch to central access; some panel members also consider clinical trajectory, number of vasopressors, additional indications for central access, and availability of central access supplies when deciding to transition to central administration.

Mean arterial pressure (MAP) targets

13. For adults with septic shock, we "recommend" an initial MAP target of 65 mmHg over higher MAP targets (strong recommendation, moderate certainty evidence) ***Remark*:** In practice, it is not feasible to maintain MAP at exactly 65 mmHg, so a reasonable range (e.g., within 5 mmHg) should be used. Vasopressors should be titrated to maintain MAP within this range	**Carryover with new remark**
14. For adults with septic shock 65 years old or older, we "suggest" an initial MAP range of 60–65 mmHg over higher ranges (conditional recommendation, low certainty evidence)	**New**

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 60 mmHg, are associated with decreased organ perfusion, which tracks linearly with MAP [149, 150]. The 2021 SSC guidelines recommended targeting an MAP of 65 mmHg or higher for initial resuscitation [65, 66]. The recommendation was based principally on an RCT in septic shock comparing patients who were prescribed vasopressors to target a MAP of 65–70 mmHg, vs a target of 80–85 mmHg [151]. This trial found no difference in mortality between arms, although a subgroup analysis demonstrated a 10.5% absolute reduction in renal replacement therapy (RRT) with higher MAP targets among patients with chronic hypertension. However, targeting a higher MAP with vasopressors was associated with a higher risk of atrial fibrillation. A limitation of this trial was that the average MAP in both arms exceeded the targeted range.

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 (RR, 1.05; 95% CI, 0.90–1.23, low certainty) [152]. The 65 trial subsequently compared "permissive hypotension" (MAP 60–65 mmHg) to "usual care" in patients 65 years old and older with distributive shock [153]. The intervention arm achieved a mean MAP of 67 mmHg, compared with 73 mmHg in the usual care arm [153]. Among 2463 patients analyzed, there was less exposure to vasopressors in the intervention arm, measured by duration of vasopressor infusion and total vasopressor dosing [153]. Ninety-day mortality in the permissive hypotension vs. usual care arm was similar (41.0% vs. 43.8%). 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 (RR 0.93; 95% CI, 0.76–1.07, low certainty) [154]. In a meta-analysis done for the guidelines limited to patients 65 years old or older, a lower blood pressure target was associated with reduced mortality at longest follow-up (RR 0.89, 95% CI, 0.81–0.98, high certainty). An open-label trial of 518 patients 65 years old or older randomized to a lower BP target (MAP 65–70 mmHg) compared with a higher BP target (MAP 80–85 mmHg) was published after the guidelines meta-analysis was completed [155]. This trial reported increased mortality associated with the higher MAP target.

In the absence of data to support a higher MAP target, the panel continues to recommend an initial MAP target of 65 mmHg over higher MAP targets (strong recommendation, moderate certainty evidence) and makes a new conditional recommendation for an initial MAP target of 60–65 mmHg 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 [153, 154].

There is a paucity of evidence from low-resource settings; however, implementation of these recommendations is likely to be feasible in all settings [156].

Admission to intensive care

15. For adults with sepsis or septic shock who require ICU admission, we "suggest" admitting the patients to the ICU within 6 h (conditional recommendation, low certainty evidence)	**Carryover**

This statement on performance was carried over, see the 2021 SSC guidelines for rationale [65, 66].

Infection

Timing of antibiotic initiation in hospital

16. For adults with possible, probable, or definite septic shock, we "recommend" administering antimicrobial therapy immediately, ideally within 1 h of recognition (strong recommendation, very low certainty evidence)	**Revisited**
17. For adults with probable or definite sepsis without shock, we "recommend" administering antimicrobial therapy immediately, ideally within 1 h of recognition (strong recommendation, very low certainty evidence)	**Revisited**
18. 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 h from the time when sepsis was first suspected (conditional recommendation, very low certainty of evidence)	**Revisited**
19. 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 (good practice statement)	**Revisited**
20. For adults with a low likelihood of infection and without shock, we "suggest" deferring antimicrobial therapy while continuing to closely monitor the patient (conditional recommendation, very low certainty of evidence)	**Revisited**

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 [157–159]. Delivering antimicrobial therapy to patients with sepsis or septic shock should, therefore, be treated as an emergency. This may include newly initiating antimicrobial therapy or broadening antimicrobial therapy in a patient who decompensates while being treated for infection. 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 [160, 161], including antimicrobial resistance, disruption to the microbiome [162], and other antibiotic-associated adverse events [163]. Consideration of unnecessary antimicrobial exposure is warranted since approximately 10–30% of patients initially treated for sepsis have a final diagnosis of non-infectious or non-bacterial conditions [164–168]. However, simultaneous improvement in timing of antimicrobial delivery for sepsis and antimicrobial stewardship is possible [169]. Evaluating the likelihood of infection (Table 3) and severity of illness for each patient with suspected sepsis should inform the necessity and urgency of antimicrobial therapy [160, 161] (Fig. 2).

We identified a systematic review and meta-analysis which included 42 observational studies through May 22, 2022 comprising 190,896 patients [170]. We combined the data from this meta-analysis with two additional observational studies published after May 22, 2022 [171, 172] and two RCTs [13, 173]. 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 h (vs. longer), 3 h (vs. longer), and 6 h (vs. longer) from presentation, albeit with wide CIs that included no difference. This association was present in both combined and in separate

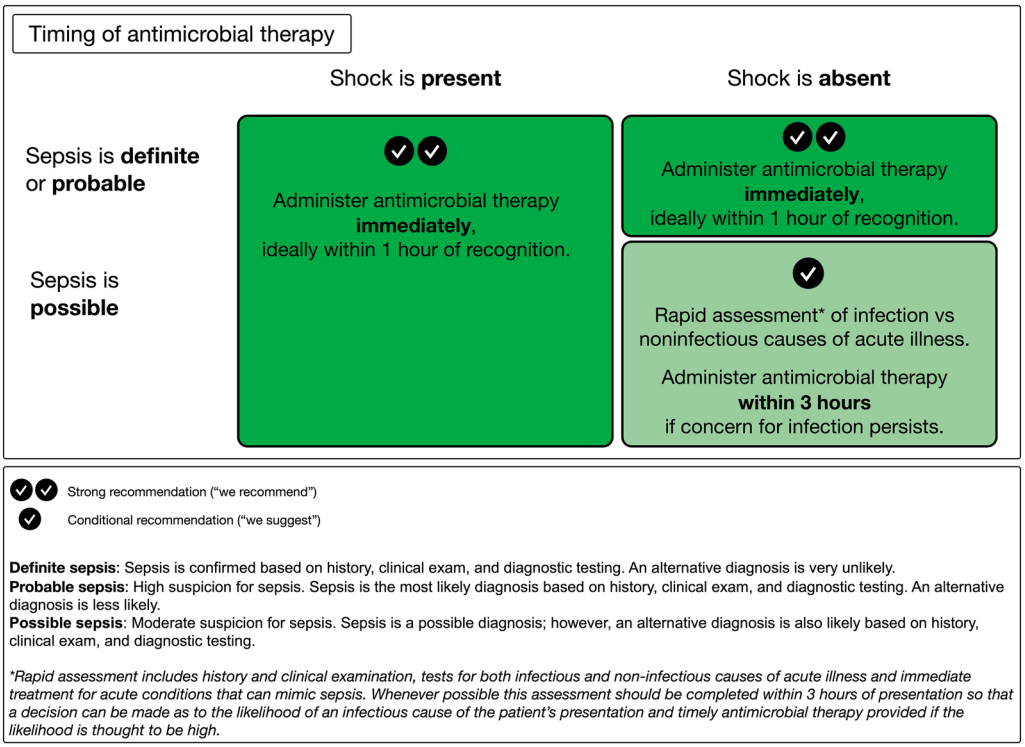

Fig. 2 Antimicrobial timing framework

analyses, including the primary analyses and in sensitivity analyses restricting the evidence to studies using the Sepsis-3 definition, as well as those providing adjusted estimates. 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 h, were selected based on the available summary estimates, while balancing the weaknesses of the underlying evidence (observational studies at high risk of bias with CIs that included no difference, and limited power in some analyses) against the high morbidity and mortality of sepsis. The two RCTs did not show an association between early treatment and reduced mortality but they primarily included patients without septic shock, and the median differences in time-to-antibiotics between the early vs. later antibiotic arms were well under 3 h [13, 173].

Despite the growth in evidence since the 2021 SSC guidelines [65, 66], the overall certainty of evidence was adjudicated as very low due to persistent risk of bias (the main body of evidence comprised 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.

To increase the certainty of evidence for the effects of early antimicrobial therapy in adults with sepsis or septic shock, large high-quality multicenter (international) RCTs would be needed. Whether these are feasible from practical, resource, and ethical perspectives is unlikely.

The recommendations on timing of antimicrobial therapy are unchanged from the 2021 SSC guidelines [65, 66].

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, the panel issued a strong recommendation to administer antimicrobial therapy immediately (within 1 h) in adults with possible, probable, and definite septic shock and in adults with probable or definite sepsis (Table 3). 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 h) assessment of infectious and non-infectious etiologies of illness. This assessment may include additional history, clinical examination, and diagnostic testing to determine whether antimicrobial therapy should

be administered. Antimicrobial therapy should be administered as soon as bacterial infection appears to be the most likely etiology of the patient's illness and after no more than 3 h if a substantial concern for bacterial infection persists.

Limited data from low-resource settings suggest that timely administration of antimicrobial therapy in patients with sepsis and septic shock is also beneficial and feasible in these settings [174–178]. Access and availability of a wide range of antimicrobial therapy may vary, however [179–183]. Similarly, the availability and turnaround time for laboratory testing, rapid diagnostic tests, and imaging also vary widely by regions and settings [176]. For this reason, the components of the rapid assessment for infectious vs. non-infectious causes of illness will vary by setting. 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" [184].

Timing of antibiotic initiation en route to hospital

21. 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 recommendation, very low certainty evidence) **New**

Remark: 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

Prehospital sepsis treatment is one way to reduce the time to antibiotic administration for the half of sepsis patients who arrive by ambulance [51–53]. Prehospital interventions are common in other conditions and have improved outcomes for acutely ill patients [185–188].

Three systematic reviews evaluated the impact of prehospital IV antibiotics on survival [58, 189, 190]. Most studies were observational. Meta-analysis of observational studies was uncertain, but suggested a possible reduction in mortality with prehospital antibiotics (OR 0.58; 95% CI, 0.41–0.84, very low certainty). Meta-analysis of RCTs also suggested that prehospital antibiotics may reduce 28-day mortality (OR 0.85; 95% CI, 0.66–1.09, low certainty), with most of the estimate weight attributed to a single trial. One high-quality trial showed no difference in 28-day mortality (RR 0.95; 95% CI, 0.74–1.24) 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 [173]. The two studies with the lowest relative mortality reduction had the lowest control group mortality, whereas the two studies with the greatest mortality reduction had the highest control group mortality [173, 191–193]. Given this relationship, the 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).

The panel also considered emergency medical services (EMS) system characteristics. In EMS systems with short transport times and rapid hospital antibiotic delivery, prehospital antibiotics may have limited benefit, whereas the impact may be greater in settings with longer transport times or prolonged within hospital delays. Some studies with the greatest time-to-antibiotic reductions were those in which delays occurred after hospital arrival [192]. Consequently, the panel limited this recommendation to those in whom the total medical contact delay (time from EMS arrival to in-hospital evaluation) [194] was projected to exceed 60 min, consistent with the recommendation to administer antimicrobial therapy within 1 h for patients with septic shock.

Prehospital antibiotic administration may not be feasible in all settings (e.g., LMIC) due to logistical, financial, and regulatory constraints; therefore, early sepsis identification and rapid hospital transport remain the highest priority. In other settings, tiered response systems mean that antibiotic availability may be limited to a small number of EMS agencies.

Based on the evidence, the panel determined that the balance of effects probably favors prehospital antibiotic administration in patients with sepsis and hypotension and who have an anticipated time to in-hospital medical evaluation of over 60 min. Prehospital antibiotic delivery, if implemented, should be integrated into regional sepsis care models to ensure availability and safety for patients most likely to benefit. Wherever possible, blood cultures should be collected before antibiotic administration.

Biomarker-guided initiation of antimicrobial therapy

22. 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 recommendation, very low certainty evidence) **Carryover**

This statement on performance was carried over, see the 2021 SSC guidelines for rationale [65, 66].

Source control

23. 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)	**Carryover**
24. 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 h of diagnosis of sepsis or septic shock requiring source control (conditional recommendation, very low certainty evidence)	**Revisited**

Source control is a fundamental principle in the management of sepsis and septic shock [66, 195]. It encompasses surgical and procedural interventions to remove the source of infection, reduce the pathogen burden, or correct anatomical issues that impede normal clearance of infection. Examples include draining an abscess, debriding infected necrotic tissue, removing a potentially infected device, or relieving anatomical blockage such as a biliary stricture [196]. Common foci of infection that are amenable to source control include intra-abdominal abscesses, peritonitis due to gastrointestinal perforation, cholangitis, cholecystitis, pelvic abscesses, pyelonephritis associated with obstruction or abscess, necrotizing soft-tissue infection, other deep space infections (e.g., empyema or septic arthritis), and infections related to implanted devices including central catheters [196, 197]. Source control should be achieved as soon as possible following initial resuscitation [198, 199], but the optimal timeframe is unclear.

We identified 11 relevant observational studies [198–208]. Studies defined early source control in various ways, most commonly as source control within 6 h 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 (RR 0.70; 95% CI, 0.51–0.95, very low certainty), 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 1-year mortality (RR 0.80; 95% CI, 0.71–0.95, very low certainty), as compared with late source control. ICU LOS may be slightly reduced (MD 2.4 d fewer; 95% CI, 6.3 d fewer to 1.5 d more, very low certainty), while the impact of hospital LOS (MD 1.1 d fewer, 8.5 d fewer to 6.3 d more) was trivial.

Based on the association between early source control and improved clinical outcomes, the panel issued a conditional recommendation for early source control in adults with sepsis or septic shock and a specific anatomical diagnosis or source of infection that requires source control, as compared with late source control. Any required source control intervention in patients with sepsis or septic shock should ideally be implemented as soon as medically and logistically practical and safe after the diagnosis is made [200]. Given the observational studies that typically reported early source control as within 6 h, the panel proposed this timeframe, but earlier source control is consider better when feasible. Prolonged efforts at medical stabilization without source control for severely ill patients, particularly those with septic shock, are unlikely to succeed [209].

The recommendation for early source control is consistent with the 2021 SSC guidelines, which included a best practice statement in favor of early source control [65, 66], as well as other guidelines [210–214].

Additional data on the optimal source control interventions, for example, invasive vs. minimally invasive source control and percutaneous drainage vs. surgery, and relevant measures of adequate resuscitation before source control procedures are research priorities.

Empiric multidrug resistant (MDR) pathogen coverage

25. 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 recommendation, very low certainty evidence) ***Remark***: 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	**New**
26. 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 recommendation, very low certainty evidence)	**New**

The decision on whether to include an antimicrobial agent active against specific multidrug-resistant (MDR) pathogen(s) of concern in the empiric treatment regimen for adults with sepsis or septic shock depends upon (1) the likelihood that the patient's infection is caused by a specific MDR pathogen, (2) the risk of undesirable effects associated with withholding empiric treatment for a specific MDR pathogen, (3) the risk of undesirable effects associated with empiric treatment that includes coverage for a specific MDR pathogen in a person without infection with this specific MDR pathogen, and (4) patient's severity of illness. MDR pathogens, defined as those with acquired non-susceptibility to least one agent in three of more antimicrobial categories [215, 216], include *Acinetobacter baumannii*, extended-spectrum β-lactamase (ESBL)-producing Gram-negative bacteria, carbapenem-resistant

Enterobacterales (CRE), vancomycin-resistant *Enterococcus*R *pseudomonas*, and methicillin-resistant *S. aureus* (MRSA) [217]. The incidence of different MDR pathogens varies by setting and by patient characteristics [217, 218]. Patient-related risk factors for MDR pathogens include colonization with the MDR pathogen of concern in the prior year, infection with the MDR pathogen of concern in the prior year, prolonged use of broad-spectrum antibiotics, and prolonged hospitalization in a hospital with a high prevalence of the MDR pathogen of concern [219–222].

We identified 1 relevant RCT examining *A. baumannii* [223], 4 RCTs examining ESBL-producing Gram-negative bacteria [224–227], 5 RCTs examining CRE [228–232], and a systematic review of 15 observational studies examining MRSA infections [233].

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 (OR 0.71; 95% CI, 0.56–0.92, very low certainty). This effect was driven by the observational data evaluating MRSA infection. There was no observed difference in short-term mortality for patients with *A. baumannii*, ESBL-producing Gram-negative bacteria, or CRE treated with agents active against these pathogens vs. agents that were not.

The panel determined that the balance between the desirable and undesirable effects of empiric MDR coverage varies by setting and patient-related characteristics and that MDR coverage in every adult with sepsis or septic shock would be unacceptable and result in increased harm, particularly as a minority of sepsis cases worldwide are caused by MDRs [4, 234–236]. However, selective use of empiric MDR coverage is warranted in patients with risk factors for MDR infection, including in many patients with hospital-acquired infections.

Additional data on the efficacy and safety of empiric MDR pathogen coverage are warranted, along with studies evaluating nasal swab testing, rapid diagnostic tools, and clinical prediction rules for the selection of patients for specific MDR coverage.

Failure to cover specific MDR pathogens in a patient with sepsis or septic shock caused by that specific pathogen may be harmful, but unnecessary specific MDR coverage in a patient without that specific pathogen may also be harmful. Therefore, the panel issued a conditional recommendation for using empiric MDR coverage in patients with a likelihood of infection with a specific MDR pathogen.

Specific guidance on antibiotic selection is beyond the scope of this guideline. We direct readers to relevant European Society of Clinical Microbiology and Infectious Diseases and Infectious Diseases Society of America guidelines on the treatment of MDR pathogens [216, 237]. Also, where available, consultation with infectious disease specialists and/or clinical microbiologists should be considered to help with selection of antimicrobial therapy in patients with risk factors for MDR pathogens.

Empiric antifungal coverage

27. For adults with sepsis or septic shock, we "suggest against" using empirical antifungal therapy (conditional recommendation, low certainty evidence) ***Remark***: 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	**Revisited**

Sepsis and septic shock due to fungi are most commonly observed in patients in the ICU and are associated with poor outcomes [103, 238–241]. While prompt initiation of early appropriate empiric antibacterial therapy is warranted in adults with sepsis or septic shock, the impact of adding empiric antifungal therapy is less certain [239, 242–244]. Although patients with sepsis or septic shock may not benefit from empiric antifungals in general, selected patients with a high absolute risk for fungal infection probably will benefit. Risk factors for fungal infection include immunosuppression, prolonged exposure to antibacterial drugs, prolonged hospitalization, and an intra-abdominal source of infection [245].

