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GUIDELINES

Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021

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Introduction

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Sepsis and septic shock are major healthcare problems, impacting millions of people around the world each year and killing between one in three and one in six of those it affects [2–4].[1] Early identification and appropriate management in the initial hours after the development of sepsis improve outcomes.

The recommendations in this document are intended to provide guidance for the clinician caring for adult patients with sepsis or septic shock in the hospital setting. Recommendations from these guidelines cannot replace the clinician's decision-making capability when presented with a unique patient's clinical variables. These guidelines are intended to reflect best practice (Table 1).

Screening and early treatment

Screening for patients with sepsis and septic shock

Recommendation
1. For hospitals and health systems, we **recommend** using a performance improvement programme for sepsis, including sepsis screening for acutely ill, high-risk patients and standard operating procedures for treatment
Strong recommendation, moderate quality of evidence for screening
Strong recommendation, very low-quality evidence for standard operating procedures

Rationale

Sepsis performance improvement programmes generally consist of sepsis screening, education, measurement

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of sepsis bundle performance, patient outcomes, and actions for identified opportunities [25, 26]. Despite some inconsistency, a meta-analysis of 50 observational studies on the effect of performance improvement programmes showed that these programmes were associated with better adherence to sepsis bundles along with a reduction in mortality (OR 0.66; 95% CI 0.61–0.72) in patients with sepsis and septic shock [27]. The specific components of performance improvement did not appear to be as important as the presence of a programme that included sepsis screening and metrics.

Sepsis screening tools are designed to promote early identification of sepsis and consist of manual methods or automated use of the electronic health record (EHR). There is wide variation in diagnostic accuracy of these tools with most having poor predictive values, although the use of some was associated with improvements in care processes [28–31]. A variety of clinical variables and tools are used for sepsis screening, such as systemic inflammatory response syndrome (SIRS) criteria, vital signs, signs of infection, quick Sequential Organ Failure Score (qSOFA) or Sequential Organ Failure Assessment (SOFA) criteria, National Early Warning Score (NEWS), or Modified Early Warning Score (MEWS) [26, 32]. Machine learning may improve performance of screening tools, and in a meta-analysis of 42,623 patients from seven studies for predicting hospital-acquired sepsis the pooled area under the receiving-operating curve (SAUROC) (0.89; 95% CI 0.86–0.92); sensitivity (81%; 95% CI 80–81), and specificity (72%; 95% CI 72–72) was higher for machine learning than the SAUROC for traditional screening tools such as SIRS (0.70), MEWS (0.50), and SOFA (0.78) [32].

Screening tools may target patients in various locations, such as in-patient wards, emergency departments, or intensive care units (ICU) [28–30, 32]. A pooled analysis of three RCTs did not demonstrate a mortality benefit of active screening (RR 0.90; 95% CI 0.51–1.58) [33–35]. However, while there is wide variation in sensitivity and specificity of sepsis screening tools, they are an important component of identifying sepsis early for timely intervention.

Standard operating procedures are a set of practices that specify a preferred response to specific clinical circumstances [36]. Sepsis standard operating procedures, initially specified as Early Goal Directed Therapy have evolved to "usual care" which includes a standard approach with components of the sepsis bundle, early identification, lactate, cultures, antibiotics, and fluids [37]. A large study examined the association between implementation of state-mandated sepsis protocols, compliance, and mortality. A retrospective cohort study of 1,012,410 sepsis admissions to 509 hospitals in the United States in a retrospective cohort examined mortality before (27 months) and after (30 months) implementation of New York state sepsis regulations, with a concurrent control population from 4 other states [38]. In this comparative interrupted time series, mortality was lower in hospitals with higher compliance with achieving the sepsis bundles successfully.

Lower resource countries may experience a different effect. A meta-analysis of 2 RCTs in Sub-Saharan Africa found higher mortality (RR 1.26; 95% CI 1.00–1.58) with standard operating procedures compared with usual care, while it was decreased in one observational study (adjusted hazard ratio [HR]; 95% CI 0.55–0.98) [39].

Recommendation

2. We **recommend against** using qSOFA compared to SIRS, NEWS, or MEWS as a single screening tool for sepsis or septic shock

Strong recommendation, moderate-quality evidence

Rationale

The qSOFA uses 3 variables to predict death and prolonged ICU stay in patients with known or suspected sepsis: a Glasgow Coma Score < 15, a respiratory rate ≥ 22 breaths/min and a systolic blood pressure ≤ 100 mmHg. When any two of these variables are present simultaneously the patient is considered to be qSOFA positive. Data analysis used to support the recommendations of the 3rd International Consensus Conference on the Definitions of Sepsis identified qSOFA as a predictor of poor outcome in patients with known or suspected infection, but no analysis was performed to support its use as a screening tool [5]. Since that time numerous studies have investigated the potential use of the qSOFA as a screening tool for sepsis [40–42]. The results have been contradictory as to its usefulness. Studies have shown that qSOFA is more specific but less sensitive than having two of four SIRS criteria for early identification of infection induced organ dysfunction [40–43]. Neither SIRS nor qSOFA are ideal screening tools for sepsis and the bedside clinician needs to understand the limitations of each. In the original derivation study, authors found that only 24% of infected patients had a qSOFA score 2 or 3,

but these patients accounted for 70% of poor outcomes [5]. Similar findings have also been found when comparing against the National Early warning Score (NEWS) and the Modified Early warning Score (MEWS) [44]. Although the presence of a positive qSOFA should alert the clinician to the possibility of sepsis in all resource settings; given the poor sensitivity of the qSOFA, the panel issued a strong recommendation against its use as a single screening tool.

Recommendation

3. For adults suspected of having sepsis, we **suggest** measuring blood lactate

Weak recommendation, low-quality evidence

Rationale

The association of lactate level with mortality in patients with suspected infection and sepsis is well established [45, 46]. Its use is currently recommended as part of the SSC Hour-1 sepsis bundle for those patients with sepsis [47, 48], and an elevated lactate is part of the Sepsis-3 definition of septic shock [49]. It has been suggested that lactate can also be used to screen for the presence of sepsis among undifferentiated adult patients with clinically suspected (but not confirmed) sepsis. Several studies have assessed the use of lactate in this context [50–52].

The lactate cutoffs determining an elevated level ranged from 1.6 to 2.5 mmol/L, although diagnostic characteristics were similar regardless of the cutoff. Sensitivities range from 66 to 83%, with specificities ranging from 80 to 85%. Pooled positive and negative likelihood ratios from the three studies are 4.75 and 0.29, respectively. Studies showed an association between the use of point-of-care lactate measurements at presentation and reduced mortality; however, the results are inconsistent [53]. In summary, the presence of an elevated or normal lactate level significantly increases or decreases, respectively, the likelihood of a final diagnosis of sepsis in patients with suspected sepsis. However, lactate alone is neither sensitive nor specific enough to rule-in or rule-out the diagnosis on its own. Lactate testing may not be readily available in many resource-limited settings [54–61]. Therefore, we issued a weak recommendation favouring the use of serum lactate as an adjunctive test to modify the pretest probability of sepsis in patients with suspected but not confirmed sepsis.

Initial resuscitation

Recommendations

4. Sepsis and septic shock are medical emergencies, and we **recommend** that treatment and resuscitation begin immediately

Best Practice Statement

5. For patients with sepsis induced hypoperfusion or septic shock we **suggest** that at least 30 mL/kg of intravenous (IV) crystalloid fluid should be given within the first 3 h of resuscitation

Weak recommendation, low-quality evidence

6. For adults with sepsis or septic shock, we **suggest** using dynamic measures to guide fluid resuscitation, over physical examination or static parameters alone

Weak recommendation, very low-quality evidence

Remarks

Dynamic parameters include response to a passive leg raise or a fluid bolus, using stroke volume (SV), stroke volume variation (SVV), pulse pressure variation (PPV), or echocardiography, where available

7. For adults with sepsis or septic shock, we **suggest** guiding resuscitation to decrease serum lactate in patients with elevated lactate level, over not using serum lactate

Weak recommendation, low-quality evidence

Remarks

During acute resuscitation, serum lactate level should be interpreted considering the clinical context and other causes of elevated lactate

8. For adults with septic shock, we **suggest** using capillary refill time to guide resuscitation as an adjunct to other measures of perfusion

Weak recommendation, low-quality evidence

Rationale

Timely, effective fluid resuscitation is crucial for the stabilisation of sepsis-induced tissue hypoperfusion in sepsis and septic shock. Previous guidelines recommend initiating appropriate resuscitation immediately upon recognition of sepsis or septic shock and having a low threshold for commencing it in those patients where sepsis is not proven but is suspected. Although the evidence stems from observational studies, this recommendation is considered a best practice and there are no new data suggesting that a change is needed.

The 2016 SSC guideline issued a recommendation for using a minimum of 30 ml/kg (ideal body weight) of IV crystalloids in initial fluid resuscitation. This fixed volume of initial resuscitation was based on observational evidence [62]. There are no prospective intervention 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 length of stay in ICU, irrespective of comorbidities, including end-stage kidney disease and heart failure [63]. In the

PROCESS [64], ARISE [65] and PROMISE [66] trials, the average volume of fluid received pre-randomisation was also in the range of 30 ml/kg, suggesting that this fluid volume has been adopted in routine clinical practice [67].

Most patients require continued fluid administration following initial resuscitation. Such administration needs to be balanced with the risk of fluid accumulation and potential harm associated with fluid overload, in particular, prolonged ventilation, progression of acute kidney injury (AKI) and increased mortality. One of the most important principles of managing complex septic patients is the need for a detailed initial assessment and ongoing re-evaluation of the response to treatment. To avoid over- and under-resuscitation, fluid administration beyond the initial resuscitation should be guided by careful assessment of intravascular volume status and organ perfusion. Heart rate, central venous pressure (CVP) and systolic blood pressure alone are poor indicators of fluid status. Dynamic measures have demonstrated better diagnostic accuracy at predicting fluid responsiveness compared with static techniques. Dynamic measures include passive leg raising combined with cardiac output (CO) measurement, fluid challenges against stroke volume (SV), systolic pressure or pulse pressure, and increases of SV in response to changes in intrathoracic pressure. In a systematic review and meta-analysis, dynamic assessment to guide fluid therapy was associated with reduced mortality (RR 0.59; 95% CI 0.42–0.83), ICU length of stay (MD −1.16 days; 95% CI −1.97 to −0.36), and duration of mechanical ventilation (−2.98 h; 95% CI −5.08 to −0.89) [3]. However, in one other meta-analysis, there was no significant difference in mortality between septic patients resuscitated with a volume responsiveness-guided approach compared with standard resuscitative strategies [68]. Most data arise from high income settings and a paucity of evidence exists in resource-limited settings to guide optimal titration of fluid resuscitation as well as the appropriate safety endpoints. An RCT in patients with sepsis and hypotension in Zambia showed that early protocolised resuscitation with administration of IV fluids guided by jugular venous pressure, respiratory rate, and arterial oxygen saturation only, was associated with significantly more fluid administration in the first 6 h [median 3.5L (IQR 2.7–4.0) versus 2.0L (IQR 1.0–2.5)] and higher hospital mortality (48.1% versus 33%) than standard care [69].

If fluid therapy beyond the initial 30 ml/kg administration is required, clinicians may use repeated small boluses guided by objective measures of SV and/or CO. In post-cardiac surgery patients, fluid challenges of 4 ml/kg compared to 1–3 ml/kg increased the sensitivity of detecting fluid responders and non-responders based on measurement of CO [70]. In resource-limited regions where measurement of CO or SV may not be possible, a > 15% increase in pulse pressure could indicate that the patient is fluid responsive utilizing a passive leg-raise test for 60–90 seconds [71, 72].

Serum lactate is an important biomarker of tissue hypoxia and dysfunction, but is not a direct measure of tissue perfusion [73]. Recent definitions of septic shock include increases in lactate as evidence of cellular stress to accompany refractory hypotension [1]. Previous iterations of these guidelines have suggested using lactate levels as a target of resuscitation in the early phases of sepsis and septic shock, based on earlier studies related to goal-directed therapy and meta-analyses of multiple studies targeting reductions in serum lactate in comparison to "standard care" or increases in central venous oxygen saturation [74, 75]. The panel recognises that normal serum lactate levels are not achievable in all patients with septic shock, but these studies support resuscitative strategies that decrease lactate toward normal. Serum lactate level should be interpreted considering the clinical context and other causes of elevated lactate. As with sepsis screening, lactate measurement may not always be available in some resource-limited settings.

When advanced haemodynamic monitoring is not available, alternative measures of organ perfusion may be used to evaluate the effectiveness and safety of volume administration. Temperature of the extremities, skin mottling and capillary refill time (CRT) have been validated and shown to be reproducible signs of tissue perfusion [76, 77]. The ANDROMEDA-SHOCK study evaluated whether a resuscitation strategy targeting CRT normalisation was more effective than a resuscitation strategy aiming at normalisation or decreasing lactate levels by 20% every 2 h in the first 8 h of septic shock [58]. At day 3, the CRT group had significantly less organ dysfunction as assessed by SOFA score [mean SOFA score 5.6 (SD 4.3) versus 6.6 (SD 4.7); $p = 0.045$]. 28-day mortality was 34.9% in the peripheral perfusion group and 43.4% in the lactate group, but this difference did not reach statistical significance (HR 0.75; 95% CI 0.55–1.02). Despite the absence of a clear effect on mortality, using CRT during resuscitation has physiologic plausibility and is easily performed, non-invasive, and no cost. However, this approach should be augmented by careful, frequent, and comprehensive patient evaluation to predict or recognise fluid overload early, particularly where critical care resources are constrained. Relevant consideration of the background pathology or pathological processes pertinent to the patient should also inform management [69, 78].

Mean arterial pressure

Recommendation
9. For adults with septic shock on vasopressors, we **recommend** an initial target mean arterial pressure (MAP) of 65 mm Hg over higher MAP targets
Strong recommendation, moderate-quality evidence

Rationale

MAP is a key determinant of mean systemic filling pressure, which in turn, is the major driver of venous return and CO. Increasing MAP therefore usually results in increased tissue blood flow and augments the supply side of tissue perfusion. While some tissues, such as the brain and kidneys have the ability to auto-regulate blood flow, MAPs below a threshold, usually understood to be approximately 60 mm Hg, are associated with decreased organ perfusion, which tracks linearly with MAP [79]. Previous SSC guidelines recommended targeting a MAP of greater than 65 mm Hg for initial resuscitation. The recommendation was based principally on a RCT in septic shock comparing patients who were given vasopressors to target a MAP of 65–70 mm Hg, versus a target of 80–85 mm Hg [80]. This study found no difference in mortality, although a sub-group analysis demonstrated a 10.5% absolute reduction in renal replacement therapy (RRT) with higher MAP targets among patients with chronic hypertension. In addition, targeting higher MAP with vasopressors was associated with a higher risk of atrial fibrillation. A limitation of this study was that the average MAP in both arms exceeded the targeted range. A meta-analysis of two RCTs on this topic supported that higher MAP targets did not improve survival in septic shock (RR 1.05; 95% CI 0.90–1.23) [81].

A recent RCT, monitored to ensure protocol and MAP target compliance, compared a "permissive hypotension" (MAP 60–65 mm Hg) group with a "usual care" group that received vasopressors and MAP targets set by the treating physician in patients aged 65 years and older with septic shock [82, 83]. The intervention group in this study achieved a mean MAP of 66.7 mm Hg, compared with 72.6 mm Hg in the usual care group. Among 2463 analysed patients, there was significantly less exposure to vasopressors in the intervention group, measured by duration of vasopressor infusion and total vasopressor doses expressed in norepinephrine equivalents. Ninety-day mortality in the permissive hypotension and usual care groups was similar (41.0% vs 43.8%).

Given the lack of advantage associated with higher MAP targets and the lack of harm among elderly patients with MAP targets of 60–65 mm Hg, the panel recommends targeting a MAP of 65 mm Hg in the initial resuscitation of patients with septic shock who require vasopressors.

Admission to intensive care

Recommendation
10. For adults with sepsis or septic shock who require ICU admission, we **suggest** admitting the patients to the ICU within 6 h
Weak recommendation, low-quality evidence

Rationale

The outcome of critically ill patients depends on timely application of critical care interventions in an appropriate environment. Outside the ICU, septic patients are typically seen in the emergency department (ED) and hospital wards. Delayed admissions of critically ill patients from ED are associated with decreased sepsis bundle compliance and increased mortality, ventilator duration, and ICU and hospital length of stay [84]. Data on the optimal time for transfer to the ICU stem from observational studies and registry databases.

In an observational study of 401 ICU patients, authors reported an increase in ICU mortality of 1.5% for each hour delay of ED to ICU transfer [85]. A retrospective observational study of 14,788 critically ill patients in the Netherlands showed a higher hospital mortality for the higher ED to ICU time quintiles (2.4–3.7 h and > 3.7 h) compared with the lowest ED to ICU time quintile (< 1.2 h) [86]. When adjusted for severity of illness, an ED to ICU time > 2.4 h was associated with increased hospital mortality in patients with higher illness severity (ORs of 1.20 (95% CI 1.03–1.39). Patients with sepsis were not studied separately.

Another study evaluated 50,322 ED patients admitted to 120 US ICUs [87]. Mortality increased when ED stay exceeded 6 h (17% vs 12.9%, $p < 0.001$). Among hospital survivors, the delayed admission group had a longer hospital stay, higher mortality, and higher rates of mechanical ventilation and central venous catherisation. Similarly, another study of 12,380 ward patients in 48 UK hospitals showed that [88] delayed admission to ICU led to higher 90-day mortality and further physiological deterioration.

Based on existing data, timely admission of critically ill patients to an ICU environment may result in better patient outcomes. There is also evidence of improved patient satisfaction, increased patient safety, better patient flow and improved staff morale [89]. However, although critical care services are likely best delivered in an ICU environment, there are multiple reasons why immediate transfer of critically ill patients with sepsis to an ICU may not always be possible, in particular in lower and middle income countries (LMIC), where ICU bed availably can be limited. In this case, regular assessment, evaluation, and appropriate treatment should not be delayed, independent of patient location.

Infection

Diagnosis of infection

Recommendation

11. For adults with suspected sepsis or septic shock but unconfirmed infection, we **recommend** continuously re-evaluating and searching for alternative diagnoses and discontinuing empiric antimicrobials if an alternative cause of illness is demonstrated or strongly suspected

Best Practice statement

Rationale

In previous versions of these guidelines, we highlighted the importance of obtaining a full screen for infectious agents prior to starting antimicrobials wherever it is possible to do so in a timely fashion [12, 13]. As a best practice statement, we recommended that appropriate routine microbiologic cultures (including blood) should be obtained before starting antimicrobial therapy in patients with suspected sepsis and septic shock if it results in no substantial delay in the start of antimicrobials (i.e. < 45 min). This recommendation has not been updated in this version but remains as valid as before.

The signs and symptoms of sepsis are nonspecific and often mimic multiple other diseases [90–92]. Since there is no "gold standard" test to diagnose sepsis, the bedside provider cannot have a differential diagnosis of sepsis alone in a patient with organ dysfunction. Indeed, a third or more of patients initially diagnosed with sepsis turn out to have non-infectious conditions [90, 93, 94]. Best practice is to continually assess the patient to determine if other diagnoses are more or less likely, especially since a patient's clinical trajectory can evolve significantly after hospital admission, increasing or decreasing the likelihood of a diagnosis of sepsis. With this uncertainty, there can be significant challenges in determining when it is "appropriate" to de-escalate or discontinue antibiotics.

Another major challenge is implementing a system that reminds clinicians to focus on the fact that the patient is still receiving antibiotics each day, especially as providers rotate in and out of the care team. Systems that promote such reassessment by automatic stop orders, electronic prompts, or mandatory check lists all seem useful in theory, but each has disadvantages in terms of provider acceptance or assuring that providers thoughtfully assess the need for antibiotics rather than checking a box in the electronic record or reflexively acknowledging a prompt, without considering its underlying rationale [95].

We did not identify any direct or indirect evidence assessing this important issue. Thus, clinicians are strongly encouraged to discontinue antimicrobials if a non-infectious syndrome (or an infectious syndrome that does not benefit from antimicrobials) is demonstrated or strongly suspected. Since this situation is not always apparent, continued reassessment of the patient should optimise the chances of infected patients receiving antimicrobial therapy and non-infected patients avoiding therapy that is not indicated.

Time to antibiotics

Recommendations

12. For adults with possible septic shock or a high likelihood for sepsis, we **recommend** administering antimicrobials immediately, ideally within 1 h of recognition

Strong recommendation, low quality of evidence (Septic shock)

Strong recommendation, very low quality of evidence (Sepsis without shock)

13. For adults with possible sepsis without shock, we **recommend** rapid assessment of the likelihood of infectious versus non-infectious causes of acute illness

Best Practice Statement

Remarks

Rapid assessment includes history and clinical examination, tests for both infectious and non-infectious causes of acute illness and immediate treatment for acute conditions that can mimic sepsis. Whenever possible this should be completed within 3 h of presentation so that a decision can be made as to the likelihood of an infectious cause of the patient's presentation and timely antimicrobial therapy provided if the likelihood of sepsis is thought to be high

14. 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 antimicrobials within 3 h from the time when sepsis was first recognised

Weak recommendation, very low quality of evidence

15. For adults with a low likelihood of infection and without shock, we **suggest** deferring antimicrobials while continuing to closely monitor the patient.