We identified a relevant systematic review and meta-analysis of seven RCTs [246], including the EMPIRICUS trial [247]. No additional trials were identified, and the evidence base was unchanged from the 2021 SSC guidelines [65, 66].

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 (RR 0.93; 95% CI, 0.66–1.32, low certainty).

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.

The recommendation is consistent with other recent guidelines [210, 248].

Additional data on the efficacy and safety of empiric antifungal therapy in specific subgroups of patients with risk factors are warranted.

Failure to use empiric antifungal therapy in a patient with a fungal infection may be harmful, but unnecessary use of empiric antifungal therapy in a patient without a fungal infection may also be harmful. Therefore, the panel issued a conditional recommendation against the use of empiric antifungal therapy in all adults with sepsis or septic shock but rather to consider empiric antifungal therapy in selected patients with high absolute risk of fungal infection.

Empiric anaerobic coverage

28. For adults with sepsis or septic shock without risk factors for anaerobic infection, we "suggest" using an empiric antibiotic regimen without anaerobic coverage (conditional recommendation, very low certainty of evidence) ***Remark***: 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	**New**
29. 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 recommendation, very low certainty of evidence) ***Remark***: 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	**New**

The prevalence of sepsis and septic shock due to anaerobic bacteria is low, compared with aerobic bacteria and fungi [217]. Prompt initiation of appropriate empiric antimicrobial therapy is warranted in adults with sepsis or septic shock, and the decision to include or withhold anaerobic coverage depends on the anatomical site of infection, which influences likelihood of anaerobic infection [249]. Patients with sepsis or septic shock, particularly of lung or urinary origin, are unlikely to benefit from empiric anaerobic coverage; by contrast, selected patients with specific risk factors for anaerobic infection will likely benefit [250, 251]. Clinical scenarios with increased risk of anaerobic infection include intra-abdominal, gynecological, and obstetric sources of infection, necrotizing soft-tissue infection, head and neck infection, empyema, and CNS abscesses [252, 253].

We identified a relevant systematic review and meta-analysis of two RCTs [254] that comprised the primary evidence base. Furthermore, we identified several relevant observational studies [255–257]. The panel also discussed whether to include the ACORN trial (comparing empiric cefepime vs. piperacillin-tazobactam), but did not do so, since it did not adequately fit the PICO question [258]. ACORN was deemed too indirect as it compared two specific antibiotics, not inclusion of anti-anaerobic coverage, and many patients in the cefepime arm were co-treated with metronidazole for anti-anaerobic coverage [258].

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 (RR 1.56; 95% CI, 0.39–6.35, very low certainty). Observational studies suggested an increased risk of adverse outcomes, including increased mortality in patients treated with empiric anti-anaerobic antibiotics [255–257].

The panel agreed that routine empiric anti-anaerobic coverage is not indicated.

The recommendation is consistent with other guidelines [259, 260] and in line with research on the anaerobic microbiome [261]. It is also applicable to low-resource settings.

Additional trial data on the efficacy and safety of empiric anaerobic coverage in adults with sepsis or septic shock are warranted, given the suggestion of harm in observational studies.

Withholding empiric anaerobic coverage in an adult with anaerobic infection may be harmful, but unnecessary use of empiric anaerobic coverage in an adult without anaerobic infection may also be harmful [255–257]. Therefore, the panel issued conditional recommendations for including vs. withholding empiric anaerobic coverage based on risk of anaerobic infection.

Microbiological surveillance to guide empirical antimicrobial therapy

30. There is "insufficient evidence" to make a recommendation regarding use of departmental (*i.e.,* ICU-wide) microbiological surveillance samples of the upper respiratory tract to guide empirical antimicrobial therapy	**New**

Infections with multidrug-resistant organisms, especially healthcare-associated infections, are a global concern [262]. Active surveillance cultures can be used to identify patients colonized with multidrug-resistant organisms, which may inform preventive measures, including isolation, to reduce transmission, and to guide empiric antimicrobial therapy [217, 263]. Active surveillance cultures of the upper respiratory tract may be particularly useful to guide empiric antimicrobial therapy of respiratory infections, including ventilator-associated pneumonia (VAP).

We identified two systematic reviews on screening strategies [264, 265], implemented at the department or

unit level, to detect carbapenem-resistant Gram-negative bacteria, but none of the included trials assessed microbiological surveillance samples of the upper respiratory tract. We also identified an older diagnostic test accuracy review, but no relevant clinical outcomes were assessed [266]. Thus, the body of evidence was insufficient to make a recommendation regarding the use of microbiological surveillance samples of the upper respiratory tract to guide empirical antimicrobial therapy.

"In our practice," 36% of the panel uses departmental surveillance samples of the upper respiratory tract to guide empirical antimicrobial therapy, whereas 64% of the panel does not. Among the panel members using surveillance samples, the majority (79%) collect samples weekly.

With increasing prevalence of some multidrug-resistant organisms [267] and insufficient evidence to inform a recommendation regarding the use of surveillance cultures of the upper respiratory tract, the panel believes that knowledge about the clinical effects of surveillance cultures of the upper respiratory tract to guide empirical antimicrobial therapy is a research priority.

Pathogen-specific rapid diagnostic tests

31. 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 recommendation, low certainty evidence) **New**

Pathogen-specific rapid diagnostic tests are used to guide empiric antimicrobial therapy [268]. Such tests 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 antimicrobial therapy. This may enable clinicians to better target antimicrobial therapy, thereby improving clinical outcomes and reducing both the unnecessary prescription of broad-spectrum antimicrobial therapy and the development of antimicrobial resistance.

We identified a relevant systematic review and meta-analysis of six RCTs [269] and supplemented this with one additional RCT since its publication [270]. The review included trials assessing different types of pathogen-specific rapid diagnostic tests, including molecular testing platforms and phenotypic assays in adults with bloodstream infection.

There was possibly little to no difference in short-term mortality with the use of pathogen-specific rapid diagnostic tests, as compared with not using them (RR 1.03; 95% CI, 0.78–1.13, low certainty).

The panel agreed that the tests should not be used in every adult with sepsis or septic shock, as generalized use of them in all adults with sepsis or septic shock is expected to result in increased costs without being clearly beneficial to all patients. The use of these tests in selected patients, however, may reduce the time to appropriate and definite antimicrobial therapy, which may in turn improve outcomes and reduce antimicrobial resistance. The use of these tests in isolation may have a limited impact on patient-important outcomes [271–273], but mortality benefits have been observed when rapid diagnostic tests are paired with effective antimicrobial stewardship programs [274].

Additional trial data on the efficacy and safety of subtypes of pathogen-specific rapid diagnostic tests in high-risk patients with sepsis or septic shock, cost-effectiveness, and the long-term effects, including on antimicrobial resistance patterns, were identified as research priorities.

Although the use of pathogen-specific rapid diagnostic tests is not indicated in all adults with sepsis or septic shock, it may optimize the use of antimicrobial therapy in some. Therefore, the panel issued a conditional recommendation for the use of pathogen-specific rapid diagnostic tests in selected adults with sepsis or septic shock, based on clinical features, local pathogen- and resistance patterns, seasonality, and availability of tests and antibiotic stewardship guidance. Since most low-resource settings do not have access to these tests, the generalizability of this recommendation to LMICs is limited.

Candida fungal biomarkers to guide initiation of antifungal therapy

32. For adults with sepsis or septic shock, we "suggest against" using *Candida* fungal biomarkers to guide initiation of empiric antifungal therapy **New**
(conditional recommendation, low certainty evidence)
Remark: Use of *Candida* biomarkers to guide initiation of empiric antifungal therapy may be considered on a case-by-case basis in selected patients at high risk of *Candida* infection, including those with immunosuppression, prolonged exposure to antibiotics, prolonged hospitalization, and intra-abdominal source of infection

Sepsis and septic shock caused by fungi are less common but associated with poor outcomes [103, 238–241]. Although it is crucial to start appropriate empiric antibacterial therapy promptly in adults with sepsis or septic shock, the benefit of adding empiric antifungal therapy remains uncertain [239, 242–244]. Antifungal therapy is

associated with clinically important undesirable effects, including drug–drug interactions, nephrotoxicity, hepatotoxicity, hyponatremia, phototoxicity, visual disturbances, encephalopathy, peripheral neuropathy, and selection of resistant fungi [275–278]. Empiric use of antifungal therapy is, therefore, not indicated for all patients with sepsis or septic shock, but may be beneficial in selected patients at high absolute risk of fungal infection. Generally, patients with sepsis or septic shock may not benefit from empiric antifungals, but utilizing fungal biomarkers may help identify patients who may benefit [279].

We identified one relevant RCT that assessed the use of (1,3)-β-D-glucan to guide initiation of empiric antifungal therapy in septic patients with high risk of invasive *Candida* infection [280]. Use of (1,3)-β-D-glucan to guide initiation of empiric antifungal therapy resulted in a possible slight decrease in mortality, as compared with not using the biomarker (RR 0.95; 95% CI, 0.71–1.28, low certainty).

The panel agreed that *Candida* biomarkers should not be used to guide the initiation of empiric antifungal therapy in every adult with sepsis or septic shock, as this is expected to result in increased costs with uncertain benefits. Use in selected patients at high risk of invasive candidiasis, however, may be relevant and improve clinical outcomes and reduce antimicrobial resistance.

The recommendation is consistent with other recent guidelines [210, 248] and aligns with the conditional recommendation against empiric antifungal therapy in this guideline. The International Guideline on Candidiasis moderately recommends using serum (1,3)-β-D-glucan for diagnosis of invasive *Candida* infection, but cautions that diagnosis should not be based solely on (1,3)-β-D-glucan, and that (1,3)-β-D-glucan alone is not recommended for initiating antifungal therapy [248].

Additional trial data examining the efficacy and safety of using fungal biomarkers to guide the initiation of empiric antifungal therapy is a research priority.

Failure to give empiric antifungal therapy to a patient with fungal infection may be harmful, but unnecessary use of empiric antifungal therapy in a patient without fungal infection may also be harmful. Therefore, the panel issued a conditional recommendation against the use of *Candida* biomarkers to guide initiation of empiric antifungal therapy in adults with sepsis or septic shock, whereas their use in selected patients based on an assessment of the risk of fungal infection may be considered.

Prolonged infusion of β-lactam antibiotics

33. 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 recommendation, moderate certainty evidence)	**Revisited**

Key pharmacokinetic parameters of beta-lactam antibiotics can change in patients with sepsis and septic shock, potentially leading to sub-therapeutic concentrations [281, 282]. 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 [283, 284]. The shorter the half-life of the drug, the greater the impact of extended or continuous infusion on drug concentrations. Whether the prolonged infusion translated into improved outcomes was previously unclear, but additional evidence from large RCTs has become available.

We identified a recent systematic review and meta-analysis of 18 RCTs (9108 participants) [285], including the large international BLING III RCT [286]. 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 1000 patients, 95% CI, 42 fewer to 8 fewer). In the one RCT that assessed days alive outside of ICU and hospital, prolonged infusion of beta-lactams likely resulted in more days alive out of ICU (MD 1.5 d more, 95 CI, 0.1 fewer to 3.0 more, moderate certainty) and out of the hospital (MD 1.8 d more, 95 CI, 0.3 more to 3.3 more, high certainty) than intermittent infusion (bolus) [286].

Prolonged infusion is a viable intervention when suitable IV access is available and when resources can ensure that the beta-lactam is infused over the required duration. This may pose challenges in low-resource settings with insufficient supply of infusion pumps. Increasing the supply of necessary supplies to administer prolonged infusion of beta-lactams should be prioritized given the very high probability of mortality benefit, particularly when using beta-lactams with a shorter half-life (e.g., piperacillin-tazobactam, carbapenems).

Administering a loading dose of the antibiotic before prolonged infusion is crucial to avoid delays in reaching effective beta-lactam concentrations [287]. Throughout therapy, both extended and continuous infusions will occupy a venous catheter lumen for a longer duration than intermittent infusions, making drug stability and drug–drug compatibility important considerations to

ensure the effectiveness of antibiotic and other IV drug therapies [288, 289].

The recommendation is consistent with the 2021 SSC guidelines [65, 66], but with BLING III [286] data available, the certainty of evidence was assessed as high. This informed a strong recommendation in favor of the intervention. By contrast, the Dutch guidelines for empirical antibacterial therapy for sepsis include a strong recommendation for prolonged or continuous infusion of piperacillin-tazobactam and carbapenems, but a conditional (weak) recommendation for prolonged of continuous infusion of other beta-lactam antibiotics due to their longer half-life [290].

The research priorities include the effects of prolonged infusions on the emergence of antimicrobial resistance.

Therapeutic drug monitoring (TDM) of antimicrobial therapy

34. 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 recommendation, very low certainty evidence)	**Revisited**

Antimicrobial therapy is subject to changes in pharmacokinetic (PK) and pharmacodynamic (PD) properties in sepsis and septic shock [291, 292]. This may result in concentrations that are either too low (risking clinical failure) or too high (potentially leading to toxicity) [293]. Augmented renal clearance [294], acute kidney injury [295], hypoalbuminemia [296], RRT [297, 298], extracorporeal life support [299, 300], and other conditions affect concentrations of many antimicrobials in critically ill patients. Therapeutic drug monitoring (TDM) is a dosing intervention applying PK/PD principles that may result in more effective and safe dosing of antimicrobial therapy [301].

We identified a recent systematic review and meta-analysis of 8 RCTs (1241 participants) [302] with 6 trials assessing TDM of antibacterials and 2 trials assessing TDM of antifungals. The results of the meta-analysis were uncertain (very low certainty evidence). However, point estimates suggested a possible reduction in short-term mortality with the use of TDM, as compared with not using TDM (RR 0.92, 95% CI, 0.75–1.11, very low certainty) [302], whereas the effects for ICU LOS (MD 0.01 d fewer; 95% CI, 2.27 d fewer to 2.25 d more, very low certainty) and hospital LOS (MD 0.20 d more; 95% CI, 6.03 d fewer to 6.42 d more, very low certainty) were considered trivial. The potential effect on short-term mortality was driven by the trials assessing TDM of antibacterials.

The use of TDM to guide dosing of antimicrobial therapy may require extra resources, and may therefore result in increased costs and reduced equity, especially in resource-limited areas where there is limited access to TDM.

The recommendation is consistent with the 2021 SSC guidelines, which included a best practice statement to use accepted pharmacokinetic/pharmacodynamic principles [66], and consistent with other guidelines [301].

The research priorities include additional trial data on short- and long-term mortality, emergence of antimicrobial resistance, and health economic analyses.

Based on a potential effect of TDM on the assessed desirable outcomes and no indication of harm, the panel suggests using TDM as an optimized dosing approach applying PK/PD principles in selected adults with sepsis and septic shock, and if the necessary equipment for TDM is available.

Antimicrobial de-escalation and discontinuation

35. 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 (good practice statement)	**Revisited**
36. 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 recommendation, very low certainty evidence) ***Remark***: De-escalation involves discontinuing unnecessary antimicrobial therapy or narrowing the spectrum of antimicrobial agents where appropriate	**Revisited**
37. 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 recommendation, very low certainty evidence)	**Revisited**

Antimicrobial exposure is associated with development of antimicrobial resistance, potential toxicities, and risk for *Clostridioides difficile* infection [163, 167, 303]. Reducing both the number and the spectrum of antimicrobial agents may help avert some of these adverse outcomes and is a key goal in hospital antimicrobial stewardship [304, 305]. Broad-spectrum regimens are common during the empiric phase of treating sepsis when the causative pathogen has not yet been identified. Once pathogen identity and susceptibilities are determined, timely de-escalation of antimicrobial therapy, including stopping unnecessary antimicrobial therapy

and switching to narrower spectrum agents, is a logical approach [306].

We identified direct evidence from 26 studies, including 2 RCTs [307, 308]. Meta-analysis was uncertain (very low certainty evidence). However, point estimates suggested a possible reduction in short-term mortality (26 studies, RR 0.77, 95% CI, 0.64–0.92, very low certainty), ICU LOS (5 studies 0.93 d fewer; 95% CI, 4.42 d fewer to 2.56 d more, very low certainty), hospital LOS (4 studies, 1.7 d fewer, 95% CI, 1.8 fewer to 1.6 fewer, very low certainty), and antimicrobial resistance (6 studies, RR 0.71, 95% CI, 0.55–0.91, very low certainty) 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 2 RCTs were comparable. Nonetheless, this allows for the possibility that the observed effects of de-escalation in observational studies may be mediated by de-escalation in patients who are already improving (i.e., confounding by indication). The reported improvements in clinical outcomes with de-escalation should, therefore, be interpreted with caution [306, 309].

The recommendations on de-escalation of empiric antimicrobial therapy are consistent with other guidelines [305, 306, 310], as well as prior SSC guidelines [65, 66].

Additional data from larger RCTs are needed to confirm the proposed significant desirable effects from de-escalation, including the effect on antimicrobial resistance.

De-escalation appears safe, may offer cost savings when unnecessary antimicrobial therapy are discontinued, and likely results in a reduction in the risk of antimicrobial resistance, toxicity, and drug–drug interactions [311]. Therefore, the panel issued a strong recommendation for de-escalation of empiric antimicrobial 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 decision to de-escalate antibiotics in the absence of a confirmed pathogen depends on the clinical context and setting. In low-resource settings with limited or low-quality laboratory services and high rates of MDR pathogens, negative culture testing may not provide the same reassurance as in settings with high-quality laboratory services available, so the risk of undetected MDR pathogens should be weighed carefully before antibiotic de-escalation.

Biomarker guidance for discontinuing antifungal therapy

38. For adults with sepsis or septic shock who are receiving empiric antifungal therapy, we "suggest against" use of *Candida* fungal biomarkers to guide discontinuation of empiric antifungal therapy (conditional recommendation, low certainty evidence) **New**

Remark: Use of *Candida* biomarkers to guide discontinuation of empiric antifungal therapy may be considered on a case-by-case basis in clinically improving selected patients at high risk of *Candida* infection, including patients with immunosuppression, prolonged use of antibiotics, prolonged hospitalization, and intra-abdominal source of infection

We identified three relevant RCTs [312–314]. All three trials assessed the use of (1,3)-β-D-glucan and/or mannan biomarkers to guide discontinuation of empiric antifungal therapy in adult ICU patients with suspected invasive fungal infection.

There was possibly little to no difference in short-term mortality (3 trials, RR 1.03; 95% CI, 0.72–1.48, low certainty), a possible small increase in hospital LOS (1 trial 1.8 d more, 95% CI, 4.1 d fewer to 7.7 d more, low certainty), and a possible increase in ICU LOS (1 trial 5.5 d more, 95% CI, 0.9 d fewer to 11.9 d more, low certainty) with the use of *Candida* biomarkers to guide discontinuation of empiric antifungal therapy, as compared with not using biomarker-guided discontinuation.