Weak recommendation, very low quality of evidence

Rationale

Early administration of appropriate antimicrobials is one of the most effective interventions to reduce mortality in patients with sepsis [96–98]. Delivering antimicrobials to patients with sepsis or septic shock should therefore be treated as an emergency. The imperative to provide antimicrobials as early as possible, however, must be balanced against the potential harms associated with administering unnecessary antimicrobials to patients without infection [99, 100]. These include a range of adverse events such as allergic or hypersensitivity reactions, kidney injury, thrombocytopenia, *Clostridioides difficile* infection, and antimicrobial resistance [101–106]. Accurately diagnosing sepsis is challenging as sepsis can present in subtle ways, and some presentations that first appear to be sepsis turn out to be non-infectious conditions [90, 93, 107, 108]. Evaluating the likelihood of infection and severity-of-illness for each patient with suspected sepsis should inform the necessity and urgency of antimicrobials [99, 100].

The mortality reduction associated with early antimicrobials appears strongest in patients with septic shock, where a number of studies have reported a strong association between time-to-antibiotics and death in patients with septic shock but weaker associations in patients

without septic shock [98, 109, 110]. In a study of 49,331 patients treated at 149 New York hospitals, each additional hour of time from ED arrival to administration of antimicrobials was associated with 1.04 increased odds of in-hospital mortality, $p < 0.001$ (1.07 (95% CI 1.05–1.09) for patients receiving vasopressors vs. 1.01 (95% CI 0.99–1.04) for patients not on vasopressors) [98]. In a study of 35,000 patients treated at Kaiser Permanente Northern California, each additional hour of time from ER arrival to administration of antimicrobials was associated with 1.09 increased odds of in-hospital mortality (1.07 for patients with "severe" sepsis (lactate ≥ 2, at least one episode of hypotension, required non-invasive or invasive mechanical ventilation or has organ dysfunction) and 1.14 for patients with septic shock); which equated to a 0.4% absolute mortality increase for "severe" sepsis and a 1.8% absolute increase for septic shock [110]. Finally, in a study of 10,811 patients treated in four Utah hospitals, each hour delay in time from ED arrival to administration of antimicrobials was associated with 1.16 increased odds of in-hospital and 1.10 increased odds of 1-year mortality (1.13 in patients with hypotension vs 1.09 in patients without hypotension) [111]. Other studies, however, did not observe an association between antimicrobial timing and mortality [112–117].

It should be noted that all the aforementioned studies were observational analyses and hence at risk of bias due to insufficient sample size, inadequate risk-adjustment, blending together the effects of large delays until antibiotics with short delays, or other study design issues [118].

In patients with sepsis without shock, the association between time to antimicrobials and mortality within the first few hours from presentation is less consistent [98, 110]. Two RCTs have been published [119, 120]. One failed to achieve a difference in time-to-antimicrobials between arms [120]. The other found no significant difference in mortality despite a 90-min difference in median time interval to antimicrobial administration [119]. Observational studies do, however, suggest that mortality may increase after intervals exceeding 3–5 h from hospital arrival and/or sepsis recognition [98, 111, 119, 120]. We therefore suggest initiating antibiotics in patients with possible sepsis without shock as soon as sepsis appears to be the most likely diagnosis, and no later than 3 h after sepsis was first suspected if concern for sepsis persists at that time.

Overall, given the high risk of death with septic shock and the strong association of antimicrobial timing and mortality, the panel issued a strong recommendation to administer antimicrobials immediately, and within 1 h, in all patients with potential septic shock. In addition, for patients with confirmed/very likely sepsis, we recommend antimicrobials be administered immediately (Fig. 1). For patients with possible sepsis without shock, we recommend a rapid assessment of infectious and non-infectious etiologies of illness be undertaken to determine, within 3 h, whether antibiotics should be administered or whether antibiotics should be deferred while continuing to monitor the patient closely.

Limited data from resource-limited settings suggest that timely administration of antimicrobials in patients with sepsis and septic shock is beneficial and potentially feasible [121–126]. Access and availability of a wide range of antimicrobials in such settings may however vary [54, 55, 57, 59, 61]. The availability and turn-around time for laboratory testing, rapid infectious diagnostic, imaging, etc. varies widely by regions and settings. As such, the rapid assessment of infectious and non-infectious etiologies of illness will differ across settings, depending on what is feasible to achieve. Recent recommendations pertaining to the use of antimicrobials in patients with sepsis and septic shock in resource-limited settings are in line with the current recommendations [123].

Biomarkers to start antibiotics

Recommendation
16. For adults with suspected sepsis or septic shock, we **suggest against** using procalcitonin plus clinical evaluation to decide when to start antimicrobials, as compared to clinical evaluation alone
Weak recommendation, very low quality of evidence

Rationale

Procalcitonin is undetectable in healthy states, but rises rapidly in response to pro-inflammatory stimuli, especially bacterial infections [127]. In theory, procalcitonin levels in combination with clinical evaluation may facilitate the diagnosis of serious bacterial infections and prompt early initiation of antimicrobials. In a meta-analysis of 30 studies (3244 patients), procalcitonin had a pooled sensitivity of 77% and specificity of 79% for sepsis in critically ill patients [128].

We identified direct evidence from three RCTs that compared procalcitonin-guided protocols for antibiotic initiation vs usual care [129–131]. A meta-analysis of the three trials ($n = 1769$ ICU patients) found no difference in short-term mortality (RR 0.99; 95% CI 0.86–1.15), length of ICU stays (MD 0.19 days; 95% CI − 0.98 to 1.36) or length of hospitalisation (MD 7.00 days; 95% CI − 26.24 to 12.24). Long-term mortality, readmission rates and hospital-free days were not reported in any of the trials, and no relevant studies on the costs associated with use of procalcitonin were found. In general, knowledge about the undesirable effects was lacking, and the quality of evidence was very low. Published guidelines for the management of community-acquired pneumonia recommend initiation of antimicrobials for patients with community-acquired pneumonia regardless of procalcitonin level [132].

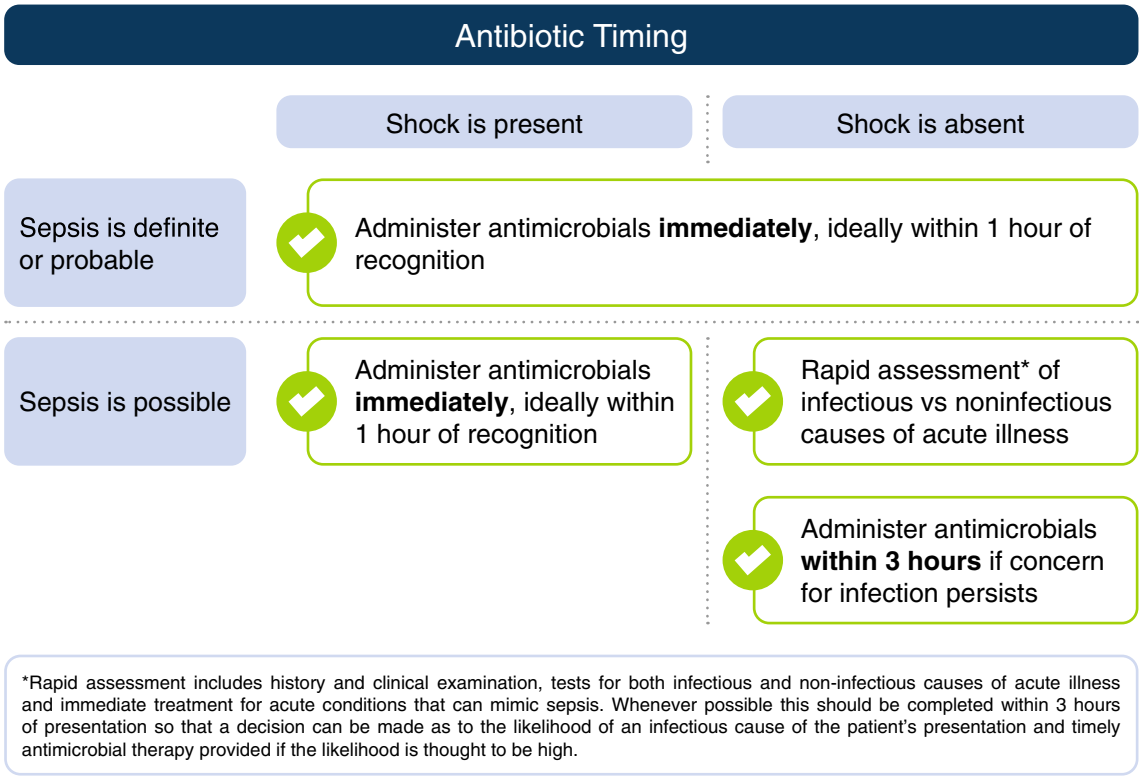

Fig. 1 Recommendations on timing of antibiotic administration

With no apparent benefit, unknown costs, and limited availability in some settings including low- and middle-income countries (LMICs), the panel issued a weak recommendation against using procalcitonin to guide antimicrobial initiation in addition to clinical evaluation.

Antimicrobial choice

Recommendations
17. For adults with sepsis or septic shock at high risk of methicillin resistant staph aureus (MRSA), we **recommend** using empiric antimicrobials with MRSA coverage over using antimicrobials without MRSA coverage *Best Practice statement*
18. For adults with sepsis or septic shock at low risk of methicillin resistant staph aureus (MRSA), we **suggest against** using empiric antimicrobials with MRSA coverage, as compared with using antimicrobials without MRSA coverage *Weak recommendation, low quality of evidence*

Rationale

The decision on whether to include an antibiotic active against MRSA in an empiric treatment regimen for sepsis and septic shock depends upon (a) the likelihood that the patient's infection is caused by MRSA, (b) the risk of harm associated with withholding treatment for MRSA in a patient with MRSA, and (c) the risk of harm associated with MRSA treatment in a patient without MRSA.

MRSA accounts for approximately 5% of culture-positive infections among critically ill patients [133], and may be decreasing according to some reports [134, 135]. The incidence of MRSA varies, however, by region (ranging from ~ 2% in Western Europe to 10% in North America) and by patient-related characteristics [133, 136, 137]. Patient-related risk factors for MRSA include prior history of MRSA infection or colonisation, recent IV antibiotics, history of recurrent skin infections or chronic wounds, presence of invasive devices, haemodialysis, recent hospital admissions and severity of illness [136, 138–142].

Observational data on the impact of including MRSA coverage in empiric regimens vary. Some studies focus on patients with documented MRSA infections, while others evaluate the impact of MRSA coverage in undifferentiated patients. Among patients with documented MRSA infections, delays of > 24–48 h until antibiotic administration are associated with increased mortality in some studies [143–147], but not in others [148–154]. Among undifferentiated patients with pneumonia or sepsis,

broad-spectrum regimens including agents active against MRSA were associated with higher mortality, particularly among patients without MRSA [137, 151, 155, 156]. The undesirable effects associated with unnecessary MRSA coverage are also supported by studies showing an association between early discontinuation of MRSA coverage and better outcomes in patients with negative nares or bronchoalveolar lavage (BAL) MRSA PCR [157–159].

Failure to cover for MRSA in a patient with MRSA may be harmful, but unnecessary MRSA coverage in a patient without MRSA may also be harmful. Data from RCTs, including the evaluation of nasal swab testing to withhold therapy for MRSA, are warranted, and studies on rapid diagnostic tools and clinical prediction rules for MRSA are needed.

Recommendations

19. For adults with sepsis or septic shock and high risk for multidrug resistant (MDR) organisms, we **suggest** using two antimicrobials with gram-negative coverage for empiric treatment over one gram-negative agent
Weak recommendation, very low quality of evidence

20. For adults with sepsis or septic shock and low risk for MDR organisms, we **suggest against** using two Gram-negative agents for empiric treatment, as compared to one Gram-negative agent
Weak recommendation, very low quality of evidence

21. For adults with sepsis or septic shock, we **suggest against** using double gram-negative coverage once the causative pathogen and the susceptibilities are known
Weak recommendation, very low quality of evidence

Rationale

Considering the increasing frequency of MDR bacteria in many parts of the world and associations between delays in active therapy and worse outcomes, the initial use of multidrug therapy is often required to ensure the empiric regimen includes at least one effective agent that is active against the offending organism [12, 13]. In the empiric phase—before causative agent(s) and susceptibilities are known, the optimal choice of antibiotic therapy depends on the local prevalence of resistant organisms, patient risk factors for resistant organisms, and the severity of illness. In the directed/targeted phase, once causative agent(s) and susceptibilities are known, sustained double gram-negative coverage is rarely necessary except for patients with highly resistant organisms.

This was borne out in a recent systematic review with meta-analysis of 10 RCTs, no differences in mortality or other patient-important outcomes between empiric mono- vs. combination antibiotic therapy in adult ICU patients with severe sepsis or septic shock were observed, also when taking disease severity into consideration [160]. Results from the largest RCT included in the meta-analysis (a comparison of sustained courses of moxifloxacin and meropenem vs meropenem alone in a low endemic resistance setting) were consistent with the findings from the meta-analysis [161].

Recommendations about the use of more than one gram-negative agent for empiric treatment over one gram-negative agent are challenging given clinical heterogeneity, including patient characteristics, source of infection, causative agents, and antibiotic resistance patterns. Local information about the resistance patterns of the most common causative agents of sepsis is essential to choose the most appropriate empiric antibiotic therapy. For this reason, we refrained from proposing recommendations regarding double gram-negative coverage in patients with sepsis or septic shock overall, but instead recommend tailoring the use of double coverage based on patients' risk of MDR pathogens. Factors to guide this decision include: proven infection or colonisation with antibiotic-resistant organisms within the preceding year, local prevalence of antibiotic-resistant organisms, hospital-acquired/healthcare associated (versus community-acquired infection), broad-spectrum antibiotic use within the preceding 90 days, concurrent use selective digestive decontamination (SDD), travel to a highly endemic country within the preceding 90 days (see https://resistancemap.cddep.org/) and hospitalisation abroad within the preceding 90 days [162–164]. In the directed/targeted phase, once causative agent(s) and susceptibilities are known, sustained double gram-negative coverage is not necessary except possibly for patients with highly resistant organisms with no proven safe and efficacious therapeutic option.

The overall quality of evidence was very low, and the direct costs of antibiotics can increase with the routine use of multiple agents for treatment. This may specifically have an impact in resource-limited settings.

In general, in patients at high risk for MDR organisms, we suggest using two gram negative agents for empiric treatment to increase the likelihood of adequate coverage, while in patients with a low risk for MDR organisms, we suggest using a single agents for empiric treatment, as there are no apparent benefits of using two agents and the a risk of antimicrobial-associated undesirable effects, including direct toxicity, *Clostridioides difficile* infection and development of antibiotic resistance [165]. Empiric double coverage of gram-negative bacilli is most important in patients at high risk for resistant organisms with severe illness, particularly septic shock.

Antifungal therapy

Recommendations
22. For adults with sepsis or septic shock at high risk of fungal infection, we **suggest** using empiric antifungal therapy over no antifungal therapy *Weak recommendation, low quality of evidence*
23. For adults with sepsis or septic shock at low risk of fungal infection, we **suggest against** empiric use of antifungal therapy *Weak recommendation, low quality of evidence*

Rationale

Sepsis and septic shock due to fungi are most commonly observed in ICUs and are associated with poor outcomes [166–170]. Some observational studies suggested that prompt initiation of appropriate empiric antifungal therapy may be associated with a reduction in mortality, however these studies do not prove a causal relationship between antifungal therapy and outcome, nor do they clarify the role of timing of treatment, and some other studies have failed to show this association [167, 171–173].

In an updated meta-analysis of empiric antifungal therapy versus no antifungal therapy in adult critically ill patients, no difference in short-term mortality was observed. In the largest and most recent RCT—EMPIRICUS—there was also no difference in outcome between patients receiving empiric antifungal therapy (micafungin) and patients receiving placebo [174]. The overall quality of evidence was low, and treatment with empiric antifungals may be associated with increased costs.

While patients with sepsis or septic shock may not in general benefit from empiric antifungals, some patients with particular risk factors for fungal infection may, for example patients with febrile neutropenia who fail to defervesce after 4–7 days of broad-spectrum antibacterial therapy are at increased risk of having fungal disease (Table 2) [175, 176]. The risk of *Candida* sepsis or septic shock for other immunosuppressed populations is highly disease- and therapy-specific. Importantly, the decision to start empiric antifungal therapy depends on the type and number of risk factors, along with the local epidemiology of fungal infections.

Accordingly, we suggest using empiric antifungal therapy in patients at high risk of fungal infection, while we suggest avoiding this if the risk is low. The choice of antifungal agent for empiric therapy depends on multiple issues including host factors, prior colonisation and infection, prior exposure to prophylactic or therapeutic antifungal therapy, comorbidities, and the toxicities and drug interactions of the therapeutic options.

Antiviral therapy

Recommendation
24. We make **no recommendation** on the use of antiviral agents

Rationale

Viral infections encompass a broad spectrum of pathogens and diseases in humans but—apart from specific clinical situations such as epidemics/pandemics—are rarely the primary cause of sepsis. In a recent large international point prevalence study, viruses were documented in less than 4% of infections [133].

Historically, influenza has been one of the more common viral causes of sepsis. However, it is unclear to what extent the primary viral infection as opposed to bacterial pneumonia co-infection is the cause of organ dysfunction in these patients [219–222]. More recently, SARS-CoV-2 (causing COVID-19) is now responsible for many cases of infection and sepsis [223]. The ongoing pandemic due to SARS-CoV-2 has resulted in the understanding of this condition changing very rapidly [224].

While there appears to be no overall effect of neuraminidase inhibitors on mortality in patients with influenza-related pneumonia, there may be an effect when administered early in the course of the disease [225]. For detailed information on specific antiviral therapy, including for influenza and SARS CoV-2, please refer to dedicated clinical practice guidelines [226–228].

Immunocompromised patients are particularly vulnerable to viral infections, including patients with neutropenia, human immunodeficiency virus (HIV) infection, haematological malignancies and haematopoietic stem cell transplantation or solid organ transplants; in these patients herpes simplex virus, Epstein-Barr virus, cytomegalovirus, and respiratory viruses such as adenoviruses, can cause severe disease [229]. Tropical and subtropical regions have endemic and epidemic outbreaks of zoonotic viral infections including those caused by Dengue, Ebola, Lassa, Marburg, Sin Nombre and Chikungunya virus. Many of these can manifest with clinical signs of sepsis, particularly in their early stages. Unfortunately, effective therapies are lacking for most of these viruses.

The desirable effects of empiric antiviral therapy are unknown, and as for other antimicrobial agents there is a risk of undesirable effects [165]. Data on cost effectiveness were not available.

Due to the rapidly changing position related to antiviral therapies in critically ill patients presenting with several acute respiratory failure, this panel decided not to issue a recommendation on antiviral therapies and to refer the reader to more specific guidelines [226].

Delivery of antibiotics

Recommendation
25. For adults with sepsis or septic shock, we **suggest** using prolonged infusion of beta-lactams for maintenance (after an initial bolus) over conventional bolus infusion *Weak recommendation, moderate quality of evidence*

Rationale

Beta-lactam antibiotics may be subject to changes in important pharmacokinetic parameters in the setting of sepsis and septic shock resulting in sub-therapeutic concentrations [230, 231]. As opposed to conventional intermittent infusion (infusion ≤ 30 min), administration by prolonged IV infusion, either as an extended infusion (antibiotic infused over at least half of the dosing interval) or as a continuous infusion, results in sustained beta-lactam concentrations which align with the pharmacodynamics of these drugs.

Two meta-analyses reported similar results supporting reduced short-term mortality (RR 0.70; 95% CI 0.57–0.87) with prolonged infusion of beta-lactams [232, 233].

No trials assessed the undesirable effects of continuous infusion, and the desirable effects were deemed important, while the overall quality of evidence was moderate. Prolonged infusion is a feasible intervention if suitable IV access is present, and resources are available to ensure the beta-lactam is infused over the necessary duration. The latter may be an issue in some resource limited settings, including LMICs.

Administration of a loading dose of antibiotic before prolonged infusion is essential to avoid delays to achieving effective beta-lactam concentrations [234]. Over the course of therapy, both extended and continuous infusions will occupy a venous catheter/lumen more than an intermittent infusion and drug-stability and drug-drug compatibility considerations are important to ensure effectiveness of antibiotic and other IV drug therapies [235].

The reduction in short-term mortality from prolonged infusion of beta-lactams is significant with the intervention being feasible with negligible cost implications and no data suggesting inferior outcomes with prolonged infusion. Accordingly, we suggest prolonged infusion of beta-lactams over conventional bolus infusion in patients with sepsis and septic shock if the necessary equipment is available. Further research is needed on long-term outcomes, on the effect on emergence of antimicrobial resistance, and on costs of prolonged versus bolus infusion of beta-lactams [236].

Pharmacokinetics and pharmacodynamics

Recommendation
26. For adults with sepsis or septic shock, we **recommend** optimising dosing strategies of antimicrobials based on accepted pharmacokinetic/pharmacodynamic (PK/PD) principles and specific drug properties *Best Practice Statement*

Rationale

Antibiotics are subject to changes in PK/PD parameters in sepsis and septic shock where resultant concentrations may be too low risking clinical failure, or too high leading to toxicity (Table 3) [237–239]. Augmented renal clearance [240], AKI [241], hypoalbuminemia [242], RRT [243, 244], and extracorporeal membrane oxygenation [245, 246] are examples of common scenarios that affect the concentrations of some antibiotics. Administration of antibiotics using an approach that adheres to PK/PD principles and using dosing regimens developed in patients with sepsis and septic shock is more likely to result in effective and safe drug concentrations compared to use of dosing recommendations provided in the manufacturer's product information [247].