The panel agreed that *Candida* biomarkers should not be used to guide discontinuation of empiric antifungal therapy in all patients, as the balance of effects favors not using them, and uncritical use would result in increased costs without clinical benefit. Their use in selected high-risk patients (e.g., patients with immunosuppression, prolonged use of antibiotics, prolonged hospitalization, and intra-abdominal source of infection) may be relevant in some settings, as it may reduce duration of antifungal treatment and thereby reduce the risk of undesirable effects, including selection and antimicrobial resistance. The recommendation is consistent with other recent guidelines [210, 248].

Additional trial data on the efficacy and safety of using fungal biomarkers to guide discontinuation of empiric antifungal therapy, including in subgroups of patients with confirmed invasive fungal infection, were identified as a research priority.

The unnecessary use of antifungal therapy is associated with undesirable effects, including selection for antimicrobial resistance. Use of *Candida* biomarkers to assist in discontinuing empiric antifungal therapy in adult ICU patients does not appear to improve outcomes.

Therefore, the panel issued a conditional recommendation against the use of *Candida* biomarkers to guide discontinuation of empiric antifungal therapy in all adults with sepsis or septic shock, whereas it may be considered in selected patients at high risk for invasive candidemia.

Duration of antimicrobial therapy

39. For adults with an initial diagnosis of sepsis or septic shock and adequate source control, we "suggest" using shorter over longer duration of antimicrobial therapy (conditional recommendation, very low certainty evidence)	**Carryover**

This statement was carried over, please see the 2021 SSC guidelines for rationale [65, 66]. Since the 2021 guidelines, the BALANCE trial comparing 7 vs. 14 days of antibiotic treatment for bloodstream infection was published, showing non-inferiority of a 7 day treatment duration—providing further support for shorter treatment durations.

Biomarker guidance for antibiotic discontinuation

40. 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 recommendation, low certainty evidence)	**Carryover**

This statement was carried over, see the 2021 SSC guidelines for rationale [65, 66]. Since the 2021 guidelines, the ADAPT-Sepsis RCT provided additional evidence that procalcitonin can be used to safely reduce antibiotic duration in patients with sepsis [315].

Selective decontamination of the digestive tract

41. In mechanically ventilated adults with sepsis or septic shock in units with a low prevalence of antimicrobial resistance, we "suggest" using selective decontamination of the digestive tract (conditional recommendation, moderate certainty evidence)	**New**

Selective decontamination of the digestive tract (SDD) is a preventive infection control strategy consisting of the administration of non-absorbable, topical antimicrobial agents to the oropharynx and upper gastrointestinal tract (oropharyngeal decontamination), with the administration of a short-term course of broad-spectrum IV antimicrobial therapy in mechanically ventilated patients. The topical antimicrobial agents used typically include a polymyxin, tobramycin and amphotericin B, targeting aerobic Gram-negative bacteria and fungi while sparing anaerobes. SDD is specifically designed to eliminate pathogenic aerobic bacteria while preserving anaerobic gut bacteria, essential to digestion and immune function. It has been suggested that SDD improves clinical outcomes, including mortality in mechanically ventilated adults, through a reduction in the incidence of VAP and bloodstream infections [316]. On the other hand, there are concerns that SDD might increase the rate of antimicrobial resistance, although this has not been confirmed in most studies [317, 318]. Recently, additional evidence from large RCTs has become available.

We identified an up-to-date systematic review and meta-analysis of 32 RCTs (24,389 participants) [319], including the large international Selective Decontamination of the Digestive Tract in ICU Patients (SuDDICU) trial [320]. Large RCTs on SDD in settings with high MDR prevalence are lacking.

The meta-analysis suggested a probable reduction in short-term mortality (30 trials, RR 0.91; 95% CI, 0.82–0.99, moderate certainty), more days alive of the ICU (1 trial, 1.75 d more; 95% CI, 0.62 more to 4.12 more, moderate certainty), more days alive outside of hospital (1 trial, 1.34 d more; 95% CI, 0.89 fewer to 3.58 more, moderate certainty), and possibly less antimicrobial resistance (RR 0.64; 95% CI, 0.50–0.81, 39–103 fewer events per 1000 patients, low certainty) with the use of SDD as compared with no SDD in mechanically ventilated adults [319]. Counter to concerns, SDD appeared to reduce antimicrobial resistance rates. The desirable effects of SDD appeared to be mainly driven by the trials with individual patient randomization and those using SDD in combination with a broad-spectrum IV antimicrobial agent targeting aerobic Gram-negative bacteria [319].

The panel found it important to consider the local prevalence of antimicrobial resistance when deciding on using SDD or not, as the balance between the desirable and undesirable effects may be different in settings with a high vs. low prevalence of antimicrobial resistance. In low-resource settings where the prevalence of antimicrobial resistance is high and there is limited availability of antimicrobial therapy, SDD should be implemented on an ICU-by-ICU basis.

The SuDDICU trial was published after SSC guideline recommendations were finalized [321]. In this trial, randomization to SDD was associated with similar 90-day mortality (27.9% vs. 29.5%), fewer new blood stream infections (4.9% vs. 6.9%), and fewer antibiotic-resistant organisms cultured (16.8% vs. 26.8%) [321].

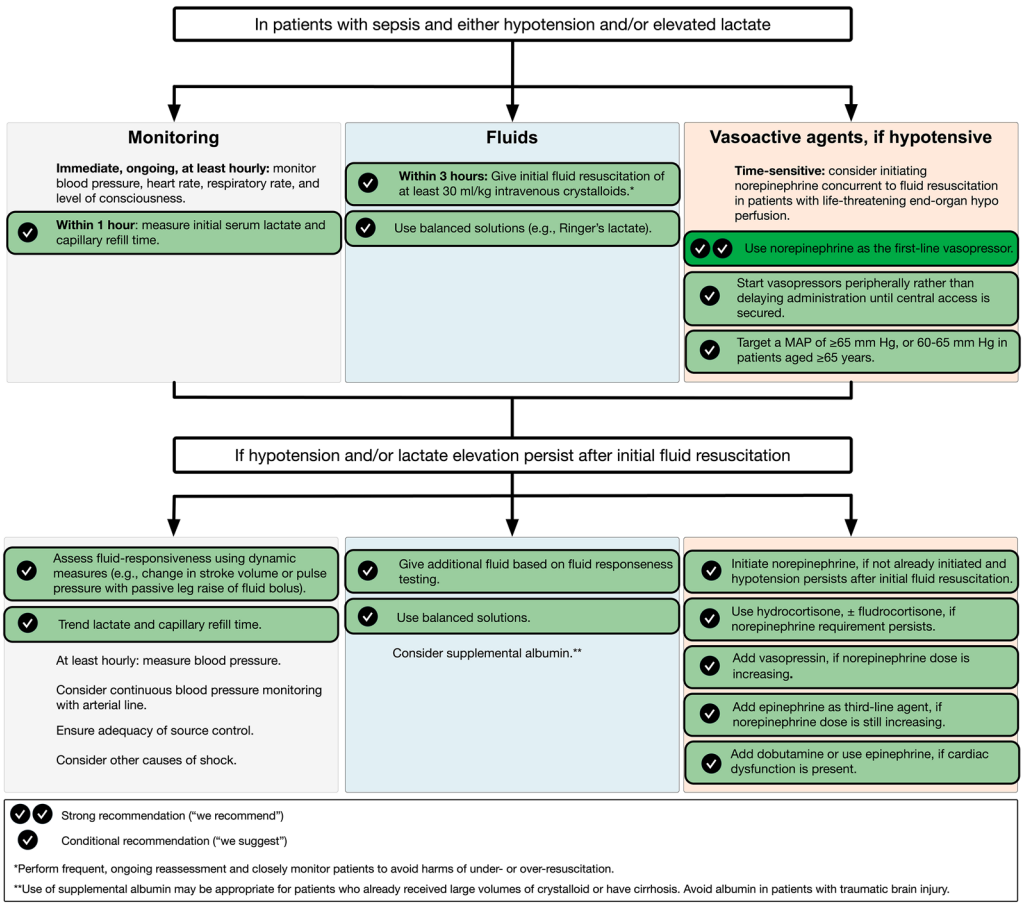

Fig. 3 Quick guide for resuscitation and hemodynamic support in adults with sepsis and septic shock. This figure is intended a quick reference summarizing hemodynamic monitoring and interventions for patients with sepsis-induced hypotension of hypoperfusion. It is not an exhaustive summary of statements on resuscitation included in the Surviving Sepsis Campaign guidelines. We prioritized inclusion of recommendations in this figure to quickly assist with bedside management, including the monitoring and interventions most commonly used in clinical practice

Based on the suggested improved clinical outcomes from SDD in mechanically ventilated adults, including a potential reduction in short-term mortality, the panel issued a conditional recommendation for the use of SDD in mechanically ventilated adults with sepsis or septic shock in settings with a low prevalence of antimicrobial resistance. In settings with a higher prevalence of antimicrobial resistance, the effects of SDD on the individual level must be balanced against the potential effects on antimicrobial resistance, although SDD has not been shown to increase antimicrobial resistance.

Hemodynamic management

A quick guide for resuscitation and hemodynamic support in adults with sepsis and septic shock is presented in Fig. 3. This figure is not a comprehensive summary of hemodynamic management recommendations in the SSC guidelines, but rather a quick reference to summarize the hemodynamic monitoring and resuscitation interventions most often used in clinical practice.

Blood pressure monitoring

42. For adults with septic shock, we "suggest" using either invasive or non-invasive blood pressure monitoring (conditional recommendation; very low certainty evidence) ***Remark***: 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 non-invasive blood pressure measurements which are inconsistent on repeated assessments	**Revisited**

Arterial catheters allow for continuous blood pressure monitoring and frequent blood sampling, hence they are commonly used in critically ill patients. However, variability in use exists across ICUs [322, 323]. Potential benefits include continuous and more accurate blood pressure 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 [65, 66] suggested invasive blood pressure monitoring as soon as practical and if resources are available based on the discordance of invasive and non-invasive measurements.

The panel identified one RCT [324] in which adults admitted to the ICU were randomized in weekly blocks to restricted use or standard use of arterial catheters. However, this study was reported only in abstract form, considered a mixed population (not just sepsis), and had minimal separation in monitoring device use between groups; therefore, it was not considered in recommendation formulation. Instead, we relied on 4 observational studies [325–328] (28,516 total patients) assessing clinical outcomes and 12 studies [329–340] (57,114 total patients) evaluating blood pressure concordance; all evidence was of very low certainty. Despite the very low certainty evidence, no difference was observed in mortality (5 studies for invasive vs. non-invasive monitoring: adjusted OR 1.06; 95% CI, 0.93–1.12) or RRT (1 study: adjusted OR 1.07; 95% CI, 0.66–1.73). Invasive monitoring was associated with more acute kidney injury (1 study: adjusted OR 1.36; 95% CI, 1.22–1.51) and longer lengths of stay (3 studies, ICU LOS: MD 1.61; 95% CI, 1.13–2.10 more days; 3 studies, hospital LOS: MD 3.51; 95% CI, 2.56–4.46 more days); yet potentially substantial residual confounding likely exists. Complications were observed in 2.89% (95% CI, 2.18–3.70%) of arterial catheters in one study. Concordance of non-invasive with invasive blood pressure measurements (defined as a < 10 mmHg difference) was 73% (95% CI, 66–81%) for mean pressure (12 studies), 65% (95% CI, 44–83%) for systolic pressure (7 studies), and 85% (95% CI, 71–96%) for diastolic pressure (6 studies).

Although concordance of non-invasive with invasive blood pressure was moderate, several panel members raised concerns that the observed discordance may lead to inappropriate vasopressor use or difficulties maintaining target blood pressure with a non-invasive approach. Ultimately, considering the very low certainty of evidence, the lack of clear associations with clinical benefit, and concerns regarding equity, patient comfort, and measurement discordance, the panel issued a conditional recommendation supporting the use of either non-invasive or invasive blood pressure monitoring. However, several panel members felt strongly that measurement discordance should lead to a suggestion to use invasive monitoring. Regional variability in standards of care was also acknowledged.

"In our practice," most panel members (62.7%) use invasive blood pressure monitoring in patients with septic shock. Of the 37.3% that routinely treat adults with septic shock without invasive monitoring, nearly all (92.0%) measure non-invasive blood pressure at least every 15 min during early shock or with escalating vasopressor doses (72.0% every 15 min, 20.0% more frequently); less frequent assessments are more common after the acute phase or with more stable vasopressor doses (28.0% every 15 min, 32.0% every 30 min, 36.0% every 60 min). Further, only 28.0% have a specific vasopressor dose at which they routinely initiate invasive monitoring (range: 0.1–0.5 μg/kg/min norepinephrine equivalents).

The multicenter EVERDAC RCT, testing a non-invasive strategy to blood pressure 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 [341]. EVERDAC found that, among 1010 patients randomized, 28-day all-cause mortality was non-inferior in the non-invasive-strategy group (34.3% mortality vs. 36.9% in the invasive strategy, $p = 0.006$ for non-inferiority) [341].

Fluid type

43. For adults with sepsis or septic shock, we "recommend" using crystalloids as first-line fluid for resuscitation (strong recommendation, moderate certainty evidence)	**Carryover**
44. For adults with sepsis or septic shock undergoing initial resuscitation, we "suggest" using balanced crystalloids over 0.9% saline (conditional recommendation, moderate certainty evidence) ***Remark***: For patients with sepsis and traumatic brain injury, we suggest using 0.9% saline	**Revisited**

45. For adults with sepsis or septic shock, we "suggest" using crystalloids alone over crystalloids with supplemental albumin for fluid resuscitation (conditional recommendation; moderate certainty evidence) ***Remark***: 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	**Revisited**
46. For adults with sepsis or septic shock, we "recommend against" using starches for resuscitation (strong recommendation, high-certainty evidence)	**Carryover**
47. For adults with sepsis and septic shock, we "suggest against" using gelatin for resuscitation (conditional recommendation, moderate certainty evidence)	**Carryover**

IV fluid administration is necessary for volume resuscitation in sepsis and septic shock, although the optimal type of fluid has been debated. Carried over from the 2021 guidelines [65, 66], we recommend using crystalloids as first line for fluid resuscitation and recommend against using starches. We also suggest against using gelatins. Please see 2021 guidelines for rationales regarding crystalloids as the first-line fluid over starches and gelatins [65, 66].

In this iteration of the guidelines, we re-evaluated whether to use balanced solutions; for example, lactated Ringer's solution, (vs. 0.9% saline) and albumin (vs. crystalloids). Although 0.9% saline remains the most widely used crystalloid [342], its use has been associated with hyperchloremic acidosis and acute kidney injury, leading to increased interest in balanced crystalloids due to their lower chloride content [342]. The 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 [343] and an individual patient data meta-analysis (IPDMA) derived from 5 high-quality RCTs and 6753 patients [344]. The largest trials included in both the review and IPDMA were SMART [345] (15,802 total patients cluster randomized in 1 center), BaSICS [346] (10,520 total patients individually randomized in 75 centers), and PLUS [347] (5037 total patients individually randomized in 53 centers).

The review showed that using balanced crystalloids probably reduced mortality compared with 0.9% saline (OR 0.94; 95% CI, 0.85–1.04, moderate certainty) and new RRT (OR 0.86, 95% CI, 0.74–0.99, high certainty) and may have had no effect on VFD (MD 0.18 higher; 95% CI, 0.45 lower to 0.81 higher, low certainty evidence). Several secondary analyses have suggested that the benefit of balanced solutions is greatest when used throughout resuscitation [348–350]. The panel considered the balance of effects to probably favor balanced crystalloids with cost, and availability of balanced solutions varying across settings, although non-proprietary balanced solutions (e.g., Ringer's lactate) are often similar in cost to 0.9% normal saline. The certainty of evidence has strengthened from the 2021 guidelines due to added data.

Theoretically, albumin maintains intravascular oncotic pressure compared with crystalloids [351]. Due to cost and the absence of clear benefit for its use, however, the 2021 guidelines provided a conditional (previously, weak) recommendation for using albumin in patients who had already received large volumes of crystalloids. We identified five new systematic reviews [352–356], a clinical practice guideline from the International Collaboration of Transfusion Medicine [357], and 2 new randomized-controlled trials [358, 359] totaling an additional 396 patients from published reports since 2020. Our current recommendation relied on 6 RCTs of 4,383 patients with sepsis or septic shock, or their subgroups in larger trials [351, 358–362], including 3,013 (69%) from the ALBIOS [351] and SAFE [362] trials. We found probably no effect of albumin on 28-day mortality (RR 1.01, 95% CI, 0.90–1.14, moderate certainty). 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. The variability across trials in the albumin dose, concentration, and indication reduced evidence certainty due to inconsistency.

Considerations should be made for different populations. For patients with traumatic brain injury, evidence suggests harm with the use of balanced crystalloids [363] or albumin [364], 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 [365]. Similarly, evidence suggesting higher blood pressures [351], higher static filling pressures [366], and lower net fluid balances [351] 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 [367].

Liberal vs. conservative approach to resuscitation

48. 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 recommendation, low certainty evidence) **Revisited**

Remark: 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)

Determining the optimal volume of fluid resuscitation for patients with sepsis or septic shock is difficult. Restrictive and liberal approaches to ongoing resuscitation have been evaluated in multiple trials [121, 368–372], but the studies vary widely with respect to definitions for restrictive and liberal strategies, eligibility criteria, setting, timing, and duration of the interventions.

To inform our updated recommendations, we considered 4 RCTs [133, 371, 373, 374] 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 (RR 1.00; 95% CI, 0.91–1.10, moderate certainty). Furthermore, there were probably no differences in VFD, (MD 0.14 d fewer, 95% CI, − 2.11 to 1.83, low certainty), RRT (RR 0.99, 95% CI, 0.83–1.19, moderate certainty), renal replacement-free days (MD 0.43 d more, 95% CI, − 0.59 to 1.45, moderate certainty), and vasopressor-free days (MD 0.49 d more, 95% CI, − 0.37 to 1.35, moderate certainty).

The panel judged desirable and undesirable effects to be trivial. Costs of a restrictive approach (due to vasopressor use and requisite monitoring in certain settings) were considered potentially higher, with equity probably reduced. In addition, given the differences in renal replacement-free days and vasopressor requirements between approaches, 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. In low-resource settings (e.g., LMICs with limited access to invasive mechanical ventilation), the potential harms associated with fluid overload are greater, providing support for a restrictive or more personalized approach to resuscitation [119].

The 2025 ESCIM clinical practice guidelines made no recommendation regarding liberal vs. restrictive approaches to fluid resuscitation, stating: "In adults with sepsis or septic shock who need fluid resuscitation for circulatory failure, we cannot recommend for or against systematic restrictive or liberal fluid resuscitation" [123]. In general, both the SSC statement and ESICM practice guidelines acknowledge the equivalence between liberal and restrictive strategies and provide support for more personalized approaches to resuscitation, as discussed in the next statement. We chose to make a conditional "ether/or" recommendation rather than a statement of no recommendation based on our process for selecting type of statement (Fig. 1).