We did not identify any relevant data quantifying the value of dosing based on PK/PD principles in adults with sepsis and septic shock. Although there are no data on this topic directly derived from adults with sepsis and septic shock, data from a broader patient population, critically ill patients, support an increased likelihood of achieving effective and safe antibiotic concentrations when applying PK/PD principles to dosing [248]. The application of PK/PD principles can be aided by clinical pharmacists [249]. Some studies in critically ill patients have reported benefits in terms of clinical cure [237, 250–253].

Applying a PK/PD approach to antibiotic dosing requires support from knowledgeable clinician team members [254], use of a patient population-specific guideline document [255], use of therapeutic drug monitoring [256], and/or use of dosing software [238, 248]. Some of these potential approaches to application of PK/PD-based dosing require extra resources, some of which may not be available in all settings, in which case freely available resources such as dosing nomograms can be used [234, 257, 258]. Guidance on how to apply a PK/PD approach for specific drug classes have been described elsewhere [237]. Further research is needed on short- and long-term mortality outcomes, effect on emergence of antimicrobial resistance, impact on drug stability within prolonged infusions and health economics of different PK/PD-based approaches to dosing (see Table 3).

Table 1 Table of current recommendations and changes from the previous 2016 recommendations

2021 TABLE OF RECOMMENDATIONS

NEW and **UPDATED** recommendations are highlighted with a blue background

SCREENING FOR PATIENTS WITH SEPSIS AND SEPTIC SHOCK

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

MODERATE — Screening

VERY LOW — Standard operating procedures

2016 STATEMENT

*"We **recommend** that hospitals and hospital systems have a performance improvement programme for sepsis including sepsis screening for acutely ill, high risk patients."*

MODERATE — 2 We **recommend against** using qSOFA compared to SIRS, NEWS, or MEWS as a single screening tool for sepsis or septic shock.

VERY LOW — 3 For adults suspected of having sepsis, we **suggest** measuring blood lactate.

INITIAL RESUSCITATION

BEST PRACTICE — 4 Sepsis and septic shock are medical emergencies, and we **recommend** that treatment and resuscitation begin immediately.

LOW — 5 For patients with sepsis induced hypoperfusion or septic shock we **suggest** that at least 30 mL/kg of intravenous (IV) crystalloid fluid should be given within the first 3 hours of resuscitation.

2016 STATEMENT

*"We **recommend** that in the initial resuscitation from sepsis-induced hypoperfusion, at least 30ml/kg of intravenous crystalloid fluid be given within the first 3 hours."*

VERY LOW — 6 For adults with sepsis or septic shock, we **suggest** using dynamic measures to guide fluid resuscitation, over physical examination, or static parameters alone.

LOW — 7 For adults with sepsis or septic shock, we **suggest** guiding resuscitation to decrease serum lactate in patients with elevated lactate level, over not using serum lactate.

LOW — 8 For adults with septic shock, we **suggest** using capillary refill time to guide resuscitation as an adjunct to other measures of perfusion.

MEAN ARTERIAL PRESSURE

MODERATE — 9 For adults with septic shock on vasopressors, we **recommend** an initial target mean arterial pressure (MAP) of 65 mm Hg over higher MAP targets.

BEST PRACTICE STATEMENT

NO RECOMMENDATION

WEAK RECOMMENDATION

STRONG RECOMMENDATION

WEAK RECOMMENDATION AGAINST

STRONG RECOMMENDATION AGAINST

HIGH QUALITY EVIDENCE

MODERATE QUALITY EVIDENCE

LOW QUALITY EVIDENCE

VERY LOW QUALITY EVIDENCE

UPGRADE

DOWNGRADE

NO CHANGE FROM PREVIOUS GUIDELINES

NEW / CHANGED RECOMMENDATION

Table 1 (continued)

ADMISSION TO INTENSIVE CARE

LOW	10 For adults with sepsis or septic shock who require ICU admission, we **suggest** admitting the patients to the ICU within 6 hours.

INFECTION

BEST PRACTICE	11 For adults with suspected sepsis or septic shock but unconfirmed infection, we **recommend** continuously re-evaluating and searching for alternative diagnoses and discontinuing empiric antimicrobials if an alternative cause of illness is demonstrated or strongly suspected.
	12 For adults with possible septic shock or a high likelihood for sepsis, we **recommend** administering antimicrobials immediately, ideally within one hour of recognition.
LOW	Septic shock
VERY LOW	Sepsis without shock
	2016 STATEMENT *"We **recommend** that administration of intravenous antimicrobials should be initiated as soon as possible after recognition and within one hour for both a) septic shock and b) sepsis without shock."*
BEST PRACTICE	13 For adults with possible sepsis without shock, we **recommend** rapid assessment of the likelihood of infectious versus non-infectious causes of acute illness.
VERY LOW	14 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 antimicrobials within 3 hours from the time when sepsis was first recognized.
	2016 STATEMENT *"We **recommend** that administration of intravenous antimicrobials should be initiated as soon as possible after recognition and within one hour for both a) septic shock and b) sepsis without shock."*
VERY LOW	15 For adults with a low likelihood of infection and without shock, we **suggest** deferring antimicrobials while continuing to closely monitor the patient.
	2016 STATEMENT *"We **recommend** that administration of intravenous antimicrobials should be initiated as soon as possible after recognition and within one hour for both a) septic shock and b) sepsis without shock."*
VERY LOW	16 For adults with suspected sepsis or septic shock, we **suggest against** using procalcitonin plus clinical evaluation to decide when to start antimicrobials, as compared to clinical evaluation alone.

BEST PRACTICE STATEMENT

NO RECOMMENDATION

WEAK RECOMMENDATION

STRONG RECOMMENDATION

WEAK RECOMMENDATION AGAINST

STRONG RECOMMENDATION AGAINST

HIGH QUALITY EVIDENCE

MODERATE QUALITY EVIDENCE

LOW QUALITY EVIDENCE

VERY LOW QUALITY EVIDENCE

UPGRADE

DOWNGRADE

NO CHANGE FROM PREVIOUS GUIDELINES

NEW / CHANGED RECOMMENDATION

Table 1 (continued)

BEST PRACTICE	17 For adults with sepsis or septic shock at high risk of MRSA, we **recommend** using empiric antimicrobials with MRSA coverage over using antimicrobials without MRSA coverage. *2016 STATEMENT* *"We **recommend** empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage."*
LOW	18 For adults with sepsis or septic shock at low risk of MRSA, we **suggest against** using empiric antimicrobials with MRSA coverage, as compared with using antimicrobials without MRSA coverage. *2016 STATEMENT* *"We **recommend** empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage."*
VERY LOW	19 For adults with sepsis or septic shock and high risk for multidrug resistant (MDR) organisms, we **suggest** using two antimicrobials with gram-negative coverage for empiric treatment over one gram-negative agent.
VERY LOW	20 For adults with sepsis or septic shock and low risk for multidrug resistant (MDR) organisms, we **suggest against** using two gram-negative agents for empiric treatment, as compared to one gram-negative agent.
VERY LOW	21 For adults with sepsis or septic shock, we **suggest against** using double gram-negative coverage once the causative pathogen and the susceptibilities are known.
LOW	22 For adults with sepsis or septic shock at high risk of fungal infection, we **suggest** using empiric antifungal therapy over no antifungal therapy. *2016 STATEMENT* *"We **recommend** empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage."*
LOW	23 For adults with sepsis or septic shock at low risk of fungal infection, we **suggest against** empiric use of antifungal therapy. *2016 STATEMENT* *"We **recommend** empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage."*
	24 We make no recommendation on the use of antiviral agents.
MODERATE	25 For adults with sepsis or septic shock, we **suggest** using prolonged infusion of beta-lactams for maintenance (after an initial bolus) over conventional bolus infusion.
BEST PRACTICE	26 For adults with sepsis or septic shock, we **recommend** optimising dosing strategies of antimicrobials based on accepted pharmacokinetic/pharmacodynamic (PK/PD) principles and specific drug properties.

BEST PRACTICE STATEMENT

NO RECOMMENDATION

WEAK RECOMMENDATION

STRONG RECOMMENDATION

WEAK RECOMMENDATION AGAINST

STRONG RECOMMENDATION AGAINST

HIGH QUALITY EVIDENCE

MODERATE QUALITY EVIDENCE

LOW QUALITY EVIDENCE

VERY LOW QUALITY EVIDENCE

UPGRADE

DOWNGRADE

NO CHANGE FROM PREVIOUS GUIDELINES

NEW / CHANGED RECOMMENDATION

Table 1 (continued)

BEST PRACTICE	27 For adults with sepsis or septic shock, we **recommend** rapidly identifying or excluding a specific anatomical diagnosis of infection that requires emergent source control and implementing any required source control intervention as soon as medically and logistically practical.
BEST PRACTICE	28 For adults with sepsis or septic shock, we **recommend** prompt removal of intravascular access devices that are a possible source of sepsis or septic shock after other vascular access has been established.
VERY LOW	29 For adults with sepsis or septic shock, we **suggest** daily assessment for de-escalation of antimicrobials over using fixed durations of therapy without daily reassessment for de-escalation.
VERY LOW	30 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.
LOW	31 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 antimicrobials over clinical evaluation alone.
HEMODYNAMIC MANAGEMENT	
MODERATE	32 For adults with sepsis or septic shock, we **recommend** using crystalloids as first-line fluid for resuscitation.
LOW	33 For adults with sepsis or septic shock, we **suggest** using balanced crystalloids instead of normal saline for resuscitation. *2016 STATEMENT* *"We **suggest** using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock"*
MODERATE	34 For adults with sepsis or septic shock, we **suggest** using albumin in patients who received large volumes of crystalloids.
HIGH	35 For adults with sepsis or septic shock, we **recommend against** using starches for resuscitation.
MODERATE	36 For adults with sepsis and septic shock, we **suggest against** using gelatin for resuscitation. *2016 STATEMENT* *"We **suggest** using crystalloids over gelatins when resuscitating patients with sepsis or septic shock."*

BEST PRACTICE STATEMENT

NO RECOMMENDATION

WEAK RECOMMENDATION

STRONG RECOMMENDATION

WEAK RECOMMENDATION AGAINST

STRONG RECOMMENDATION AGAINST

HIGH QUALITY EVIDENCE

MODERATE QUALITY EVIDENCE

LOW QUALITY EVIDENCE

VERY LOW QUALITY EVIDENCE

UPGRADE

DOWNGRADE

NO CHANGE FROM PREVIOUS GUIDELINES

NEW / CHANGED RECOMMENDATION

Table 1 (continued)

!!		37 For adults with septic shock, we **recommend** using norepinephrine as the first-line agent over other vasopressors.
	HIGH	Dopamine
	MODERATE	Vasopressin
	LOW	Epinephrine
	LOW	Selepressin
	VERY LOW	Angiotensin 2
!	MODERATE	38 For adults with septic shock on norepinephrine with inadequate mean arterial pressure levels, we **suggest** adding vasopressin instead of escalating the dose of norepinephrine.
!	LOW	39 For adults with septic shock and inadequate mean arterial pressure levels despite norepinephrine and vasopressin, we **suggest** adding epinephrine.
!	LOW	40 For adults with septic shock, we **suggest against** using terlipressin.
!	LOW	41 For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we **suggest** either adding dobutamine to norepinephrine or using epinephrine alone.
!	LOW	42 For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we **suggest against** using levosimendan.
!	VERY LOW	43 For adults with septic shock, we **suggest** invasive monitoring of arterial blood pressure over non-invasive monitoring, as soon as practical and if resources are available.
!	VERY LOW	44 For adults with septic shock, we **suggest** starting vasopressors peripherally to restore mean arterial pressure rather than delaying initiation until a central venous access is secured.
?		45 There is insufficient evidence to make a recommendation on the use of restrictive versus liberal fluid strategies in the first 24 hours of resuscitation in patients with sepsis and septic shock who still have signs of hypoperfusion and volume depletion after the initial resuscitation.

2016 STATEMENT

*"We **suggest** using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock."*

*"We **suggest** using crystalloids over gelatins when resuscitating patients with sepsis or septic shock."*

BEST PRACTICE STATEMENT

NO RECOMMENDATION

WEAK RECOMMENDATION

STRONG RECOMMENDATION

WEAK RECOMMENDATION AGAINST

STRONG RECOMMENDATION AGAINST

HIGH QUALITY EVIDENCE

MODERATE QUALITY EVIDENCE

LOW QUALITY EVIDENCE

VERY LOW QUALITY EVIDENCE

UPGRADE

DOWNGRADE

NO CHANGE FROM PREVIOUS GUIDELINES

NEW / CHANGED RECOMMENDATION

Table 1 (continued)

VENTILATION

?		46 There is insufficient evidence to make a recommendation on the use of conservative oxygen targets in adults with sepsis-induced hypoxemic respiratory failure.
!	LOW	47 For adults with sepsis-induced hypoxemic respiratory failure, we **suggest** the use of high flow nasal oxygen over non-invasive ventilation.
?		48 There is insufficient evidence to make a recommendation on the use of non-invasive ventilation in comparison to invasive ventilation for adults with sepsis-induced hypoxemic respiratory failure.
!!	HIGH	49 For adults with sepsis-induced ARDS, we **recommend** using a low tidal volume ventilation strategy (6 mL/kg), over a high tidal volume strategy (>10 mL/kg).
!!	MODERATE	50 For adults with sepsis-induced severe ARDS, we **recommend** using an upper limit goal for plateau pressures of 30 cm H2O, over higher plateau pressures.
!	MODERATE	51 For adults with moderate to severe sepsis-induced ARDS, we **suggest** using higher PEEP over lower PEEP.
!	LOW	52 For adults with sepsis-induced respiratory failure (without ARDS), we **suggest** using low tidal volume as compared to high tidal volume ventilation.
!	MODERATE	53 For adults with sepsis-induced moderate-severe ARDS, we **suggest** using traditional recruitment maneuvers.
!!	MODERATE	54 When using recruitment maneuvers, we **recommend against** using incremental PEEP titration/strategy.
!!	MODERATE	55 For adults with sepsis-induced moderate-severe ARDS, we **recommend** using prone ventilation for greater than 12 hours daily.
!	MODERATE	56 For adults with sepsis induced moderate-severe ARDS, we **suggest** using intermittent NMBA boluses, over NMBA continuous infusion.
!	LOW	57 For adults with sepsis-induced severe ARDS, we **suggest** using Veno-venous (VV) ECMO when conventional mechanical ventilation fails in experienced centres with the infrastructure in place to support its use.

ADDITIONAL THERAPIES

!	MODERATE	58 For adults with septic shock and an ongoing requirement for vasopressor therapy we **suggest** using IV corticosteroids.

2016 STATEMENT

↑ ! MODERATE

*"We **suggest against** using intravenous hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (see goals for Initial Resuscitation). If this is not achievable, we **suggest** intravenous hydrocortisone at a dose of 200 mg per day."*

BEST PRACTICE STATEMENT

NO RECOMMENDATION

WEAK RECOMMENDATION

STRONG RECOMMENDATION

WEAK RECOMMENDATION AGAINST

STRONG RECOMMENDATION AGAINST

HIGH QUALITY EVIDENCE

MODERATE QUALITY EVIDENCE

LOW QUALITY EVIDENCE

VERY LOW QUALITY EVIDENCE

↑ UPGRADE

↓ DOWNGRADE

NO CHANGE FROM PREVIOUS GUIDELINES

NEW / CHANGED RECOMMENDATION

Table 1 (continued)

!	LOW	59 For adults with sepsis or septic shock we **suggest against** using polymyxin B hemoperfusion. *2016 STATEMENT* *"We make no recommendation regarding the use of blood purification techniques."*
?		60 There is insufficient evidence to make a recommendation on the use of other blood purification techniques.
!!	MODERATE	61 For adults with sepsis or septic shock we **recommend** using a restrictive (over liberal) transfusion strategy.
!	LOW	62 For adults with sepsis or septic shock we **suggest against** using intravenous immunoglobulins
!	MODERATE	63 For adults with sepsis or septic shock, and who have risk factors for gastrointestinal (GI) bleeding, we **suggest** using stress ulcer prophylaxis.
!!	MODERATE	64 For adults with sepsis or septic shock, we **recommend** using pharmacologic venous thromboembolism (VTE) prophylaxis unless a contraindication to such therapy exists.
!!	MODERATE	65 For adults with sepsis or septic shock, we **recommend** using low molecular weight heparin over unfractionated heparin for VTE prophylaxis
!	LOW	66 For adults with sepsis or septic shock, we **suggest against** using mechanical VTE prophylaxis, in addition to pharmacological prophylaxis, over pharmacologic prophylaxis alone.
!	LOW	67 In adults with sepsis or septic shock and AKI, we **suggest** using either continuous or intermittent renal replacement therapy.
!	MODERATE	68 In adults with sepsis or septic shock and AKI, with no definitive indications for renal replacement therapy, we **suggest against** using renal replacement therapy.
!!	MODERATE	69 For adults with sepsis or septic shock, we **recommend** initiating insulin therapy at a glucose level of ≥ 180mg/dL (10mmol/L).
!	LOW	70 For adults with sepsis or septic shock we **suggest against** using IV vitamin C.
!	LOW	71 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.
!	LOW	72 For adults with septic shock and severe metabolic acidemia (pH ≤ 7.2) and acute kidney injury (AKIN score 2 or 3), we **suggest** using sodium bicarbonate therapy.
!	VERY LOW	73 For adult patients with sepsis or septic shock who can be fed enterally, we **suggest** early (within 72 hours) initiation of enteral nutrition.

BEST PRACTICE STATEMENT

NO RECOMMENDATION

WEAK RECOMMENDATION

STRONG RECOMMENDATION

WEAK RECOMMENDATION AGAINST

STRONG RECOMMENDATION AGAINST

HIGH QUALITY EVIDENCE

MODERATE QUALITY EVIDENCE

LOW QUALITY EVIDENCE

VERY LOW QUALITY EVIDENCE

UPGRADE

DOWNGRADE

NO CHANGE FROM PREVIOUS GUIDELINES

NEW / CHANGED RECOMMENDATION

Table 1 (continued)

LONG-TERM OUTCOMES AND GOALS OF CARE

BEST PRACTICE	74 For adults with sepsis or septic shock, we **recommend** discussing goals of care and prognosis with patients and families over no such discussion.
LOW	75 For adults with sepsis or septic shock, we **suggest** addressing goals of care early (within 72 hours) over late (72 hours or later).
	76 For adults with sepsis or septic shock, there is insufficient evidence to make a recommendation on any specific standardized criterion to trigger goals of care discussion.
BEST PRACTICE	77 For adults with sepsis or septic shock, we **recommend** that the principles of palliative care (which may include palliative care consultation based on clinician judgement) be integrated into the treatment plan, when appropriate, to address patient and family symptoms and suffering.
LOW	78 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.
VERY LOW	79 For adult survivors of sepsis or septic shock and their families, we **suggest** referral to peer support groups over no such referral.
VERY LOW	80 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.
	81 For adults with sepsis or septic shock, there is insufficient evidence to make a recommendation on the use of any specific structured handoff tool over usual handoff processes.
BEST PRACTICE	82 For adults with sepsis or septic shock and their families, we **recommend** screening for economic and social support (including housing, nutritional, financial, and spiritual support), and make referrals where available to meet these needs.
VERY LOW	83 For adults with sepsis or septic shock and their families, we **suggest** offering written and verbal sepsis education (diagnosis, treatment, and post-ICU/post-sepsis syndrome) prior to hospital discharge and in the follow-up setting.
BEST PRACTICE	84 For adults with sepsis or septic shock and their families, we **recommend** the clinical team provide the opportunity to participate in shared decision making in post-ICU and hospital discharge planning to ensure discharge plans are acceptable and feasible.
VERY LOW	85 For adults with sepsis and septic shock and their families, we **suggest** using a critical care transition programme, compared to usual care, upon transfer to the floor.
BEST PRACTICE	86 For adults with sepsis and septic shock, we **recommend** reconciling medications at both ICU and hospital discharge.
BEST PRACTICE	87 For adult survivors of sepsis and septic shock and their families, we **recommend** including information about the ICU stay, sepsis and related diagnoses, treatments, and common impairments after sepsis in the written and verbal hospital discharge summary.