Fluid resuscitation guided by dynamic measures

49. For adults with sepsis or septic shock, we "suggest" using dynamic measures to guide fluid resuscitation over physical examination or static measures alone (conditional recommendation, low certainty evidence) **Revisited**

Remark: 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)

Patients with sepsis or septic shock often require additional IV fluid following an initial 30 mL/kg fluid resuscitation. However, additional resuscitation fluid must be balanced against the risk of fluid accumulation and potential harm associated with fluid overload; for example, prolonged mechanical ventilation, progression of acute kidney injury, and increased mortality. As discussed in the prior statement, liberal and restrictive fluid strategies were judged to be equivalent based on the EtD summary of judgments.

To avoid over-resuscitation or under-resuscitation, fluid administration beyond the initial resuscitation phase should be guided by careful assessment of intravascular volume status, organ perfusion, and fluid responsiveness. Heart rate, central venous pressure, and systolic blood pressure are poor indicators of whether a patient will benefit from additional IV fluid. Rather, dynamic measures better predict fluid responsiveness than static measures [375]. 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 [375].

We identified 3 meta-analyses [375–377] examining the use of dynamic measures to guide fluid resuscitation, with 18 total RCTs included across the 3 analyses. The majority of RCTs were single-center studies with fewer

than 100 patients. In a separate meta-analysis done for these SSC guidelines and inclusive of all 18 RCTs, fluid management guided by dynamic measures likely reduces mortality (18 RCTs; RR 0.91; 95% CI, 0.79–1.06, moderate certainty, translating to 28 fewer deaths per 1000 patients; 95% CI, 65 fewer to 19 more), likely results in a large reduction in need for RRT (6 trials, RR 0.75; 95% CI, 0.58–0.98, moderate certainty, translating to 71 fewer patients receiving RRT; 95% CI, 119 fewer to 6 fewer), and may result in a slight increase in ventilation-free days (MD 0.79 more days; 95% CI, 1.28 fewer days to 2.86 more days, very low certainty). In the only multicenter RCT focused on patients with sepsis-induced hypotension, fluid management guided by dynamic measures was associated with a lower net fluid balance at 72 h (MD − 1.37L; 95% CI, −2.53L to −0.21L), lower receipt of RRT, and lower receipt of invasive mechanical ventilation [378].

Most data informing fluid resuscitation in sepsis originate from high-resource settings, and there is limited evidence from low-resource settings to guide either the best fluid resuscitation approach or suitable safety endpoints. An RCT in patients with sepsis and hypotension in Zambia showed that early protocolized resuscitation with fluid administration, guided by static measures and vital signs only (jugular venous pressure, respiratory rate, and arterial oxygen saturation), was associated with significantly more fluid administration in the first 6 h (median 3.5 L vs. 2.0 L) and higher hospital mortality than standard care (48.1% vs. 33%) [121].

Point of care ultrasound (POCUS), non-invasive cardiac monitoring, and invasive cardiac monitoring can be employed to measure stroke volume (SV). However, 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 the use of POCUS-guided resuscitation probably reduces 28-day mortality (RR 0.88; 95% CI, 0.78–0.99) [379]. Although dynamic echocardiographic estimation of SV and changes in this parameter can be useful, this modality requires technical expertise and experience that may not be readily available in low-resource settings. 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 in guiding resuscitation [156].

The SSC guideline suggestion to use dynamic measures to guide fluid resuscitation is consistent with the ESCIM clinical practice guideline recommendation: "In adults with sepsis or septic shock who require fluid resuscitation for circulatory failure, we suggest using an individualized approach compared with a non-individualized approach during the optimization phase" [123].

Cardiac output monitoring devices

50. For adults with septic shock, there is "insufficient evidence" to make a recommendation on using minimally invasive or non-invasive cardiac output monitoring in addition to usual care ***Remark***: Minimally invasive cardiac output monitoring refers to devices requiring an arterial catheter. Non-invasive 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	**New**

Cardiac output has historically been measured by pulmonary artery catheterization [380–382], but this technique is invasive and lacks proven benefit in sepsis [383, 384]. More recently, minimally invasive (using a peripheral arterial catheter and pulse power or pulse wave analysis) and non-invasive (using surface sensors and pulse wave analysis, bioreactance, bioimpedance, or other techniques) monitors have been developed [385], which allow continuous assessment of cardiac output with potentially fewer risks than pulmonary artery catheterization [386].

Three RCTs [387–389] of two hundred twenty-five patients evaluated the use of minimally invasive cardiac output monitors in septic shock, with pulse wave analysis used in all three. These studies demonstrate an uncertain effect on 28-day mortality (RR 0.92; 95% CI, 0.60–1.43, very low certainty evidence), a possible reduction in ICU LOS of (MD 2.09 d fewer; 95% CI, 0.85–3.34 d fewer, low certainty evidence) and invasive mechanical ventilation duration (MD 1.42 d fewer; 95% CI, 0.43–2.4 d fewer, low certainty evidence), but no information on potential adverse events related to the peripheral arterial catheters. Three RCTs [378, 390, 391] of three hundred ten patients assessed the impact of non-invasive cardiac output monitors in septic shock, all of which used bioreactance. Pooled analysis showed an uncertain effect on 28-day mortality (RR 0.77; 95% CI, 0.42–1.42, very low certainty evidence), ICU LOS (MD 1.03 d fewer; 95% CI, 3.51 fewer to 1.45 more, very low certainty evidence), hospital LOS (MD 0.74 d fewer; 95% CI, 1.73 fewer to 0.15 more, low certainty evidence), and organ dysfunction (any: RR

1.11; 95% CI, 0.52–2.37 and acute kidney injury: RR 1.82; 95% CI, 0.51–1.32, both very low certainty evidence).

The small number of patients evaluated in studies of both minimally invasive and non-invasive cardiac output monitors led the panel to conclude there was insufficient evidence to issue a recommendation addressing their use. However, given the cost of these devices, concerns exist about their availability in low-resource settings impacting equity.

We did not consider critical care ultrasound in our evidence synthesis. However, a recent SCCM guideline on critical care ultrasonography included conditional recommendations for use of critical care ultrasound in the management of adults with septic shock and to inform volume management in acutely ill adults [392].

"In our practice," 74.6% of panel members have minimally invasive (using an arterial catheter) cardiac output monitors and 31.3% of panel members have non-invasive (bioreactance) monitors available at their hospital. Of those with availability, 24.0% of panel members use minimally invasive monitors and 23.8% use non-invasive monitors in a majority (≥ 50%) of their patients with septic shock. The panel strongly encourages additional research into the efficacy, safety, and cost-effectiveness of these newer modalities for cardiac output monitoring.

Serial lactate measurement

51. For adults with sepsis and elevated lactate or septic shock, we "suggest" using serial lactate measurements to guide resuscitation (conditional recommendation, low certainty evidence) ***Remark***: Fluid administration should be individualized after initial fluid bolus and monitoring of lactate decrement, rather than continuing fluids until lactate normalization is achieved	**Revisited**

Serum lactate is a critical biomarker for assessing tissue hypoxia and dysfunction, though it does not directly measure tissue perfusion [393]. 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 [1].

Recent evidence has refined lactate-targeted resuscitation strategies. 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 [394–398]. For example, focusing on serial lactate measurements and clearance rates (e.g., ≥ 10% reduction every 2 h) rather than static normalization has been associated with better clinical outcomes, including shorter ICU stays and lower severity scores [395]. These findings highlight the importance of dynamic monitoring over single-timepoint measurements.

The panel 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. Access to lactate testing may be limited in some low-resource settings [179–183, 399–401]. Although lactate-guided therapy demonstrates utility, variability in study designs and unclear optimal clearance thresholds contribute to the conditional recommendation and low certainty of evidence [394–398]. 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 [184].

Capillary refill time

52. 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 recommendation, low certainty evidence)	**Revisited**

CRT is a marker of peripheral tissue perfusion [402]. It is one of the few bedside physical examination measure that may serve as both a triage and monitoring tool for resuscitation efforts in patients with sepsis or septic shock [403, 404]. Although ambient lighting, temperature, skin pigmentation, and peripheral vascular disease must be considered during interpretation, CRT may be performed in various clinical settings [403, 405].

Among critically ill patients, abnormal or prolonged CRT is associated with increased mortality, similar to other resuscitation targets such as lactate and MAP [406]. However, MAP and lactate do not always correlate with CRT for patients in shock, suggesting that CRT provides distinct hemodynamic information during resuscitation [407, 408]. In contrast to lactate, CRT can change quickly (e.g., within 10 min), allowing for more timely assessment of response to resuscitative interventions such as a fluid challenge or vasopressor administration [409].

We 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 s or targeted resuscitation using lactate measured

every 2 h with a goal of normalization or reduction by 20% [400, 410]. The 28-day mortality risk ratio was 0.82 (95% CI, 0.65–1.04) with an absolute mortality reduction of 74 per 1000 deaths (95% CI, 144 fewer, 16 more). The remaining outcomes were assessed from the ANDROMEDA-SHOCK trial [400] for 90-day mortality and RRT with risk ratio 0.88 (95% CI, 0.71–1.09) and 0.71 (95% CI, 0.47–1.10), and absolute risk reduction of 56 per 1000 deaths (95% CI, 135–42) and 57 fewer RRT per 1000 (95% CI, 105–20), respectively. 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 s appeared safe without compromising tissue perfusion [410].

Although the small sample size, limited number of events, and wide CIs constrained the evidence to low certainty, the balance of effects probably favors the use of CRT as part of a targeted resuscitation strategy. Although there are limited studies to assess resource utilization, and the ANDROMEDA-SHOCK trial [400] used a standardized approach requiring training, the panel determined that CRT is feasible, reproducible, and may be readily implemented in low-resource settings in conjunction with other validated tools of resuscitation.

The multicenter ANDROMEDA-SHOCK-2 RCT [411, 412], testing a CRT-guided resuscitation protocol in patients with septic shock, was published after evidence synthesis and recommendations were finalized. In this trial, 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. Specifically, the win ratio for the hierarchical composite primary outcome of mortality, duration of vital support, and length of hospital stay at 28 days was 1.16 (95% CI, 1.02–1.33, $p = 0.04$).

IV vasopressors

53. For adults with septic shock, we "recommend" using norepinephrine as the first-line agent over dopamine, epinephrine, or selepressin (strong recommendation) Dopamine. High-certainty evidence Epinephrine. Low-certainty evidence Selepressin. Low-certainty evidence	**Carryover**
54. For adults with septic shock, we "suggest against" using terlipressin (conditional recommendation, low certainty evidence)	**Carryover**
55. For adults with septic shock, we "suggest" using norepinephrine as the first-line agent over vasopressin or angiotensin II *(conditional recommendation)* Vasopressin. Low-certainty evidence Angiotensin II. Very-low-certainty evidence	**Revisited**
56. For adults with septic shock on escalating doses of norepinephrine, we "suggest" adding vasopressin (conditional recommendation, moderate certainty evidence)	**Revisited**
57. For adults with septic shock and inadequate MAP levels despite norepinephrine and vasopressin, we "suggest" adding epinephrine (conditional recommendation, very-low-certainty evidence) ***Remark***: In settings where vasopressin is not available, epinephrine can be added to norepinephrine alone	**Revisited**
58. For adults with septic shock with concomitant cardiac dysfunction, we "suggest" using either norepinephrine or epinephrine as first-line vasopressor (conditional recommendation, very low certainty evidence) ***Remark***: 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	**New**

Consistent with the 2021 SSC guidelines, the panel identified norepinephrine as the first-line vasopressor for treatment of septic shock. Comparisons to dopamine, epinephrine, and selepressin were carried over; comparisons of norepinephrine (a catecholamine) to vasopressin (which directly induces vasoconstriction via V1a receptors, stimulates V1b receptors in the anterior pituitary leading to adrenocorticotropic hormone secretion and subsequent cortisol production [413], and attenuates endothelial-driven vasodilation through purinergic and oxytocin receptors [413]) and angiotensin II (which induces vasoconstriction via angiotensin II type 1 receptors, stimulates aldosterone release, and enhances myocardial contractility) were re-evaluated.

The panel identified 2 RCTs of 658 total patients randomized to vasopressin vs. norepinephrine as first-line vasopressor [414, 415]. Meta-analysis found there was possibly no difference in mortality (RR 1.07; 95% CI, 0.90–1.28, low certainty evidence), but probably less use of RRT (RR 0.70, CI 0.53–0.92, moderate certainty evidence) with vasopressin. Although evidence was of low or very low certainty, vasopressin did not appear to result in differences in life-threatening arrhythmia or ischemia (digital, mesenteric, or myocardial).

The panel identified no RCTs comparing angiotensin II to norepinephrine as first-line therapy; 2 RCTs of 341 total patients already on norepinephrine who were randomized to the addition of angiotensin II vs. norepinephrine alone were considered as indirect evidence [416, 417]. Meta-analysis found that the addition of angiotensin II may result in a reduction in mortality (RR 0.85; 95% CI, 0.69–1.06, low certainty evidence) but with an uncertain effect on ventricular arrhythmias,

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 (and the data on angiotensin II were indirect), the panel weighed strongly that vasopressin and angiotensin II tend to be more expensive and less available than norepinephrine, especially in low-resource settings [418]. In the low-resource settings without access to norepinephrine, epinephrine has been recommended as an acceptable alternative by a Delphi panel of experts [184].

Consistent with the 2021 SSC guidelines [65, 66], the panel suggests sequentially adding vasopressin and then epinephrine for patients requiring escalating doses of norepinephrine to maintain mean arterial blood pressure. To evaluate the addition of vasopressin in this context, we performed a meta-analysis of 9 RCTs [419–426] (1,439 total patients, including 778 [54.1%] from the only multicenter trial, VASST [419]). Meta-analysis found a probable reduction in mortality with adding vasopressin compared with increasing norepinephrine alone (RR 0.89; 95% CI, 0.79–1.01, moderate certainty). Although 28-day mortality did not differ between groups in VASST (vasopressin 35.4% vs. norepinephrine 39.3%, $p=0.26$), subgroup analyses suggested that adding vasopressin may benefit patients in less severe shock (norepinephrine equivalent dose < 15 μg/min; 28-day mortality 26.5% vs. 35.7%, $p=0.05$). Compared with norepinephrine monotherapy, adjunctive vasopressin probably results in less atrial fibrillation (RR 0.66; 95% CI, 0.42–1.05, moderate certainty evidence), but possibly more digital ischemia (RR 2.87; 95% CI, 0.84–9.82, low certainty). These findings are consistent with published meta-analyses [427].

"***In our practice***," 85.1% of panel members add vasopressin in patients with septic shock on escalating doses of norepinephrine. Panelists using vasopressin initiate it at a median dose of 0.3 μg/kg/min of norepinephrine (IQR 0.2–0.5 μg/kg/min). This dosing is similar to a recent observational study in which a reinforcement machine learning model suggested initiating vasopressin at a median 0.20 μg/kg/min (IQR 0.08–0.45 μg/kg/min), as compared with clinician initiation of vasopressin at a median 0.37 μg/kg/min (IQR 0.17–0.69 μg/kg/min) [428].

The panel relied on an indirect estimate from a published network meta-analysis [429] (31 RCTs with 5928 patients and 11 comparators) to evaluate the addition of epinephrine vs. escalating norepinephrine. Results found an uncertain effect on mortality of combined epinephrine and norepinephrine over norepinephrine alone (OR 0.65; 95% CI, 0.19–2.18, very low certainty evidence), but no data were available for the addition of epinephrine to both norepinephrine and vasopressin. There was also an uncertain effect on arrhythmias (OR 1.68; 95% CI, 0.05–60.10, very low certainty evidence). 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, we suggested adding epinephrine to norepinephrine alone in settings where vasopressin is not available.

"In our practice," 55.2% of panel members add epinephrine in patients with septic shock on escalating doses of norepinephrine. Panelists using epinephrine initiate it at a median dose of 0.8 μg/kg/min of norepinephrine (IQR 0.5–1.0 μg/kg/min).

Despite the potential theoretical benefits of adding a vasopressor with a completely different mechanism of action, a PICO question examining second- or third-line use of angiotensin II was not prioritized. We did, however, examine trials on the addition of angiotensin II as indirect evidence for the PICO question on first-line vasopressor selection, as discussed above.

Overall, given the high mortality of septic shock and low certainty of evidence informing practice, there is a need for further studies to inform vasopressor selection and titration. Specifically, further study is needed to confirm whether adding vasopressin and epinephrine improves outcomes, to address the timing of adjunctive vasopressor initiation (at what norepinephrine dose and when in the septic shock course), to address the benefits of multimodal vasopressor strategies, and to identify potential subgroups underlying heterogeneity of treatment effect. There are ongoing clinical trials to assess first-line vasopressor selection (NCT02118467) and initiation of vasopressin (NCT06217562; NCT06464510).

Although both norepinephrine and epinephrine are catecholamines, their pharmacological profiles and clinical effects differ [430]. Norepinephrine acts predominantly on alpha-1 receptors, producing strong vasoconstriction. It has mild beta-1 activity providing limited inotropic support without affecting heart rate or myocardial oxygen demand [430]. Epinephrine, in contrast, exerts potent beta-1, beta-2, and alpha-1 receptor stimulation resulting in combined vasoconstriction and robust inotropic and chronotropic effects. For this reason, epinephrine may benefit patients with septic shock and concomitant cardiac dysfunction. However, epinephrine's benefits may be offset by drawbacks including tachyarrhythmias, increased myocardial oxygen consumption, and a rise in serum lactate—complicating lactate use as a perfusion biomarker [430].

The panel identified no trials evaluating patients with septic shock and concurrent cardiac dysfunction. We identified one randomized trial (the CAT Study [431]) of 280 patients, 158 with sepsis, which found epinephrine as compared with norepinephrine had an uncertain

effect on mortality (HR 0.85; 95% CI, 0.53–1.32, very low certainty) [431], consistent with the indirect effect from a network meta-analysis (33 RCTs, 3470 patients, 16 different comparators; OR for norepinephrine vs. epinephrine 1.35; 95% CI, 0.71—2.56) [432]. In the CAT study, there was possibly no difference in vasopressor-free days (epinephrine median 26.3, IQR 17.2–27.3 vs. norepinephrine 24.2, 7.7–26.5, $p=0.13$, low certainty), and indirect evidence suggests epinephrine may increase tachyarrhythmias and lactic acidosis [431, 433]. In this context, the panel did not favor epinephrine over norepinephrine—or vice versa—for adults with septic shock requiring vasopressors in the setting of concomitant cardiac dysfunction.

Methylene blue

59. For adults with refractory septic shock and escalating vasopressor requirements, there is "insufficient evidence" to make a recommendation on IV methylene blue	**New**
Remark: 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	
Remark: "In our practice," 69% of panelists "never" or "almost never" use methylene blue as rescue therapy, 23% "sometimes" use it, 6% "usually" use it, and 1.5% "almost always" use it	

Methylene blue is a phenothiazine derivative that is standardly used for treatment of methemoglobinemia at doses of 1.0–2.0 mg/kg over 5–30 min, which can be repeated 1 h later if symptoms persist. 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 downstream inhibition of soluble guanylate cyclase [434].