BEST PRACTICE STATEMENT

NO RECOMMENDATION

WEAK RECOMMENDATION

STRONG RECOMMENDATION

WEAK RECOMMENDATION AGAINST

STRONG RECOMMENDATION AGAINST

HIGH QUALITY EVIDENCE

MODERATE QUALITY EVIDENCE

LOW QUALITY EVIDENCE

VERY LOW QUALITY EVIDENCE

UPGRADE

DOWNGRADE

NO CHANGE FROM PREVIOUS GUIDELINES

NEW / CHANGED RECOMMENDATION

Table 1 (continued)

BEST PRACTICE	88	For adults with sepsis or septic shock who developed new impairments, we **recommend** hospital discharge plans include follow-up with clinicians able to support and manage new and long-term sequelae.
	89	For adults with sepsis or septic shock and their families, there is insufficient evidence to make a recommendation on early post-hospital discharge follow-up compared to routine post-hospital discharge follow-up.
	90	For adults with sepsis or septic shock, there is insufficient evidence to make a recommendation for or against early cognitive therapy.
BEST PRACTICE	91	For adult survivors of sepsis or septic shock, we **recommend** assessment and follow-up for physical, cognitive, and emotional problems after hospital discharge.
VERY LOW	92	For adult survivors of sepsis or septic shock, we **suggest** referral to a post-critical illness follow-up programme if available.
VERY LOW	93	For adult survivors of sepsis or septic shock receiving mechanical ventilation for >48hours or an ICU stay of >72 hours, we **suggest** referral to a post-hospital rehabilitation programme.

BEST PRACTICE STATEMENT

NO RECOMMENDATION

WEAK RECOMMENDATION

STRONG RECOMMENDATION

WEAK RECOMMENDATION AGAINST

STRONG RECOMMENDATION AGAINST

HIGH QUALITY EVIDENCE

MODERATE QUALITY EVIDENCE

LOW QUALITY EVIDENCE

VERY LOW QUALITY EVIDENCE

UPGRADE

DOWNGRADE

NO CHANGE FROM PREVIOUS GUIDELINES

NEW / CHANGED RECOMMENDATION

Use of therapeutic drug monitoring has been described for all drugs, although it is not widely available for most.

Source control

Recommendation

27. For adults with sepsis or septic shock, we **recommend** rapidly identifying or excluding a specific anatomical diagnosis of infection that requires emergent source control and implementing any required source control intervention as soon as medically and logistically practical

Best Practice Statement

Rationale

Appropriate source control is a key principle in the management of sepsis and septic shock [12, 13]. Source control may include drainage of an abscess, debriding infected necrotic tissue, removal of a potentially infected device, or definitive control of a source of ongoing microbial contamination [262]. Foci of infection readily amenable to source control include intra-abdominal abscesses, gastrointestinal perforation, ischaemic bowel or volvulus, cholangitis, cholecystitis, pyelonephritis associated with obstruction or abscess, necrotizing soft tissue infection, other deep space infection (e.g., empyema or septic arthritis), and implanted device infections [262].

Source control of infectious foci was associated with improved survival in recent observational and cluster randomised studies [120, 263, 264]. Source control should be achieved as soon as possible following initial resuscitation [265, 266]. While there are limited data to conclusively issue a recommendation regarding the timeframe in which source control should be obtained, smaller studies suggest that source control within 6–12 h is advantageous [265–271]. Studies generally show reduced survival beyond that point. The failure to show benefit with source control implemented in less than 6 h may be a consequence of the limited number of patients and the heterogeneity of the intervention. Therefore, any required source control intervention in sepsis and septic shock should ideally be implemented as soon as medically and logistically practical after the diagnosis is made [120]. Clinical experience suggests that without adequate source control, many severe presentations will not stabilise or improve despite rapid resuscitation and provision of appropriate antimicrobials. In view of this fact, prolonged efforts at medical stabilisation in lieu of source control for severely ill patients, particularly those with septic shock, are generally not advised [272].

The selection of optimal source control methods must weigh the benefits and risks of the specific intervention, the patient's preference, clinician's expertise, availability, risks of the procedure, potential delays, and the probability of the procedure's success. In general, the least invasive option that will effectively achieve source control should be pursued. Open surgical intervention should be considered when other interventional approaches are inadequate or cannot be provided in a timely fashion. Surgical exploration may also be indicated when diagnostic uncertainty persists despite radiologic evaluation, when the probability of success with a percutaneous procedure is uncertain, or when the undesirable effects of a failed procedure are high. Logistic factors unique to each institution, such as surgical or interventional staff availability, may also play a role in the decision. Future research is needed to investigate the optimal timing and method of source control in patients with sepsis and septic shock with a source of infection amenable to drainage.

Recommendation

28. For adults with sepsis or septic shock, we **recommend** prompt removal of intravascular access devices that are a possible source of sepsis or septic shock after other vascular access has been established

Best Practice Statement

Rationale

Removal of a potentially infected intravascular access device is considered a part of adequate source control [262]. An intravascular device suspected to be a source of sepsis should be removed after establishing another site for vascular access and following successful initial resuscitation [265, 266]. In the absence of septic shock or fungemia, some implanted tunnelled catheter infections may be treated effectively with prolonged antimicrobial therapy if removal of the catheter is not practical [273]. However, catheter removal with adequate antimicrobial therapy is definitive and is the preferred treatment in most cases.

We identified one relevant RCT [274] and two observational studies [275, 276]. There was no evidence of a difference in mortality, however, the studies were hampered by significant limitations, including risk of confounding by indication (the observational studies) and imprecision (the RCT), which is why the results should be interpreted cautiously. The quality of evidence was very low.

De-escalation of antibiotics

Recommendation

29. For adults with sepsis or septic shock, we **suggest** daily assessment for de-escalation of antimicrobials over using fixed durations of therapy without daily reassessment for de-escalation

Weak recommendation, very low quality of evidence

Rationale

Antimicrobial exposure is linked to the development of antimicrobial resistance and efforts to reduce both the

number of antibiotics administered and their spectrum of therapy are therefore important strategies in patients with sepsis and septic shock [165]. This is particularly relevant in empiric therapy where broad-spectrum therapy is recommended, as the causative pathogen has not yet been identified. Once both the pathogen(s) and susceptibilities are known, antimicrobial de-escalation—i.e. stopping an antimicrobial that is no longer necessary (in case of combination therapy) or changing an antimicrobial to narrow the spectrum is encouraged. Given the adverse societal and individual risks to continued unnecessary antimicrobial therapy, thoughtful de-escalation of antimicrobials based on adequate clinical improvement is appropriate even if cultures are negative. Early discontinuation of all antimicrobial therapy if infection is ruled out is advisable [277]. Antimicrobial de-escalation should ideally be done as soon as possible, and rapid diagnostic techniques may facilitate this.

We identified direct evidence from 13 studies (1968 patients) [277], including 1 RCT [278]. In our meta-analysis, we observed improved short-term mortality in patients who were de-escalated (RR 0.72; 95% CI 0.57–0.91) (Supplementary Appendix 2). Long-term mortality was evaluated in one study only and did not demonstrate a difference (RR 0.99; 95% CI 0.64–1.52). De-escalation was associated with shorter length of stay in the hospital (MD −5.56 days; 95% CI −7.68 to −3.44), but not in the ICU (MD −2.6 days; 95% CI −5.91 to 0.72).

Most studies were observational, and there are concerns that de-escalation is used primarily in patients who are getting better, which is why the reported improved short-term mortality should be interpreted with caution [277, 279].

De-escalation is in generally safe, may offer cost savings when unnecessary antibiotics are discontinued, and reduced risk of antimicrobial resistance and reduced toxicity and side-effects may be important [280]. Based on the overall very low quality of evidence, RCTs are warranted along with more studies on antimicrobial resistance.

Duration of antibiotics

Recommendation
30. 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
Weak recommendation, very low quality of evidence

Rationale

Restricting antimicrobial therapy to the shortest course associated with better outcomes is an important part of antimicrobial stewardship [281–285]. The optimal duration of antimicrobial therapy for a given patient with sepsis or septic shock depends on many factors, including host, microbe, drug, and anatomical site (Table 2) [99, 100].

There have been considerable efforts over the past two decades to clarify the optimal duration of antimicrobial therapy by comparing "short" courses with traditional ("longer") courses. There are data from RCTs in specific conditions such as pneumonia [286–289], urinary tract infections [290], bacteremia [291, 292], and intraabdominal infections [293]. In many of the trials, the shorter course was just as effective as the longer course but associated with fewer adverse consequences. Very few trials, however, focussed exclusively on critically ill patients with sepsis or septic shock, and the overall quality of evidence was very low.

Given the lack of definitive and generalizable data regarding the optimal duration of therapy for patients who are critically ill, it is not surprising that there is considerably practice variation [281, 294]. Specialist consultation appears to be associated with improved patient outcomes for a variety of infectious syndromes [295–300]. This has generally been ascribed to improvements in microbial appropriateness of the empiric antimicrobial regimen provided. However, it is also possible that reducing the duration of unnecessary therapy may account for at least part of the benefit.

Thus, for adults with an initial diagnosis of sepsis or septic shock and adequate source control, we suggest a shorter course of antibiotics, as this is less costly, has fewer undesirable effects without impacting adversely on outcomes (see Table 4).

Biomarkers to discontinue antibiotics

Recommendation
31. 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 antimicrobials over clinical evaluation alone
Weak recommendation, low quality of evidence

Rationale

Shorter durations of antimicrobial therapy are in general recommended; however, critically ill patients often receive antimicrobials for more days than necessary [288, 301, 306]. While typically clinical evaluation alone is used to decide duration, biomarkers could

Table 2 Examples of risk factors for fungal infection

Risk factors for Candida sepsis
Candida colonisation at multiple sites [177–179]
Surrogate markers such as Serum Beta-D-Glucan assay [177]
Neutropenia [180, 181]
Immunosuppression [173, 180, 181]
Severity of illness (High APACHE score) [182, 183]
Longer ICU length of stay [183]
Central venous catheters and other intravascular devices [168, 180, 181, 184]
Persons who inject drugs [185]
Total parenteral nutrition [186]
Broad spectrum antibiotics [178, 187]
Gastrointestinal tract perforations and anastomotic leaks [186, 188–190]
Emergency gastrointestinal or hepatobiliary surgery [190]
Acute renal failure and haemodialysis [186, 188]
Severe thermal injury [191–193]
Prior surgery [186]
Risk factors for endemic yeast (cryptococcus, histoplasma, blastomyces, coccidioidomycosis)
Antigen markers such as cryptococcal, histoplasma or blastomyces assays [194–196]
HIV infection [197–200]
Solid organ transplantation [199, 201–203]
High dose corticosteroid therapy [199]
Haematopoietic stem cell transplantation [204]
Certain biologic response modifiers [205, 206]
Diabetes mellitus [207]
Risk factor for invasive mold infection
Neutropenia [204, 208]
Surrogate markers such as Serum or Bronchoalveolar Lavage Galactomannan Assay [209–211]
Haematopoietic stem cell transplantation [204, 208, 212]
Solid organ transplantation [202, 212–214]
High dose corticosteroid therapy [215, 216]
Certain biologic response modifiers [206, 217, 218]

The decision to start empirical antifungal therapy depends on the type and number of risk factors, along with the locale epidemiology of fungal infections

offer additional information. C Reactive Protein is often used in this regard. Procalcitonin has been studied most extensively both in critically ill and non-critically ill patients, both for initiation and discontinuation of therapy [307].