We updated an existing systematic review of six RCTs [434], identifying two additional small RCTs [435, 436], comparing IV methylene blue to usual care or placebo in patients with septic shock. Dosing regimens of methylene blue in these RCTs varied (e.g., one-time infusion of 0.5–2.0 mg/kg; 100 mg every 6 h; 2.0 mg/kg followed by 0.25–2.0 mg/kg daily or hourly). Although there is very low certainty evidence for its impact upon mortality (RR 0.79; 95% CI, 0.60–1.03, very low certainty), methylene blue likely results in a reduction in duration of vasopressors (MD − 1 d; 95% CI, − 1.8 to − 0.20, moderate certainty). Certainty of evidence for other outcomes, such as duration of ventilation and LOS, is low. Although studies of other iNOS inhibitors have demonstrated increased mortality [437], the largest study of methylene blue included only 90 patients and had no longer term mortality data [438]. Values and preferences would play an important role in choosing whether to use IV methylene blue as a rescue therapy in refractory septic shock, given the lack of evidence regarding longer term mortality and functional outcomes, which may be quite poor in this very sick population. The role of shared decision-making was supported by the patient panel.

Methylene blue may be more acceptable to patients with otherwise potentially survivable illness and recovery to a patient-acceptable quality of life; in moribund patients for whom longer term survival or an acceptable quality of life are unlikely, it is less likely to be acceptable. 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., countries without access to 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. "In our practice," 69% of panelists "never" or "almost never" use methylene blue as rescue therapy, 23% "sometimes" use it, 6% "usually" use it, and 1.5% "almost always" use it.

Inotropes

60. 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 recommendation, very low certainty evidence)	**Revisit**
Remark: For patients requiring vasopressors to maintain mean arterial pressure at target, inotropes should be used in addition to (not instead of) vasopressors	
61. 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	**Revisit**
(conditional recommendation, very low certainty evidence)	
Remark: Data were insufficient to make a recommendation for dobutamine vs. milrinone	
62. For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we "suggest against" using levosimendan	**Carryover**
(conditional recommendation, low certainty evidence)	

Sepsis-induced cardiac dysfunction is common among patients with septic shock and may contribute to worsened clinical outcomes [439]. Cardiac dysfunction should be suspected following evaluation with bedside echocardiography [440] or cardiac output monitoring devices. After adequate fluid resuscitation and restoration of arterial blood pressure, inotropes may be beneficial for patients with cardiac dysfunction and persistent hypoperfusion. In patients with septic shock,

dobutamine has been shown to increase oxygen delivery, improve intramucosal acidosis, reduce lactate levels, and enhance microcirculatory recruitment [441]. Although the physiologic rationale for using inotropes in patients with cardiac dysfunction is intuitive, there are potential harms from excessive vasodilation and tachycardia [441]. Importantly, no RCTs have directly assessed the balance between these potential benefits and harms in this population.

A network meta-analysis [432] including 33 trials with 3470 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 (OR 0.69; 95% CI, 0.32–1.47, very low-certainty evidence). Considering the intuitive physiologic effects, potential benefits from the network meta-analysis, feasibility, acceptability, and negligible cost, with probably no impact on equity, the panel 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.

Several inotropes exist. Dobutamine and epinephrine are the commonly used inotropes, yet no high-quality evidence supports the superiority of one over the other. A single randomized, double-blind trial involving 330 patients across 19F ICUs compared epinephrine vs. norepinephrine plus dobutamine and found no difference in 90-day mortality (RR 0.96; 95% CI, 0.78–1.19, low certainty evidence), ICU LOS, or vasopressor-free days. The incidence of life-threatening arrhythmia was similar in both groups. Therefore, consistent with the 2021 SSC guidelines, the panel considered the desirable and undesirable consequences to be comparable for both drugs and, with both being acceptable and feasible, 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. Notably, epinephrine is widely available in low-resource settings, enhancing feasibility. Milrinone, a phosphodiesterase-3 inhibitor, may improve cardiac function [442]. However, 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.

"In our practice," 94.0% of the panel uses inotropes in adults with septic shock with persistent hypoperfusion and cardiac dysfunction, despite adequate fluid resuscitation and arterial blood pressure. Of these, 31.8% use inotropes often, 44.4% sometimes, and 23.8% rarely. Most of the panel (71.4%) use dobutamine, whereas 12.7% use milrinone, 14.3% use epinephrine, and none of the panelists use levosimendan. The factors that drive panel members' choice of inotropes include details of cardiac dysfunction (31.7%); heart rate/arrhythmias (27.0%); renal failure (7.9%), and pulmonary hypertension (7.9%).

Given the high prevalence of cardiac dysfunction in sepsis, this area remains a research priority. Trials are urgently needed to assess the impact of inotropes in sepsis, define which patients benefit, and determine optimal timing, dosing, and weaning strategies. Ongoing trials (e.g., NCT04166331) are expected to inform future practice.

Midodrine

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

Need for IV vasopressors is a common indication for ICU admission, while ongoing need for low-dose vasopressors may delay transfer out of the ICU when clinical status is otherwise improving [443, 444]. IV vasopressors are associated with adverse events and traditionally require central venous access [445]. Midodrine, an oral medication with alpha-agonist properties, has some evidence of benefit in orthostatic [446] and intradialytic hypotension [447] and therefore may have utility as a vasopressor-sparing agent.

The most comprehensive meta-analysis addressing this question in vasodilatory shock was recently published and included seven small RCTs [448]. The panel considered this review, with specific focus on the septic shock subgroup which was informed by 4 small RCTs including 180 patients. 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 (MD 0.98 d more; 95% CI, 1.28 fewer to 3.24 more, low certainty evidence) and reduce hospital LOS (MD 0.73 d fewer; 95% CI, 5.00 fewer to

3.54 more, low certainty evidence) and ICU LOS (MD 0.8 d fewer; 95% CI, 1.83 fewer to 0.23 more, low certainty).

The 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. Although the drug is cheap in most jurisdictions, there were concerns about availability in low-resource settings and the potential impact on equity. Safety and the ability to reliably maintain target blood pressure were also concerns. Finally, the panel worried that while midodrine may be acceptable in post-resuscitation shock, it is perhaps less so in the acute phase, earlier shock management.

"In our practice," 32.8% of panel members use midodrine in adults with septic shock. Among those who use midodrine, 86.4% use it after the acute phase of septic shock to facilitate discontinuation of IV vasopressors, whereas 9.1% use it in the early acute phase of mild septic shock to avoid initiating IV vasopressors. Panel members consider its use for patients with prolonged low-dose IV vasopressor requirements who have otherwise clinically improved, patients with chronic renal failure, and patients with cirrhosis.

Ultimately, the panel decided there was insufficient evidence to make a recommendation but felt this question must be a future research priority given the promising, but non-definitive results from phase II RCTs.

Beta-blockers

64. For adults with septic shock, we "suggest against" using beta-blockers as a treatment for septic shock (conditional recommendation; very low certainty evidence) **New**

Remark: This recommendation is based on evidence for short-acting, IV beta-blockers (esmolol and landiolol) prescribed for treatment of septic shock

Although the use of beta-blockers in septic shock may seem counterintuitive, pre-clinical data suggests it may improve outcomes [448]. The exact mechanism remains unclear; however, it may be related to decreased myocardial workload and optimized myocardial energy efficiency [449]. Despite promising animal studies, the RCT data addressing this question have produced variable results [450–452].

The panel considered the most comprehensive meta-analysis [453] addressing this question which was recently published and included 12 RCTs and 1170 patients. Pooled analysis demonstrated an uncertain effect of beta-blockers on mortality (RR 0.76; 95% CI, 0.62–0.93, very low certainty), bradycardia (RR 3.14; 95% CI, 0.91–10.82, very low certainty), ICU LOS (MD 0.75 d fewer; 95% CI, 3.43 fewer to 1.93 more, very low certainty), and hospital LOS (MD 1.03 d more; 95% CI, 1.92 fewer to 3.98 more, very low certainty). Beta-blockers were probably associated with a reduction in new-onset tachyarrhythmias (RR 0.37; 95% CI, 0.18–1.78, moderate certainty), but also probably associated with an increased duration of vasopressor use (MD 1.04 d more; 95% CI, 0.37–1.72 d more, moderate certainty).

The panel judged both desirable and undesirable effects to be trivial and given moderate costs associated with IV beta-blockers, variability in their availability (especially of shorter-acting beta-blockers), and the potential impact on health equity, decided a conditional recommendation against this intervention was most appropriate. Also factoring into the panel decision was the very-low-certainty evidence for most outcomes of interest, including mortality and LOS, and an evidence summary informed by mostly small, single-center RCTs. The role of beta-blockers in sepsis—including the optimal timing of administration, agent selection, and identification of subgroups most likely to benefit—is a key research priority. Given the promising but preliminary findings from phase II RCTs, a large, multicenter RCT assessing patient-important outcomes is warranted to address these critical questions.

Respiratory support

Monitoring of hypoxemia

65. 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 recommendation, very low certainty evidence) **New**

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 by pulse oximeter may substitute for Pao_2/Fio_2 ratio, but is less accurate in patients in shock, with darker skin tones, and/or with oxygen saturations < 90% or > 97%

Arterial blood gas (ABG) measurement is the gold standard for assessing oxygenation, but is invasive, costly, and not available in all settings. Pulse oximetry is non-invasive, more universally available, and can provide continuous monitoring that is easy to interpret, though its accuracy is reduced in low perfusion states. Measurement of the ratio of arterial oxygen tension (Pao_2) to Fio_2 (Fio_2) is required for the hypoxemia criterion for the diagnosis of acute respiratory distress syndrome (ARDS). However, a growing body of evidence also supports the use of the ratio of pulse oximetry-based measurements

such as oxygen saturation (Spo_2) to Fio_2 for the clinical diagnosis and management of ARDS.

Our 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 an Spo_2/Fio_2 ratio for a Pao_2/Fio_2 ratio and found the Spearman correlation co-efficient ranged between 0.5 and 0.8 [454]. Furthermore, the Pao_2/Fio_2 ratio could most often be derived using a simple linear equation first described by Rice and colleagues [455]. However, the correlation is less accurate when oxygen saturations are less than 90% or greater than 97% (related to the shape of the oxyhemoglobin dissociation curve). In addition, 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 that was not detected by pulse oximetry [456]. A systematic review that examined accuracy of arterial oxygenation by pulse oximetry including 44 studies, reported an overestimation of arterial oxygen saturation (Sao_2) by pulse oximetry in patients with darker skin tones [457]. The lower the Sao_2, the greater the degree of overestimation bias. However, different pulse oximeters models were used in the included studies, and participants' skin tones were not measured objectively.

Based on this evidence, the 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 new global consensus definition of ARDS allows for the use of pulse oximetry-based measurements for the diagnosis of ARDS [458]. The use of Spo_2/Fio_2 less than 315 (if $Spo_2 < 97\%$) has been suggested for use in low-resource settings when an ABG is unavailable, as an alternative to Pao_2/Fio_2 for the diagnosis of ARDS (mild) in non-intubated patients with ARDS and to categorize the severity in intubated patients with ARDS. Clinicians should exercise caution substituting an S/F ratio for a P/F ratio for patients in shock, with darker skin tones and with oxygen saturations less than 90% or greater than 97%. In the future, ARDS definitions may go beyond these syndromic concepts in favor of treatable traits [459].

The increasing recognition of diagnostic inaccuracy should also spur further clinical research in this space with consideration of the development of pulse oximeters that can overcome these inaccuracies. However, until such time, improving equity in routine ABG testing is paramount to mitigate occult hypoxemia.

Oxygen targets

66. 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 recommendation, low certainty evidence) **New**

Remark: 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 $Spo_2 \geq 96$

Remark: "In our practice", panelists target Spo_2 between 90% (IQR 90–92%) to 96% (IQR 94–98%) for patients with sepsis and acute hypoxemic respiratory failure

This recommendation is based on 10 RCTs (24,022 patients) reporting 28-day or 90-day mortality [460–469]. Meta-analysis of these trials demonstrated that lower, conservative oxygen targets may result in little to no difference in short-term mortality (RR 1.02; 95% CI, 0.99–1.05, translating to 7 more deaths per 1000 patients, 95% CI, 4 fewer to 18 more, low certainty). There may also be little to no difference in the duration of mechanical ventilation (0.29 more days, 95% CI, 0.76 fewer to 1.34 more, low certainty) or mechanical ventilation-free days (1.7 fewer with lower oxygen targets 95% CI, 5.88 fewer to 2.48 more, low certainty), but these estimates were each based on one trial [466, 470]. Given the trivial effect size for critical outcomes with lower vs. higher oxygen targets, lower oxygen targets may result in little to no difference in mortality or other outcomes at the individual level. However, given the large number of patients with sepsis and acute hypoxemic respiratory failure, a small effect size might still have an important population impact. However, in low-resource settings where oxygen therapy or mechanical ventilators are limited, titrating to lower oxygen targets may be more beneficial overall.

Although the higher, liberal oxygen targets in included trials were similar (generally $Spo_2 \geq 96\%$), 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, one trial [469] found no difference in ventilator-free days at 28 days with intermediate vs. higher oxygen targets (median ventilator-free days [VFD] 21 d [IQR 0–25] vs. 21 d [IQR 0–26]). The evidence did not provide guidance on whether a precise target within the higher oxygen target range (e.g., 96–97% vs. 98–100%) is optimal. However, the 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.

This recommendation differs from a recent rapid practice guideline [471] that suggested against the routine use of higher oxygen targets. In contrast to the rapid practice guideline, we excluded trials that specifically targeted patients without sepsis, for example, trials focused on patients with acute exacerbation of chronic obstructive pulmonary disease (COPD), cardiac arrest, stroke, or other acute neurologic injury. In addition, the SSC guidelines analysis included more recently published trials [464, 465, 468]. A further analysis done to support this guideline, updating a previous Cochrane meta-analysis [472], revealed no effect on mortality (RR 1.0 for mortality, 95% CI, 0.95–1.04, low certainty) when including all trials regardless of focus on sepsis or not.

The 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 [473]. However, this was a retrospective analysis including a limited number of patients with sepsis [473]. The results from the MEGA-ROX trial which aims to enroll 40,000 patients will lend greater confidence to any estimate and provide another opportunity to assess for heterogeneity of treatment effect for oxygen targets among patients with sepsis (NCT04092468).

"In our practice," panelists target Spo_2 between 90% (IQR 90–92%) and 96% (IQR 94–98%) for patients with sepsis and acute hypoxemic respiratory failure.

Non-invasive respiratory support

67. For adults with sepsis and acute hypoxemic respiratory failure, we "suggest" using high-flow nasal cannula (HFNC) therapy over conventional oxygen therapy **New**
(conditional recommendation, very low certainty evidence)
Remark: This recommendation pertains to patients with a Pao_2/Fio_2 ratio < 200 or Spo_2/Fio_2 ratio < 235

68. For adults with sepsis and acute hypoxemic respiratory failure, we "suggest" using HFNC as the initial therapy over non-invasive positive pressure ventilation (conditional recommendation, low certainty evidence) **New**

69. For adults with sepsis and acute hypoxemic respiratory failure, we "suggest" using HFNC over high flow alternating with non-invasive positive pressure ventilation (conditional recommendation, very low certainty evidence) **New**

Conventional, low-flow oxygen therapy is commonly administered for treatment of hypoxemia. However, it cannot deliver a Fio_2 exceeding 0.6–0.7 in the upper airways, even with a non-rebreathing facemask, and is limited by flow rates of less than or equal to 15 L/min. Alternatively, high-flow nasal cannula (HFNC) can achieve Fio_2 exceeding 0.8–0.9 and deliver flow rates up to 60 L/min of humidified gas, reducing work of breathing by mitigating the effect of anatomic dead space and potentially achieving low levels of positive airway pressure.

Patients with sepsis and acute hypoxemic respiratory failure might benefit from non-invasive positive pressure ventilation (NIPPV) to avoid intubation, invasive ventilation, and associated complications. However, HFNC oxygen therapy is easier to apply, generally more comfortable for the patient, allows for eating and speaking, and avoids various complications of NIPPV including increased risk of gastric insufflation, aspiration, and damage to facial skin.

The evidence 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 [474–484]. The evidence for suggesting HFNC over NIPPV is based on 7 RCTs (2,465 patients) [480, 485–490]. This evidence for suggesting HFNC over alternating HFNC and NIPPV is based on 2 RCTs (515 patients) [474, 491]. The main causes of acute respiratory failure in the included trials were infections and included trials focused on COVID-19 and respiratory failure in immunosuppressed patients. Trials focusing on patients with cardiogenic pulmonary edema or acute exacerbation of COPD were excluded.

In meta-analysis, HFNC therapy resulted in an uncertain but potential reduction in mortality (RR 0.90; 95% CI, 0.74–1.10, very low certainty); trivial reduction in hospital LOS (0.57 d; 95% CI, 1.52 fewer to 0.37 more, moderate certainty); [475, 477–480, 483, 484]; and uncertain but potential increase in VFDs (2.93 d more; 95% CI, 0.39 more to 5.47 more, very low certainty), as compared with conventional oxygen therapy [474, 477, 479, 484]. HFNC had an uncertain but possible reduction in need for intubation (RR 0.88; 95% CI, 0.77–1.00, very low certainty). With exception of hospital LOS (moderate certainty evidence), all other outcomes (mortality, VFD, and need for intubation) were graded as very-low-certainty evidence, and all were downgraded for imprecision. Data on severe adverse events (RR with HFNC 0.47 (95% CI, 0.22–1.02, low certainty evidence) were also limited by imprecision. 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 200 mmHg or Fio_2 greater than 0.6 [474, 480].

In meta-analysis, HFNC was associated with a possible decrease in mortality (RR 0.89; 95% CI, 0.74–1.08,

low certainty) [480, 485–490] and shorter duration of mechanical ventilation (MD 1.00 d fewer, 95% CI, 1.04 fewer to 0.95 fewer, moderate certainty), as compared with NIPPV [480, 490]. There was no effect on hospital LOS (0.19 d more; 95% CI, 0.45 fewer to 0.83 more, high certainty) [480, 485, 486, 488–490], an uncertain effect on ventilation-free days at 28 d (0.67 d fewer (95% CI, 1.43 fewer to 0.09 more, very low certainty) [485, 486, 488, 489], 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) [486, 489] and 2 more per 1000 patients for cardiac arrest (9 fewer to 23 more, moderate certainty) [489].

In meta-analysis, HFNC had an uncertain effect on mortality (RR 0.69, 95% CI, 0.30–1.58, very low certainty) [474, 491], as compared with alternating HFNC and NIPPV. HFNC was associated with shorter hospital LOS (MD 2 d fewer, 95% CI, 5.3 fewer to 1.3 more, low certainty) [491] and more ventilator-free days (MD 4 d more; 95% CI, 1.65 more to 6.35 more, low certainty) as compared with alternating therapy [474, 491].

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 [474]. The panel considered that HFNC probably costs more than conventional oxygen therapy due to requiring more disposables and oxygen, but that shorter duration of mechanical ventilation might result in an important cost reduction. Both HFNC and NIPPV require disposables, with alternating HFNC and NIPPV requiring even more. We did not identify any direct data analyzing cost-effectiveness. Although stakeholders are likely to find HFNC acceptable in places where it is available, incorporation of HFNC into care pathways for patients with sepsis and acute hypoxemic respiratory failure should be weighed against available oxygen supply. Given its higher oxygen consumption relative to low-flow oxygen therapy modalities [492], HFNC oxygen therapy might reduce the available oxygen supply and limit the number of patients who could be treated with supplemental oxygen therapy. In low-resource settings without HFNC, NIPPV has been suggested as reasonable alternative by an expert Delphi panel [184].

Awake proning

70. For adults with sepsis and acute hypoxemic respiratory failure who are not intubated, we "suggest" a trial of awake proning (conditional recommendation, very low certainty evidence) **New**

Remarks: 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

Awake self-proning has been proposed as a method to improve oxygenation, reduce work of breathing, optimize ventilation perfusion matching, and potentially reduce the risk of further lung injury among patients with acute hypoxic respiratory failure [493].

We identified 17 RCTs (3537 patients) to inform this recommendation [100, 494–509]. Awake proning may result in a slight reduction in the requirement for intubation (RR 0.82, 95% CI, 0.73–0.93, low certainty) [494–500, 503–505, 507, 509]. 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 (RR 0.89; 95% CI, 0.64–1.24, very low certainty) [495, 497, 498, 502, 503, 505–509], increased hospital-free days (MD 3.6 d more, 95% CI, 0.95 fewer to 8.15 more, very low certainty) [494], and increased VFD (MD 0.78 d more, 95% CI, 1.28 d fewer to 2.84 more) [494, 500, 507, 508], 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 (RR 2.54, 95% CI, 0.61–10.58, very low certainty) [494, 496, 498, 499, 503].

Two recently published systematic reviews of awake proning for COVID-19 patients both found that the intervention was associated with a reduced need for intubation and mechanical ventilation [493, 510]. In contrast to our analysis, an individual patient-level meta-analysis also concluded that mortality was reduced with awake proning (RR 0.70, 95% CI, 0.59–0.84) [493]. However, our evidence synthesis differed in analytic approach as well as inclusion criteria (RCTs only; awake proning vs. no proning, no assessment of proning duration).

Awake proning can be accomplished with minimal cost and appears safe but has been studied only in patients with COVID-19. These results will be important for another future pandemic, because of the low cost and wide availability of proning. In addition, there is considerable equity in low-resource settings where there may be a shortage of ventilators. Since the duration of proning depends on patient tolerance (and patients should not be sedated to achieve proning when not intubated), we are

unable to make a recommendation on the duration of awake proning.

Invasive mechanical ventilation

71. 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 recommendation, high certainty of evidence)	**Carryover**
72. 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 recommendation, low certainty evidence) ***Remarks***: Patients should be screened regularly for development of ARDS, as ARDS diagnosis is often missed or delayed in clinical practice	**New**
73. For adults with sepsis and ARDS, we "recommend" using an upper limited goal for plateau pressure of 30 cm H20) over higher plateau pressures (strong recommendation, high certainty of evidence)	**Carryover**
74. For adults with sepsis and moderate-severe ARDS, we "suggest" using higher positive end-expiratory pressure (PEEP) over lower PEEP (conditional recommendation, moderate certainty of evidence)	**Carryover**
75. For adults with sepsis and moderate-severe ARDS, we "recommend against" using an incremental PEEP titration strategy (strong recommendation, moderate certainty of evidence)	**Carryover**
76. For adults with sepsis and moderate-severe ARDS, we "suggest" using prone ventilation for greater than 12 h daily (conditional recommendation, moderate certainty of evidence)	**Carryover**
77. For adults with sepsis and moderate-severe ARDS, we "suggest" using intermittent NMBA boluses over continuous NMBA infusion (conditional recommendation, moderate certainty of evidence)	**Carryover**

Most statements on invasive mechanical ventilation were carried over, please see 2021 guidelines for rationale [65, 66].

There is a lack of guidance regarding the optimal tidal volume for mechanically ventilated patients without ARDS, particularly considering low vs. moderate tidal volumes. We identified two RCTs comparing low (4–6 mL/kg IBW) vs. moderate tidal volumes (8–10 mL/kg IBW) in general populations of mechanically ventilated critically ill patients, including those with acute hypoxemic respiratory failure and sepsis, which informed our recommendation [511, 512]. Meta-analysis revealed possibly no difference in mortality at 90 days (RR 1.04; 95% CI, 0.89–1.22), although CIs could not exclude harm. We similarly found no important difference between low and moderate tidal volumes in hospital LOS (MD 0.66 d shorter; 95% CI, 3.5 d shorter to 2.17 d longer, low certainty), duration of mechanical ventilation (MD 0.65 d shorter; 95% CI, 1.52 d shorter to 0.23 d longer, moderate certainty), VFD at day 28 (MD 0.05 d more; 95% CI, 1.34 d fewer to 1.45 d more, very low certainty), and in incidence of ARDS (RR 0.85; 95% CI, 0.49–1.47, low certainty) and pneumonia (RR 1.10; 95% CI, 0.66–1.82, low certainty) within 7 days of ICU admission. One trial suggested that there may be an increased risk for delirium in the lower tidal volume group (RR 1.19; 95% CI, 0.99–1.42, moderate certainty) [512].

In practice, clinicians commonly ventilate patients with moderate tidal volumes not represented in these two trials (e.g., 7 mL/kg IBW) [513]. We advise clinicians to carefully screen their patients for ARDS to ensure appropriate tidal volumes are used because under-recognition of ARDS occurs in a significant proportion (48.7–52.4%) of patients who meet criteria [514, 515]. Even in patients with known ARDS, there are barriers to maintaining evidence-based mechanical ventilatory strategies, and clinicians should ensure they do not routinely expose patients who are mechanically ventilated to higher tidal volumes (e.g., > 10 mL/kg IBW) [516, 517].

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.

Veno-venous ECMO

78. 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 recommendation, low certainty of evidence)	**Carryover**

This statement was carried over, please see the 2021 guidelines for rationale [65, 66].

Adjunctive therapies for the management of sepsis

This section of the guideline addresses adjunctive therapies specifically for the management of sepsis. Recommendations pertain to the use of therapies for the management of sepsis. It is recognized that some of these therapies may be prescribed for reasons other than sepsis and may continue when a patient has sepsis (e.g., continuation of vitamin D for treatment of preexisting vitamin D deficiency).

IV Corticosteroids

79. For adults with septic shock, we "suggest" using IV corticosteroids (conditional recommendation, low certainty evidence) **Revisited**

Corticosteroids have been studied extensively in adults with multiple types of infection, including sepsis and septic shock, with a recent meta-analysis identifying 45 RCTs including 9543 patients [518]. Corticosteroids may result in a small reduction in 28-day mortality (RR 0.92; 95% CI, 0.83–1.01, low certainty) and long-term mortality at 60 days or later (RR 0.94; 95% CI, 0.88–1.00, low certainty), although these results are limited by imprecision and inconsistency, given the heterogeneity of populations and interventions across trials. We a priori evaluated subgroups based on population (sepsis vs. septic shock; pneumonia; ARDS) and corticosteroid regimen (with or without mineralocorticoid; high vs. low dose; short vs. long course; intermittent vs. continuous infusion). These subgroup analyses were likely underpowered, but demonstrated similar direction of effect favoring steroids, except for sepsis without shock (RR 1.09; 95% CI, 0.91–1.31). Corticosteroids result in a greater incidence of shock reversal at 7 days (RR 1.29; 95% CI, 1.13–1.46, high certainty); increases in hyperglycemia (RR 1.19; 95% CI, 1.10–1.28) and hypernatremia (RR 1.64; 95% CI, 1.32–2.03, moderate certainty); and an uncertain effect on neuromuscular weakness (RR 1.13; 95% CI, 0.48–2.65, very low certainty). The panel judged most patients and clinicians would consider these potential adverse events to be outweighed by the potential benefits on mortality and shock reversal and thus made a conditional recommendation favoring IV corticosteroids in patients with septic shock. Given the widespread availability and low cost of hydrocortisone, this recommendation is also applicable to low-resource settings.

The panel chose not to make separate recommendations for patients with pneumonia or ARDS, acknowledging that while subsets of these populations may have sepsis, and benefit from corticosteroids, they are beyond the scope of this guideline and instead addressed in other guidelines [392, 519, 520]. Our conditional recommendation for use of corticosteroids in septic shock is consistent with a recent SCCM guideline on the use of steroids in sepsis, ARDS, and pneumonia [392].

A recent dose–response meta-analysis [518] of steroids found no increased benefit above 260 mg/day of hydrocortisone or equivalent, consistent with the low-dose steroid regimen studied in the largest trial, ADRENAL [521] (200 mg IV hydrocortisone × 7 d) and previous SSC guidance [65, 66]. "In our practice," 88.4% of panel member use IV corticosteroids in patients with septic shock. Among panel members who use IV corticosteroids, 90% prescribe 200 mg hydrocortisone-equivalent per 24-h period, 86% as intermittent doses rather than as continuous infusion. Timing of steroid initiation was more varied. "In our practice," 34% initiate steroids at vasopressor doses of less than 0.2 μg/kg/min norepinephrine, 38% at 0.2–0.3 μg/kg/min, and 28% at greater than 0.3 μg/kg minutes; 32% within 2 h of vasopressor initiation, 34% within 2–4 h, and 33% more than 4 h after vasopressors are started. 63% of the panel never provide concomitant fludrocortisone; 26% sometimes does, and only 10% "usually" or "always" provide it. When given for the sole purpose of septic shock in a patient who is clinically improving, 61% of panelists stop steroids without a taper, whereas 39% taper before discontinuing.

Antipyretics

80. 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 recommendation, very low certainty of evidence) **New**

Remark: This recommendation 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

Fever is a cardinal sign of infection and has been viewed as both a potentially adaptive and maladaptive response to infection. In patients with sepsis or septic shock, it is unclear if antipyretic therapies to treat fever result in clinical benefit or harm. We used a systematic review of 13 RCTs [522], 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. mortality at 28–90 days, with very low certainty due to imprecision (RR 1.02; 95% CI, 0.86–1.21, very low certainty). Three trials reported an uncertain effect on shock reversal at a variety of time points (RR 1.20; 95% CI, 0.84–1.72, very low certainty). Similarly, there was an uncertain effect on LOS (MD −0.12 d; 95% CI, 0.72–0.49, very low certainty).

Given the additional work required for fever control (e.g., medication administration, cooling blankets, etc.) and the absence of clinical benefit, the panel made a conditional recommendation against the use of antipyretic therapy for the purposes of temperature control. The panel made a remark supporting the use of these techniques for symptom control, recognizing that many patients may be uncomfortable with fever and benefit from these therapies for symptom management. The trade-off of symptomatic treatment is that worsening or new fever and infection may be missed, potentially delaying diagnoses. The patient panel agreed with this

assessment, noting that for patients with severe infection, missed diagnoses from masking fever would be worse than foregoing symptomatic treatment of fever, but that this decision would need to be made on a case-by-case basis.

IV Vitamin C

81. For adults with sepsis or septic shock, we "suggest against" using IV vitamin C in patients with sepsis or septic shock (conditional recommendation, low certainty evidence)	**Revisited**

We updated two previous systematic reviews [523, 524] and identified 6 additional trials [525–530] for a total of 55 RCTs evaluating IV vitamin C as monotherapy or in combination with thiamin and corticosteroids. Many trials were small, single-center, and at high risk of bias. We found possibly no difference in mortality at 90 days, reported in seven RCTs at low risk of bias (RR 1.06; 95% CI, 0.95–1.18, low certainty evidence). Among trials reporting mortality at a shorter endpoint (28–30 d), we found a significant subgroup effect, with low-risk-of-bias trials not demonstrating an effect (RR 0.97; 95% CI, 0.82–1.13) and high-risk-of-bias trials suggesting a reduction in mortality (RR 0.85; 95% CI, 0.58–0.92), p value for subgroup differences 0.05. There may be a trivial reduction in the duration of vasopressors (MD 18.7 h; 95% CI, − 25.25 to − 12.11 h, low certainty), and certainty of evidence for all outcomes was low or very low. Although the included studies demonstrated a low risk of adverse events, IV vitamin C can result in factitious hyperglycemia, and the largest trial (LOVIT) proactively modified glucose monitoring strategies to avoid this risk [531]. 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. It is unlikely that small, single-center RCTs, or studies using similar doses to those already evaluated will result in practice-changing evidence on this topic. Despite the current body of evidence, patient representatives to the guidelines panel indicated enthusiasm about ongoing research on vitamin C at different duration or dosage.

IV Immunoglobulin (IVIG)

82. For adults with sepsis or septic shock, we "suggest against" using IV immunoglobulins (conditional recommendation, low certainty evidence)	**Revisited**

We did not identify any new large RCTs evaluating IV immunoglobulin (IVIG) in sepsis or septic shock since the 2021 guidelines [532]. In addition to IgM-enriched vs. non-enriched IgM, we also evaluated subgroups of high- vs. low-dose IVIG. Please see the 2021 SSC guidelines for rationale [65, 66].

Blood purification

83. For adults with sepsis or septic shock, we "suggest against" using blood purification techniques, including hemoperfusion, high-dose hemofiltration, or plasma exchange (conditional recommendation, very low certainty evidence)	**Revisited**
84. For adults with sepsis or septic shock, we "suggest against" using polymyxin B hemoperfusion (conditional recommendation, low certainty evidence)	**Carryover**

Blood purification has been proposed and studied as an adjunctive therapy for sepsis. The rationale for this therapy is to modulate the host immune response by removing excess inflammatory mediators (e.g., inflammatory cytokines or lipopolysaccharides) and/or restoring deficient plasma proteins, thereby improving clinical outcomes by mitigating the manifestations of a dysfunctional immune response [533–535].

We updated existing systematic reviews of blood purification techniques, which included RCTs of hemoperfusion/hemadsorption (41 RCTs), hemofiltration (26 RCTs), and plasmapheresis (4 RCTs) [534, 535]. Despite many RCTs, we are uncertain of the impact of blood purification on mortality. Although there is a signal for a reduction in short-term mortality (28–30 d) with all three techniques (hemoperfusion RR 0.83; 95% CI, 0.71–0.98, low certainty; hemofiltration RR 0.61; 95% CI, 0.61–0.90, low certainty; plasmapheresis RR 0.64; 95% CI, 0.46–0.89, low certainty), the certainty of evidence is low due to varying factors for each technique (hemoperfusion—inconsistency, imprecision; hemofiltration—risk of bias, inconsistency; and plasmapheresis—very serious imprecision). Few trials report on longer-term mortality outcomes for hemoperfusion (four RCTs) and hemofiltration (five RCTs), and these do not demonstrate a beneficial effect for hemoperfusion (RR 1.11; 95% CI, 0.94–1.30, low certainty) or hemofiltration (RR 0.93; 95% CI, 0.78–1.11, very low certainty). There are inconsistent findings suggestive of benefit in non-mortality outcomes. There are many potential reasons for inconsistency across studies, including differences in study quality and impact on co-treatment (e.g., anticoagulation dosing, antimicrobial dosing, absorption of norepinephrine by the blood purification technique). The earliest trials, including some with the largest effects, are over 20 years old and provide sepsis care inconsistent with current standards [536, 537]. The panel reviewed subgroup analyses based upon mechanism (endotoxin absorption vs. inflammatory

mediators) and did not find sufficient evidence to provide a separate recommendation. The substantial resource requirements and impacts upon health equity of these treatments in the absence of clear benefit led to a conditional recommendation against any of these therapies.

There is an important need for more research to identify sepsis phenotypes which may benefit from blood purification treatments (e.g., cutoff levels of lipopolysaccharide or inflammatory markers), and rigorous trials with high-quality ancillary care to ensure the blood purification technique is delivered consistently, safely, and effectively. Rigorous, multicenter RCTs are needed to explore this important area of sepsis research; small single-center RCTs are unlikely to result in practice-changing evidence. There are ongoing trials meeting these criteria, such as the Tigris RCT, NCT03901807 [538]. The Tigris RCTs is evaluating polymyxin B hemoperfusion in a specific subpopulation of patients with septic shock (endotoxin activity assay 0.60–0.89 units and multi-organ failure), informed by an exploratory post hoc analysis of the EUPHRATES RCT suggesting potential benefit in this subpopulation [533, 538, 539].

Vitamin D

85. For adults with sepsis and septic shock, we "suggest against" using vitamin D therapy for sepsis treatment (conditional recommendation, very low certainty of evidence) **New**

Remark: This recommendation 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

Preclinical data suggest that vitamin D has immunomodulatory properties and is essential for lung function [540]. Vitamin D has, thus, been proposed and tested as a therapy to improve outcomes in critically ill patients [540].

We updated an existing systematic review of vitamin D therapy in sepsis, including 11 RCTs [541]. There are uncertain effects of vitamin D therapy on mortality (RR 0.84; 95% CI, 0.68, 1.04, from 9 trials of 2003 patients, very low certainty), duration of mechanical ventilation (MD − 3.74; 95% CI, − 9.18 to 1.70; from 1 trial of 50 patients, very low certainty), and ICU LOS (MD − 4.94; 95% CI, − 8.28 to − 1.59; from 7 trials of 819 patients, very low certainty) in patients with sepsis. Evidence was rated down for risk of bias in the included studies, inconsistency of results, indirectness of data (including studies of general ICU patients), and imprecision. Vitamin D therapy may have little to no impact on adverse events including hypercalcemia (RR 1.30; 95% CI, 0.59, 2.83; from 1 trial of 1036 patients, low certainty) and renal stones (RR 0.14; 95% CI, 0.01, 2.76; from 1 trial of 1014 patients, low certainty) [540]. In the VIOLET trial, the subgroup of patients with sepsis (350 patients) had a higher 90-day mortality risk with high-dose (540,000 international units) enteral vitamin D supplementation (absolute risk increase 12.4%; 95% CI, 3.2–21.6%) [540]. 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. The panel noted this recommendation does not pertain to patients who are on lower doses of vitamin D supplementation for other indications, or standard-dose vitamin D supplementation for treatment of vitamin D deficiency.

IV XueBiJing

86. For adults with sepsis or septic shock, we "suggest against" using XueBiJing injection outside of jurisdictions where it has regulatory approval (conditional recommendation, very low certainty evidence) **New**

XueBiJing is an herbal product (containing Carthami Flos, Paeoniae Radix Rubra, Chuanxiong Rhizoma, Salviae Miltiorrhizae Radix et Rhizoma, and Angelicae Sinensis Radix) that was licensed in 2004 for treatment of sepsis in China [542]. XueBiJing has several potential mechanisms of action against sepsis including antagonistic effects on endotoxin and inflammatory mediators [542].

We updated two systematic reviews [543, 544] of XueBiJing in severe infection, identifying a total of 30 RCTs, of which only 22 could be located. Although the evidence suggests that XueBiJing injection may result in a large reduction in mortality at 28–30 days (RR 0.68; 95% CI, 0.45–1.32, low certainty), as well as moderate-to-large improvements in important outcomes, such as ICU LOS (MD 3.16 d fewer; 95% CI, 4.56 d fewer to 1.77 d fewer, low certainty), the panel had substantial concerns about risk of bias in many included studies and the applicability of the evidence to general sepsis populations outside of China, where all trials were conducted. The two largest high-quality RCTs [542, 545] demonstrate high control group mortality rates despite recruiting relatively non-sick populations (53% and 62% of patients ventilated; with 28-d mortality rates of 26% and 25%, respectively), and a low use of steroids (~ 14%) [542, 545]. These data suggest the included trial's populations may be different from those treated in other ICUs around the world, resulting in indirectness. Lastly, there are substantial feasibility issues as XueBiJing is not available in most countries, and a route to approval of an IV herbal injection

in many jurisdictions is unclear. How the medication would interact with other therapies commonly used in other healthcare systems (e.g., corticosteroids) is unclear. More research to evaluate XueBiJing's effects, including adverse events, in other settings would be required to provide adequate external validation before a recommendation could be made for more widespread use. This is a future research priority.

Additional supportive therapies in patients with sepsis

This section of the guideline addresses additional therapies that are pertinent to patients with sepsis but are not prescribed specifically for the treatment of sepsis.

Stress ulcer prophylaxis

87. 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 recommendation, moderate certainty of evidence) **Revisited**

We updated an existing systematic review [546] with 12 RCTs, including the 2024 REVISE trial [547], which evaluated the impact of proton-pump inhibitors (PPIs) on clinically important gastrointestinal bleeding. PPIs reduced the risk of clinically important gastrointestinal bleeding (9 trials; RR 0.48; 95% CI, 0.30–078, moderate certainty), with an uncertain effect on mortality (12 trials; RR 0.99; 95% CI, 0.93–1.05, very low certainty), *C. difficile* infection (6 trials; RR 0.19; 95% CI, 0.75–1.87, very low certainty), duration of mechanical ventilation (7 trials; MD 1.46 d more; 95% CI, 1.47 fewer to 4.39 more, very low certainty), and pneumonia (8 trials; RR 1.00; 95% CI, 0.92–1.09, very low certainty). Evidence was rated down for indirectness as the trials did not specifically examine patients with sepsis or septic shock. The panel suggested the use of PPIs for stress ulcer prophylaxis in adults with sepsis and septic shock at risk for clinically important bleeding. A recent 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 [548]. The panel noted that there may be an interaction between enteral nutrition and risk of clinically important bleeding. The use of enteral nutrition was reported in eight trials; future studies should examine the need for stress ulcer prophylaxis in enterally fed patients who do not have other risk factors for stress ulcer related bleeding.

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 [549].

This 2024 SCCM and American Society of Health-System Pharmacists Guideline for the Prevention of Stress-Related Gastrointestinal Bleeding in Critically Ill Adults suggests the use of stress ulcer prophylaxis to prevent clinically important bleeding [550]. However, in contrast to this guideline, it suggests the use of either PPIs of H2 receptor antagonists as first-line. We focused our PICO question on PPIs because prior network meta-analysis [550] suggested that PPIs are superior to HR receptor antagonists at preventing clinically important bleeding (RR 0.53; 95% CI, 0.34–0.83) and most recent trials examining stress ulcer prophylaxis (e.g., SUPICU, PEPTIC, REVISE) [547, 551, 552] have used PPIs.

Probiotics

88. For adults with sepsis or septic shock, we "suggest against" using probiotics (conditional recommendation, very low certainty of evidence) **New**

The microbiome (millions of microorganisms that live on and within humans) performs essential functions contributing to health, immune function, and digestion [553, 554]. Microbial dysbiosis is common in critical illness, including sepsis [553, 554]. Microbiome health and clinical outcomes might, therefore, be improved with probiotic therapy (live microorganisms) or symbiotic therapy (combination of live microorganisms and prebiotics, substrates that promote growth of healthy bacteria) [553, 554].

There are over 65 RCTs evaluating probiotics or symbiotics in the ICU, including over 20 different bacterial species alone or in combination [555]. We identified 41 RCTs that evaluated mortality, finding probiotics may have little to no impact on mortality (RR 0.95; 95% CI, 0.87–1.04, low certainty). The effects of probiotics on VAP (18 RCTs RR 0.67; 95% CI, 0.54–0.83, very low certainty) and duration of invasive mechanical ventilation (12 RCTs; MD 3.28 d fewer; 95% CI, 5.67–0.90 d fewer; very low certainty) were uncertain, but point estimates suggested potential benefit. However, when restricted to trials at low risk of bias, including the large PROSPECT trial [556], these 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 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. Future trials of different organisms in sepsis-specific populations and in the recovery phase of sepsis may help to inform future recommendations.

Active fluid removal

89. For adults with septic shock after the acute resuscitation phase, we "suggest" using active fluid removal (conditional recommendation; very low certainty evidence) **New**

Remark: 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

Fluid overload in patients with sepsis and septic shock can lead to tissue edema, impaired oxygen delivery, and organ dysfunction and is associated, in observational studies, with increased mortality [557]. The management of fluid balance appears to be important, therefore, particularly in the "evacuation" or "de-escalation" phase of resuscitation [558, 559]. Recent RCTs have explored the efficacy of active fluid removal and de-resuscitation strategies.

We considered a recent meta-analysis [560] consisting of 13 RCTs [368, 372, 561–571] (2517 patients), of which 10 RCTs [372, 563–571] (2239 patients) assessed de-resuscitation strategies with diuretics only, 3 RCTs [368, 561, 562] assessed de-resuscitation strategies with diuretics plus ultrafiltration; 3 RCTs [368, 372, 562] (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 (RR 0.92, 95% CI, 0.81–1.04, very low certainty), with the use of diuretics only (RR 0.89, 95% CI, 0.78–1.01) having a potentially more favorable effect than the use of diuretics with or without RRT (RR 1.13; 95% CI, 0.83–1.53). The pooled effects on receipt of RRT (RR 0.83, 95% CI, 0.64–1.08, very low certainty), ICU LOS (MD 0.3 d longer; 95% CI, 1.07 shorter to 1.66 longer, very low certainty), vasopressor-free days (MD 0.30 d shorter; 95% CI, 4.25 shorter to 3.64 longer, very low certainty), and health-related quality of life (MD 0.1 units higher; 95% CI, 0.13 lower to 0.33 higher, very low certainty) were likewise uncertain, and the effect on ischemic complications could not be estimated. Mortality among the subgroup of sepsis patients was also uncertain (RR 1.33, 95% CI, 0.75–2.34, very low certainty). Our suggestion for active fluid removal was influenced input from patient representatives to the SSC guidelines, who placed a high value on avoiding edema.

Our suggestion to use active fluid removal after the acute resuscitation phase in septic shock is consistent with the ESICM Clinical Practice Guideline [560] 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.

Future research is needed to address this question specifically in patients with sepsis.

Blood transfusion

90. For adults with sepsis or septic shock, we "recommend" using a restrictive transfusion strategy over a liberal transfusion strategy (strong recommendation, moderate certainty of evidence) **Carryover**

This statement was carried over, see the 2021 SSC guidelines for rationale [65, 66].

Enteral nutrition

91. For adults with sepsis or septic shock, we "suggest" early (within 72 h) initiation of enteral nutrition (conditional recommendation, very low certainty of evidence) **Carryover**

This statement was carried over, see the 2021 SSC guidelines for rationale [65, 66].

Insulin therapy

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

This statement was carried over, see the 2021 SSC guidelines for rationale [65, 66].

Renal replacement therapy

93. 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 recommendation, moderate certainty of evidence)	**Carryover**
94. 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 recommendation, low certainty of evidence)	**Carryover**

These statements were carried over, see the 2021 SSC guidelines for rationale [65, 66].

Sodium bicarbonate

95. 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 recommendation, low certainty of evidence)	**Carryover**
96. For adults with septic shock, severe metabolic acidemia ($pH \leq 7.2$), and acute kidney injury (AKIN score 2 or 3), we "suggest" using sodium bicarbonate therapy (conditional recommendation, very low certainty of evidence)	**Carryover**

These statements were carried over, please see the 2021 SSC guidelines for rationale [65, 66].

Venous thromboembolism prophylaxis

97. For adults with sepsis or septic shock, we "recommend" using pharmacologic venous thromboembolism (VTE) prophylaxis unless a contraindication exists (strong recommendation, moderate certainty of evidence)	**Carryover**
98. For adults with sepsis or septic shock, we "recommend" using low-molecular-weight heparin over unfractionated heparin for VTE prophylaxis (strong recommendation, moderate certainty of evidence)	**Carryover**
99. For adults with sepsis or septic shock, we "suggest" using pharmacological VTE prophylaxis alone over pharmacological VTE prophylaxis plus mechanical VTE prophylaxis (conditional recommendation, moderate certainty of evidence)	**Carryover**

These statements were carried over, see the 2021 SSC guidelines for rationale [65, 66].

Goals of care

Goals of care discussions

100. For adults with sepsis or septic shock, clinicians should discuss goals of care and prognosis with patients and/or families (good practice statement)	**Carryover**
101. For adults with sepsis or septic shock, we "suggest" addressing goals of care early (within 72 h) over late (72 h or later) (conditional recommendation, low certainty of evidence)	**Carryover**

These statements were carried over, see the 2021 SSC guidelines for rationale [65, 66].

Standardized criteria to trigger goals of care discussions

102. For adult patients with sepsis or septic shock, there is "insufficient evidence" to issue a recommendation regarding the use of a specific standardized criterion to identify patients for goals of care discussions	**Revisited**

Goals of care (GoC) discussions are crucial to patient-centered care, especially in serious or life-threatening conditions like sepsis. Although some patients opt for all available medical interventions, others may seek limitations based on prognosis, invasiveness of interventions, and anticipated quality of life. GoC discussions help ensure treatment decisions align with patients' values and preferences. As many patients have not previously documented their GoC preferences, proactive discussions are critical.

In a recent cohort study of over 18,000 patients hospitalized with sepsis, GoC discussions did not occur consistently during hospitalization and there was marked variation in practice across hospitals [572]. Observational studies have reported on the use of electronic medical record, machine learning, and natural language processing to assess GoC documentation and timing [573, 574]. However, a standardized approach to trigger GoC discussions remains unclear.

We identified one non-randomized, before–after pilot study [575] with 84 patients, in which the intervention involved informing the treating hospitalist of the patient's predicted 30-day mortality on hospital day two to promote early GoC discussion. The impact of intervention on GoC discussion was uncertain (GoC discussion occurred in 16.7% of patients in intervention arm vs. 4.8% in the usual care arm, RR 3.50; 95% CI, 0.77–15.88, very low certainty) [575].

Due to limited evidence and inability to determine resource requirements or care equity, the panel made no recommendation on specific standardized criteria to identify patients for GoC discussions. Although we cannot recommend specific standardized criteria, patient representatives to the SSC guidelines advocated that GoC be discussed and addressed in a transparent, explicit, and authentic manner.

Advanced directives

103. Health systems should implement strategies to ensure that patients being discharged from hospital after sepsis or septic shock have the opportunity to execute advanced directives (good practice statement)	**New**
104. For adults with sepsis or septic shock, there is "insufficient evidence" to issue a recommendation on the systematic establishment of advanced care directives before hospital discharge	**New**

Advanced care directives document patient's wishes regarding life-sustaining treatments, providing clear, formal guidance to healthcare providers and family members when the patient cannot communicate or make decisions. These directives typically address a range of medical interventions and help ensure that healthcare decisions are made in alignment with the patient's values, even in the event of incapacity. Although advanced care directives can provide valuable clarity and prevent unwanted or non-concordant treatments, there is insufficient evidence to determine whether the systematic establishment of such directives, particularly before hospital discharge, leads to better patient or family outcomes.

The systematic implementation of GoC discussions, conducted alone or as part of multi-component palliative care or ethics interventions, has been studied in three RCTs, one cluster RCT, and three observational studies of patients with serious illness (including, but not limited to, patients with sepsis) [576–581]. The evaluated intervention probably led to increased changes in code status (one trial; RR, 2.15; 95% CI, 1.44–3.21, moderate certainty) [580] and may have led to increased GoC discussions (one trial; RR 1.24; 95% CI, 1.01–1.54, low certainty). The panel found these findings supportive of value-concordant care, even though GoC conversations, their perceived value, and implementation vary across regions and healthcare systems due to differing sociocultural norms and medical practices. Nonetheless, the panel assessed the evidence to be of very low certainty, so we could not generate a recommendation regarding systematically discussing and establishing advanced care directives before hospital discharge. The panel judged this to be an important issue and that health systems should implement strategies to ensure that patients can execute advanced care directives if they wish.

Time-limited trials

105. For adults with sepsis or septic shock, there is "insufficient evidence" to issue a recommendation regarding formal time-limited trials (TLTs) of critical care ***Remark***: A TLT is a collaborative plan to use life-sustaining therapy for a defined duration, after which response to therapy informs the decision as to whether to continue or escalate curative intent ICU care or to instead focus care on other goals	**New**

A time-limited trial (TLT) is an approach to communication and decision-making that complements other methods of prognostic communication and shared decision-making [582]. A TLT has been defined as "a collaborative plan among clinicians and a patient and/or their surrogate decision maker(s) to use life-sustaining therapy for a defined duration, after which the patient's response to therapy informs the decision as to whether to continue or escalate curative intent ICU care or to instead focus on care with other goals" [583]. ICU care is sometimes delivered discordantly with patient's treatment preferences [584], due to avoidance of prognostication, stemming from uncertainty about treatment responsiveness or clinical inertia [585]. TLTs may help align care with treatment preferences and limit intensity of treatment.

We identified one before–after study that assessed the impact of TLTs on relevant outcomes. In this 3-center study performed in one city, clinicians were trained to perform daily assessments to identify patients at risk for potentially non-beneficial treatments due to advanced illness. TLTs were the default communication and care-planning approach used in family meetings for these patients. During the intervention period, TLTs increased, as did high-quality family meetings. This change in practice was associated with a possible increase in "do not resuscitate" orders (RR 1.27; 95% CI, 1.10–1.45, low certainty), a possible reduction in ICU LOS (MD 2.9 d shorter, 4.89 d shorter to 0.91 d shorter, low certainty), and an unclear impact on hospital mortality (RR 1.00; 95% CI, 0.79–1.26, very low certainty) [586].

Although this study suggested some desirable outcomes with TLTs, the non-randomized design, small sample size, and concerns about whether the intervention truly reflected formal TLTs (vs. simply earlier GoC discussions) led the panel to conclude there was insufficient evidence to issue a recommendation. "In our practice," 64% of the panel use TLTs (specifically: use life-sustaining therapy for a defined duration, after which the patient's response to therapy informs the decision

to continue care directed toward recovery, transition to care focused exclusively on comfort, or extend the trial's duration), and among these, 64% "sometimes" and 27% "always" explicitly discuss the use of TLTs with the patient or surrogate decision maker.

The panel noted that the effects of integrating formal TLTs likely depend on the quality of communication and shared decision-making to which they are added—existing care may include practices functionally equivalent to TLTs. The panel further noted there is evidence of inequity in how ICU clinicians interact with minoritized populations [587, 588], and that if done poorly, or if imposed without effective shared decision-making, TLTs could worsen care and inequity. Additional research is needed to determine the impact of TLTs, to guide individualization of TLTs, on training clinicians to discuss TLTs with patients and surrogates, and on implementing consistent TLT hand-offs between ICU clinicians.

Palliative care

106. 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 (good practice statement)	**Carryover**
107. For adults with sepsis or septic shock, we "suggest against" routine formal palliative care consultation for all patients over palliative care consultation based on clinician judgement (conditional recommendation, low certainty of evidence)	**Carryover**

These statements were carried over, please see the 2021 SSC guidelines for rationale [65, 66].

Transitions of care

In-hospital transitions

108. For adults with sepsis and septic shock admitted to ICU, we "suggest" using a critical care transition program, compared with usual care, upon transfer to the floor (conditional recommendation, very low certainty evidence)	**Carryover**
109. For adults with sepsis or septic shock, we "suggest" using a handoff process of critically important information at transitions of care over no such handoff process (conditional recommendation, very low certainty evidence)	**Carryover**

These statements were carried over, see the 2021 SSC guidelines for rationale [65, 66].

Screening for economic and social support

110. Hospitals and health systems should screen patients with sepsis or septic shock for economic and social support needs (including housing, nutritional, financial, and spiritual support), and make referrals where available to meet these needs (good practice statement)	**Carryover**

This statement was carried over, see the 2021 SSC guidelines for rationale [65, 66].

Medication reconciliation

111. For adults with sepsis or septic shock, comprehensive medication reconciliation should be performed at transitions in care, including at ICU and hospital discharge (good practice statement)	**Revisited**
112. For adults with sepsis or septic shock, we "suggest" comprehensive medication reconciliation using a pharmacist-based approach at transitions in care (conditional recommendation, very low certainty evidence)	**Revisited**

Routine transitions in care among patients with sepsis increase the risk of polypharmacy and inappropriate medications. The panel generated a good practice statement on the importance of comprehensive medication reconciliation whenever a patient transitions from one setting to another.

Regarding a pharmacist-led approach to medication reconciliation at transitions in care, the panel considered 2 [589, 590] before-and-after studies that included 658 patients comparing a pharmacist-based interventions to usual care. These studies used either pharmacy-based electronic hand off tool or a computer-assisted pharmacy work list to reduce continued prescription of atypical antipsychotics and proton-pump inhibitors (pantoprazole) initiated in the ICU. The intervention may reduce the prescription of antipsychotics at ICU transfer (RR 0.84; 95% CI, 0.75–0.94, low certainty) and PPIs at hospital discharge (RR 0.16; 95% CI, 0.09–0.30, low certainty) compared with usual care.

The panel judged that there were large desirable effects, the balance of effects favors the intervention, and the intervention will be acceptable and probably feasible. Such pharmacy review may already be a quality-of-care metric in some healthcare systems. Costs may be moderate but there are no cost-effectiveness studies. The availability of pharmacy support may be limited in low-resource settings.

Hospital discharge planning

113. Clinical teams should provide adults with sepsis or septic shock and their families the opportunity to participate in shared decision-making in post-ICU and hospital discharge planning to ensure discharge plans are acceptable and feasible (good practice statement)	**Carryover**
114. 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 (good practice statement)	**Carryover**
115. For adults with sepsis or septic shock who developed new impairments, hospital discharge plans should include follow-up with clinicians able to support and manage new and long-term sequelae (good practice statement)	**Carryover**
116. Healthcare systems should implement strategies to ensure that patients, their families, and their primary care providers are provided with adequate information to navigate the transition out of hospital (good practice statement)	**New**
117. For adults who survive hospitalization with sepsis or septic shock, there is **insufficient evidence** to issue a recommendation regarding a specific structured multicomponent discharge planning process	**Revisited**

Several of these statements were carried over, please see the 2021 SSC guidelines for rationale [65, 66].

Patients with sepsis and their families often experience several transitions in care before discharge home. Discharge planning, including comprehensive summaries and medication reconciliation, are potential strategies to assure safe transition from acute care, and can provide patients and families with an overview of sepsis-related issues.

The panel completed a meta-analysis of 3 RCTs [591–593] that included a total of 592 patients comparing multi-component discharge planning protocols to usual care. Only one study [593] specifically studied sepsis survivors. Comprehensive discharge planning may improve distressing patient symptom of pain (SMD − 0.16; 95% CI, − 0.36 to 0.03, low certainty), post-traumatic stress (SMD − 0.16; 95% CI, − 0.37 to 0.04, low certainty), and hospital readmissions (RR 0.14; 95% CI, 0.02–1.14, low certainty), with an uncertain impact on anxiety, with a point estimate favoring usual care (SMD 0.19; 95% CI, − 0.09 to 0.47, very low certainty).

The panel considered that while the balance of effects, acceptability, and the equity impact probably favors the intervention, the certainty of evidence was low, there are moderate costs associated with the intervention, and implementation may not always be feasible. The specific components of the interventions in each RCT were highly variable. As such, we were unable to generate a recommendation regarding a specific structured multicomponent discharge planning process. However, the panel assessed that healthcare systems should ensure that patients, families, and their primary care clinicians are provided with adequate information to navigate the transition from hospital to community care.

Education of patients and families on sepsis

118. 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 (good practice statement)	**Carryover**
119. For adults with sepsis and septic shock and their families, we "suggest" offering written and verbal sepsis education (diagnosis, treatment, post-ICU/sepsis syndrome) before hospital discharge and in the follow-up setting (conditional recommendation, very low certainty evidence)	**Carryover**

These statements were carried over, see the 2021 guidelines for rationale [65, 66].

Education of PCPs on sepsis

120. Health systems should implement strategies to ensure clinicians have the knowledge and competency to support sepsis survivors and their families during the post-hospital recovery (good practice statement)	**New**
121. There is "insufficient evidence" to issue a recommendation regarding providing sepsis-focused educational material to primary care providers as compared with usual care	**New**

Sepsis survivors are discharged to PCPs to manage various comorbidities and sequelae after sepsis. PCP knowledge of short- and long-term consequences of sepsis may be important to help manage ongoing symptoms and disabilities. One unblinded RCT (SMOOTH) including 291 sepsis survivors from 9 ICUs examined the effect of a 12-month primary care management intervention on short-term (6-mo) and long-term (24-mo) outcomes [593]. The multi-component intervention included proactive symptom monitoring, clinical decision support for PCPs, and training for patients, nurses, and PCPs on evidence-based post-sepsis care. The trial did not show an improvement in mental health-related quality of life at 6 or 12 months [593]. The panel determined that we cannot issue a recommendation on providing educational material to PCPs due to insufficient evidence. The panel also noted that implementing PCP education would require resources and costs, limiting use in low-resource settings. The patient panel emphasized the importance of educating patients and families about sepsis and that patients

and families can anticipate benefits from educating practitioners with limited exposure to survivors of sepsis or septic shock following discharge.

Overall, there is insufficient evidence to suggest any specific approach to educating primary care providers. Nonetheless, it is important that health systems attempt to improve awareness of post-sepsis sequelae among clinicians caring for patients after sepsis. Further studies are warranted to identify types of educational programs, evaluate acceptability, assess knowledge retention among practitioners, and determine fidelity of the intervention.

Post-discharge care coordination

122. Health systems should implement strategies to support sepsis survivors and their families during the post-hospital recovery (good practice statement)	**New**
123. There is "insufficient evidence" to make a recommendation on early post-hospital discharge follow-up vs. routine post-hospital discharge follow-up	**Revisited**

We did not identify any new studies since the 2021 SSC guidelines evaluating the impact of timing of follow-up on clinical outcomes. Please see the 2021 SSC guidelines for rationale [65, 66].

Long-term outcomes and recovery

Post-hospital evaluation and management

124. Health systems should facilitate assessment and follow-up for physical, cognitive, and emotional problems after hospital discharge for sepsis or septic shock (good practice statement)	**Carryover**
125. For adult survivors of hospitalization for sepsis or septic shock, we "suggest" offering post critical illness follow-up services (conditional recommendation, low certainty evidence) ***Remark***: Follow-up services may vary in format, intensity, and duration, depending on locally available resources and patient needs	**Revisited**

Patients who survive hospitalization with sepsis or septic shock often suffer from new or worsening physical, cognitive, and emotional problems which they are often ill-equipped to navigate [7, 594].

We analyzed eight RCTs [593, 595–601] evaluating the impact of post critical illness follow-up services consisting of variable approaches to the timing of follow-up care, the type of care delivered, and the outcome measures obtained. The included RCTs provided peer support programs with multi-component interventions across transitions of care, follow-up clinics, and primary care management programs. We found probable small improvements in quality-of-life physical health component (SMD − 0.25; 95% CI, − 0.40 to − 0.11), symptoms of anxiety (MD − 1.41; 95% CI, − 2.50 to − 0.32) and post-traumatic stress (SMD − 0.20, 95% CI, − 0.37 to − 0.02), and a potential reduction in hospital readmissions (RR 0.88; 95% CI, 0.73–1.07).

One study provided cost-effectiveness data [596]; however, the heterogeneity of interventions precludes the ability to evaluate the cost-effectiveness of follow-up services, and this should be explored in future trials. The panel judged that low-resource settings might lack the resources to deliver multi-component care. In addition, rural populations might not be able to engage in the delivery of in-person interventions, which could lead to inequities. Future research should include remote interventions. Nonetheless, the panel also recognized that the provision of post-hospital care could potentially reduce health inequities in certain disadvantaged communities [602]. Although available data yielded low certainty in the efficacy of this intervention, patient experience of these programs appears positive [603], and they may provide benefit to patients, families, and clinicians. We suggest that adult survivors of hospitalization with sepsis or septic shock be provided with the opportunity to receive sepsis- and critical illness follow-up services. We acknowledge that the format, intensity, and duration of such services may vary by patient needs and locally available resources.

Despite a clear emphasis from the public panel members and other patient and family groups internationally on the importance of follow-up care for sepsis survivors [604], high-quality evidence is lacking. There is a need to prioritize research in this area. Future work should consider emerging technologies in the delivery of post-sepsis care as well as understanding patient selection and care delivery intensity.

Physical rehabilitation

126. For adult survivors of hospitalization for sepsis or septic shock who received invasive mechanical ventilation > 48 h, we "suggest" offering physical rehabilitation services after hospital discharge (conditional recommendation; low certainty evidence) ***Remark***: Physical rehabilitation services may vary in format, intensity, and duration, depending on locally available resources and patient needs	**Revisited**

New physical and functional disability is common following critical illness with sepsis or septic shock and is associated with reduced quality of life among survivors [7, 605–607].

We identified 12 RCTs evaluating physical rehabilitation vs. standard care after hospital discharge that

included 782 patients who had been mechanically ventilated for 48 h or longer [596, 608–618]. These studies included a variety of physical rehabilitation interventions designed to ameliorate physical health sequelae of critical illness or sepsis. In meta-analysis, the interventions were associated with possible improvement in various outcomes, including physical function using the six minute walk test (SMD 0.21, 95% CI, − 0.06 to 0.48, low certainty), quality of life physical health component (SMD 0.20 higher; 95% CI, − 0.10 to 0.51, low certainty), quality of life mental health component (SMD 0.29 higher; 95% CI, − 0.02 to 0.59, low certainty), cognitive function (SMD 0.55 higher; 95% CI, 0.14–0.97, low certainty), and symptoms of depression (MD − 1.10 lower; 95% CI, − 2.30 to 0.10). Adverse events were uncommon.

The panel considered that there was important variability in the included patient populations, the dosage, type, and duration of the interventions delivered, and the domain, method, and timing of outcome measures. This variability and the low certainty evidence precluded a strong recommendation.

Although there were no concerns about acceptability of physical rehabilitation as an intervention for survivors of sepsis, there were concerns about the moderate resources and costs required to deliver the intervention, and the ability to equitably deliver physical rehabilitation services remains unclear. There were insufficient data to suggest any specific approach to physical rehabilitation, and the optimal approach will vary by patient and setting.

Given the prevalence of new or worsening physical problems experienced by sepsis survivors and the importance of physical recovery to sepsis survivors and their families, the panel suggests offering post-critical illness physical rehabilitation for survivors of sepsis or septic shock, although we acknowledge that such services may vary in format, intensity, and duration depending on patient needs and locally available resources.

Mental health services

127. For adult survivors of hospitalization for sepsis or septic shock, we "suggest" offering services that support mental health after hospital discharge (conditional recommendation, low certainty evidence) ***Remark***: Mental health support services may vary in format, intensity, and duration, depending on locally available resources and patient needs	**Revisited**
128. Adult survivors of hospitalization for sepsis or septic shock who demonstrate clinical symptoms of mental health disorders should be referred to appropriate healthcare professionals for evaluation and management (good practice statement)	**Revisited**

Patients who survive sepsis often suffer a wide range of mental health symptoms in the months and years following hospital discharge [7, 619]. Although some of these conditions may have predated the hospitalization for sepsis, there is evidence to suggest that many are newly acquired, developing presumably due to sepsis itself or as a consequence of hospital and ICU treatment for sepsis. Post-sepsis mental health diagnoses are wide-ranging, and include anxiety, depression, and post-traumatic stress disorder [7, 619]. Importantly, similar findings have been reported in broader ICU survivor cohorts and following similar conditions, such as severe COVID-19, acute respiratory failure, and ARDS [607].

We identified nine RCTs testing variable interventions designed to ameliorate mental health sequelae of critical illness or sepsis [593, 600, 620–626]. In meta-analysis, the interventions increased satisfaction with care (SMD 0.48; 95% CI, 0.19–0.78, moderate certainty) and possibly decreased the depressive symptoms (RR 0.60; 95% CI, 0.32–1.09, low certainty). The effects on anxiety and PTSD symptoms were uncertain but point estimates suggested a possible decrease in anxiety symptoms (RR 0.69; 95% CI, 0.39–1.23, very low certainty) and increase in PTSD symptoms (RR 1.22; 95% CI, 0.94–1.59, very low certainty).

There was considerable variability in the populations included, the manner and type of interventions delivered, and the domain, method, and timing of outcomes across included studies. This variability hampered our ability to issue strong recommendations. Nevertheless, there was broad agreement around some core principles, and the panel suggests that adult survivors of hospitalization for sepsis or septic shock be offered services that support mental health after hospital discharge. Such services may vary in format, intensity, and duration, depending on patient needs and locally available resources. Although this conditional recommendation applies to any survivor of sepsis or septic shock, the panel acknowledged that not all survivors may experience mental health symptoms. In low-resource settings, which lack specialized personnel and have poor availability of mental health services, this recommendation is particularly challenging. The panel agreed that all patients who demonstrate signs of mental health symptoms should be referred for formal diagnostic evaluation and management by an appropriate healthcare professional.

Finally, mental health disorders can coincide with physical and cognitive impairment, and interactions can occur between these domains of impairment. Consequently, interventions targeting one domain may affect another, and the most effective interventions may require multiple components, tailored to a particular patient's condition.

Cognition-targeted therapy

129. For adult survivors of hospitalization for sepsis or septic shock, there is "insufficient evidence" to issue a recommendation regarding cognition-targeted therapies vs. usual care **New**

Remark: Where cognitive-targeted therapies are being used, it is reasonable to continue using them as they are likely acceptable and feasible

Cognitive impairment is common among patients who survive sepsis and is a major determinant of caregiving needs and costs after sepsis [605]. It has been estimated that irreversible cognitive damage after critical illness and sepsis may be associated with an additional 40 h per week of informal care provided by caregivers, the equivalent of a full-time job [605]. Therefore, strategies to improve cognitive function after sepsis are important.

We identified 4 RCTs (513 total patients) evaluating therapies designed to cognitive function after critical illness or sepsis [613, 627–629]. These cognition-focused interventions possibly reduced the prevalence of cognitive impairment at follow-up (RR 0.54; 95% CI, 0.29–1.03, low certainty), possibly improved global cognitive function using various measures (SMD 1.04; 95% CI, 0.73–1.35, low certainty), and possibly improved physical function and mental health-related quality of life. The impact on all other outcomes was uncertain, but point estimated favored the intervention.

Although the point estimates for all outcomes favored the intervention, the studies were small, and both the interventions and outcome measures varied across studies. Although the balance of effects probably favored the intervention, the resources required were moderate and the certainty of evidence was very low. The panel judged that the potential personnel, training, and resource requirements to deliver this intervention warrant higher quality evidence before this intervention can be recommended. Therefore, we were unable to issue a recommendation regarding the use of cognition-targeted interventions to improve cognitive function among survivors of sepsis or septic shock.

Cognitive impairment is common, debilitating, and associated with lasting implications for patients' independence and quality of life. Given the absence of high-quality evidence for interventions to address this complication of sepsis, there is a need for studies that identify effective and feasible cognition-targeted therapies to facilitate cognitive recovery among adults who survive hospitalization for sepsis. Researchers should prioritize evaluating the efficacy and cost-effectiveness of cognition-targeted therapies after sepsis and septic shock.

Supplementary Information
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Author contribution

Drs. Prescott and Antonelli served as guidelines co-chairs. Drs. Alhazzani and Møller served as methods co-leads. Drs. Alshamsi, Azevedo, Belley-Cote, De Waele, Derde, Dionne, Evans, Gershengorn, Hodgson, Honarmand, Kesecioglu, McIntyre, Mer, Nunnally, Oczkowski, Rochwerg served in guidelines leadership roles. Akinola, Akuamoah-Boateng, Alberto, Angus, Arabi, Azoulay, Cecconi, Convocar, De Pascale, Doi, Du, Egi, Elie-Turenne, Ferrer, Fox-Robichaud, French, Freund, Gong, Hale, Hammond, Hashmi, Heunks, Iwashyna, Jacob, Klompas, Kwizera, Leeies, Lejnieks, Levy, Machado, Maia, Masur, Maves, McGloughlin, McPeake, Mohr, Myatra, Ostermann, Peake, Pletz, Roberts, Rosa, Sawyer, Schorr, Simpson, Weng, and Wiersinga, served as guidelines panelists. Drs. Rhodes and Coopersmith served as Surviving Sepsis Campaign Leaders.

Declarations

Conflicts of interest

Dr. Fox-Robichaud reported serving as the scientific director of Sepsis Canada and as principal investigator (PI) on a study funded by the Canadian Institutes of Health Research. Dr. Rhodes reported serving as an advisor for Maquet. Dr. Kwizera reported receiving research support from Fisher and Paykel and

Vygon and serving as primary author on a trial funded by Wellcome Trust. Dr. Du reported serving as president of the Chinese Association of Critical Care Physicians and the Chinese College of Critical Care Medicine. Dr. Rochwerg reported membership on the American Thoracic Society (ATS) guideline committee for non-invasive respiratory support and the corticosteroids in sepsis guideline committee. Dr. Hodgson reported an executive role at Monash Partners, research support from the National Health and Medical Research Council (NHMRC), and membership on the European Respiratory Society/ATS ICU rehabilitation guideline committee. Dr. Angus reported serving as a senior editor for JAMA. Dr. Azoulay reported receiving lecture fees from Baxter, Gilead, Alexion, and Pfizer. Dr. Machado reported serving as PI on the NOVA trial funded by Biolab, receiving speaking fees from BioMérieux, and serving as an advisor for Baxter. Dr. Prescott reported serving as a consultant for Aurobac Therapeutics. Dr. De Waele reported serving as a consultant for Roche Diagnostics. Dr. Roberts reported serving as a consultant for BioMérieux and as primary author on a study funded by the NHMRC. Dr. McPeake reported serving as a consultant for AstraZeneca, with payments made to her institution. Dr. Wiersinga reported receiving research support from Moderna and serving as PI on a study funded by Amsterdam UMC. Dr. Kesecioglu reported receiving lecture honoraria from Dräger Medical Equipment. Dr. Doi reported receiving research support from Nipro and is a Council member of the Japanese Society of Intensive Care. Dr. Honarmand reported receiving research support from the Lawson Health Research Institute and serving on the ATS guideline committee for early mobilization. Dr. Evans reported serving as vice-chair of rapid response for CHEST and chair of the ABIM council. Dr. Alberto reported membership in the World Federation of Critical Care Nurses and serving as a reviewer for a systematic review funded by Universidad del Salvador. Dr. Heunks reported serving as a consultant for Liberate Medical and receiving research support from the ATS. Dr. Derde reported involvement in the IMPRINT and ECRAID-Base trials; receiving financial and drug contributions for the REMAP-CAP trial from Roche, Sanofi, SOBI, Faron, and Dimerix (all paid to her institution). Dr. Azevedo reported receiving speaking fees from Baxter, MSD, and Nestle. Dr. Hashmi reported membership in Asia Pacific Sepsis Alliance and ISARIC. Dr. Nunnally reported serving as co-chair of the Surviving Sepsis Campaign Research Committee and participating in activities for ASA, AHA, and SOCCA. Dr. Ostermann reported research support from Baxter and BioMérieux (paid to her institution) and coauthoring articles on hemoadsorption. Dr. Antonelli reported serving as an advisor for AstraZeneca, Grifols, Menarini, and Shionogi, and as a consultant for Baxter. Dr. Klompas reported receiving royalties from UpToDate and research support from the AHRQ and CDC. Dr. Gong reported serving as a section editor for Wolters Kluwer. Dr. Ego reported serving as vice-chair of the Japanese Society of Intensive Care Medicine. Dr. Moller reported sponsorship of the EMPRESS RCT. Dr. Leeies reported membership in the Canadian Critical Care Society and the Canadian Society for Transplantation. Dr. Hammond reported receiving research support and IV fluids from Baxter Healthcare. Dr. Mohr reported serving as primary author on a study funded by AHRQ and HRSA and serving on the board of Society for Academic Emergency Medicine. Dr. Ferrer reported receiving speaking fees from Pfizer and owning stock in Grifols. Dr. Rosa reported receiving grants from the Brazilian Ministry of Health paid to his company. Dr. Sawyer reported receiving consultancy fees from Molnlycke, Shionogi, and AbbVie and research support from the NIH. Dr. Maves reported research support from AiCuris, Biotest, Geovax, and Merck (paid to his institution) and serving as a consultant for Shionogi. Dr. Peake reported serving as co-PI on the ARISE FLUIDS trial. Dr. Jacob reported serving as PI and CSO for the STAIRS study. Dr. Oczkowski reported serving as a consultant for VitalAire. Dr. McGloughlin reported serving as a consultant for the WHO and as clinical director for the Australian Living Evidence Collaboration. Dr. Simpson reported serving on the editorial board of CHEST SEEK. Dr. Iwashyna reported coauthoring the Haines article. Dr. Arabi reported serving as PI on the SCREEN trial and chair of the Saudi Critical Care Society trials group. Dr. Freund reported serving as PI on the 1BED trial.

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