We identified direct evidence from 14 RCTs ($n = 4499$ patients) that assessed use of procalcitonin to guide antimicrobial treatment duration in patients with sepsis (two trials included critically ill patients in general) [308–321]. A meta-analysis suggested improved mortality in patients who were managed using procalcitonin versus control (RR 0.89; 95% CI 0.80–0.99), while there was no effect on length of stay in ICU or hospital. Antibiotic exposure was consistently lower in patients who were managed with procalcitonin and clinical evaluation, however, in many trials the total duration of therapy was still 7 days or longer in the intervention group. Also, the algorithms for antimicrobial therapy, frequency of procalcitonin monitoring and the thresholds (or percentage change in procalcitonin concentration) for discontinuation differed across the trials. Therefore, the overall quality of evidence was judged to be low.

The undesirable effects of using procalcitonin along with clinical evaluation to decide when to discontinue antimicrobials are considered minimal, and do not

Table 3 Guidance for PK/PD-based dosing for specific drug classes

Drug or drug class	PK/PD index associated with bacterial killing or efficacy	Drug concentration target	Considerations for optimised dosing[a]	References
Antibacterials				
Aminoglycosides	AUC_{0-24}/MIC; C_{max}/MIC	AUC 70–100 C_{max}/MIC 8–10	Use extended interval dosing with patient weight and kidney function	[237]
Beta-lactams	$fT_{>MIC}$	C_{min} > MIC	Use prolonged infusions, consider patient weight and kidney function	[253]
Colistin	AUC_{0-24}/MIC	Unspecified	Use patient weight and kidney function	[259]
Daptomycin	AUC_{0-24}/MIC; C_{max}/MIC	AUC_{0-24}/MIC > 200	Use patient weight and kidney function	[237]
Fluoroquinolones	AUC_{0-24}/MIC; C_{max}/MIC	AUC_{0-24}/MIC 80–125	Use kidney function	[237]
Vancomycin	AUC_{0-24}/MIC	AUC_{0-24}/MIC 400	Use patient weight and kidney function	[260]
Antifungals				
Fluconazole	AUC_{0-24}/MIC	AUC_{0-24}/MIC 100	Use patient weight and kidney function	[261]
Posaconazole	AUC_{0-24}/MIC	C_{min} 1–4 mg/L	Use formulation-specific dose	[261]
Voriconazole	AUC_{0-24}/MIC	C_{min} 2–6 mg/L	Use patient weight	[261]

AUC_{0-24} ratio of area under the concentration–time curve from 0 to 24 h, *MIC* minimum inhibitory concentration, *$fT_{>MIC}$* time overdosing interval that free (unbound) drug is maintained above the MIC, *C_{max}* maximum concentration in a dosing interval, *C_{min}* minimum concentration in a dosing interval

[a] Other considerations than those listed may have been listed in studies in critically ill patient sub-populations

outweigh the potential benefits [322]. Limited data on the cost-effectiveness are available, although a single centre study reported decreased hospital costs associated with PCT-guided antibiotic in medical ICU patient with undifferentiated sepsis [323]. Procalcitonin testing may not be available in all countries and healthcare settings, including LMICs.

Based on apparent benefit and no obvious undesirable effects, we suggest using procalcitonin along with clinical evaluation to decide when to discontinue antimicrobials in adults with an initial diagnosis of sepsis or septic shock and adequate source control, if the optimal duration of therapy is unclear and if procalcitonin is available.

Table 4 Planned duration of empirical antimicrobial therapy in RCTs of shorter versus longer duration of therapy according to clinical syndrome

Population/syndrome	RCT/systematic review (data extracted from)		Shorter duration	Longer duration	Outcomes
Pneumonia	[301]	Capellier (2012)	8 days	15 days	No difference
	[301, 302]	Chastre (2003)	8 days	15 days	No difference
	[302]	El Moussaoui (2006)	3 days	8 days	No difference
	[301–303]	Fekih Hassen (2009)	7 days	10 days	No difference
	[302, 303]	File (2007)	5 days	7 days	No difference
	[302, 303]	Kollef (2012)	7 days	10 days	No difference
	[302, 303]	Leophonte (2002)	5 days	10 days	No difference
	[301]	Medina (2007)	8 days	12 days	No difference
	[302, 303]	Siegel (1999)	7 days	10 days	No difference
	[302, 303]	Tellier (2004)	5 days	7 days	No difference
Bacteremia	[302]	Chaudhry (2000)	5 days	10 days	No difference
	[302]	Runyon (1991)	5 days	10 days	No difference
	[304]	Yahav (2018)	7 days	14 days	No difference
Intra-abdominal infection	[305]	Montravers (2018)	8 days	15 days	No difference
	[293]	Sawyer (2015)	Max. 5 days	Max. 10 days	No difference
Urinary tract infection	[290]	Peterson (2008)	5 days	10 days	No difference

Haemodynamic management

Fluid management

Recommendations
32. For adults with sepsis or septic shock, we **recommend** using crystalloids as first-line fluid for resuscitation *Strong recommendation, moderate quality of evidence*
33. For adults with sepsis or septic shock, we **suggest** using balanced crystalloids instead of normal saline for resuscitation *Weak recommendation, low quality of evidence*
34. For adults with sepsis or septic shock, we **suggest** using albumin in patients who received large volumes of crystalloids over using crystalloids alone *Weak recommendation, moderate quality of evidence*
35. For adults with sepsis or septic shock, we **recommend against** using starches for resuscitation *Strong recommendation, high quality of evidence*
36. For adults with sepsis and septic shock, we **suggest against** using gelatin for resuscitation *Weak recommendation, moderate quality*

Rationale

Fluid therapy is a key part of the resuscitation of sepsis and septic shock. Crystalloids have the advantage of being inexpensive and widely available. The absence of clear benefit following the administration of colloids compared to crystalloid solutions supports the use of crystalloid solutions in the resuscitation of patients with sepsis and septic shock [324]. The optimal fluid remains a subject of debate. For decades, the administration of normal saline solution (0.9% sodium chloride) has been common practice [325], but potential adverse effects that include hyperchloremic metabolic acidosis, renal vasoconstriction, increased cytokine secretion and concern about acute kidney injury (AKI) have led to increased interest in chloride-restrictive solutions, known as balanced or buffered solutions [326–330]. Subsequently, a network meta-analysis of 14 RCTs of patients with sepsis showed in an indirect comparison that balanced crystalloids were associated with decreased mortality, compared to saline [331].

There have been a number of recent RCTs assessing the question of which crystalloid may be most beneficial in patients with sepsis. In the SPLIT multicentre, double-blinded clinical trial, the comparison between balanced solutions and normal saline yielded no differences in mortality or AKI [332]. The modest volume of infused fluid, the predominance of surgical patients, and the low number of septic patients (4%) precludes generalizability of the results. In 2016, the SALT pilot trial ($n = 974$) compared balanced solutions versus normal saline; with septic patients comprising 25% and 28% of the population, respectively [333]. The primary outcome, a composite outcome including mortality, new RRT or persistent renal dysfunction (major adverse kidney event within 30 days, MAKE30), was similar between groups (24.6% vs. 24.7%). Subsequently, the SMART trial was published in 2018, a single-centre, multiple-crossover study including 15,802 patients who received balanced solutions or normal saline, alternating on a monthly basis [334]. In the pre-specified subgroup of patients admitted with sepsis in all participating ICUs, 30-day mortality was lower in those receiving balanced solutions, compared to normal saline (OR 0.80; 95% CI 0.67−0.94). Likewise, in a secondary analysis including only the 1,641 patients admitted to medical ICUs with a diagnosis of sepsis, balanced solutions were associated with reduced 30-day hospital mortality (OR 0.74; 95% CI 0.59–0.93) and MAKE30, and increased vasopressor- and RRT-free days [335].

The SMART trial was a single-centre study without individual patient randomisation and no blinded assignment of the intervention, it exposed participants to moderate amount of fluid volume, identification of sepsis subgroups was based on ICD-10 codes, and it used a composite outcome which may not be as relevant as a patient-centered outcome [336]. However, the use of balanced solutions in sepsis may be associated with improved outcomes compared with chloride-rich solutions. No cost-effectiveness studies compared balanced and unbalanced crystalloid solutions. Therefore, we considered the desirable and undesirable consequences to favour balanced solutions, but as the quality of the evidence is low, we issued a weak recommendation. Two ongoing large RCTs will provide additional data and inform future guideline updates [337, 338].

Although albumin is theoretically more likely to maintain oncotic pressure than crystalloids [339], it is more costly and there is no clear benefit with its routine use. Since the publication of the 2016 guidelines [12] two single-centre trials and two meta-analyses have been published on this topic [324, 340–342]. A Cochrane review including RCTs with 12,492 patients comparing albumin versus crystalloids found no difference in 30-day (RR 0.98; 95% CI 0.92–1.04) or 90-day mortality (RR 0.98; 95% CI 0.92–1.04) or need for RRT between groups (RR 1.11; 95% CI 0.96–1.27) [324]. This meta-analysis included patients with critical illness, and while the main solution included in the analysis was albumin, some studies in other analyses included fresh frozen plasma. A second meta-analysis, which also included critically ill patients, found lower static filling pressures (MD −2.3 cm H_2O; 95% CI 3.02–1.05) and mean arterial pressure (MAP) (MD −3.53 mmHg; 95% CI −6.71 to −0.36) with crystalloid use, but no difference in mortality at 28 days (RR 1.0; 95% CI 0.92–1.10) or 90 days (RR 1.32; 95% CI 0.76–2.29) [340]. The largest clinical trial in sepsis, the ALBIOS trial comparing a combination of albumin and crystalloids to crystalloids alone in

1818 patients with sepsis or septic shock did not demonstrate a difference in 28-day (RR 1.0; 95% CI 0.87–1.14) or 90-day mortality (RR 0.94; 95% CI 0.85–1.05) [339]. Of note, in this trial, albumin was given as a 20% solution, with a treatment goal of a serum albumin concentration of 30 g/L until ICU discharge or 28 days. A meta-analysis of studies including septic patients did not show a significant difference in mortality (RR 0.98; 95% CI 0.89–1.08). In addition, the risk of new organ failures (RR 1.02; 95% CI 0.93–1.11), ventilator-free days or vasopressor-free days did not differ. Although albumin use resulted in a larger treatment effect in the septic shock subgroup (RR 0.88; 95% CI 0.77–0.99) than in the sepsis subgroup (RR 1.03; 95% CI 0.91–1.17), the subgroup analysis did not detect a subgroup effect (*P*-interaction = 0.19).

The lack of proven benefit and higher cost of albumin compared to crystalloids contributed to our strong recommendation for the use of crystalloids as first-line fluid for resuscitation in sepsis and septic shock. The suggestion to consider albumin in patients who received large volumes of crystalloids is informed by evidence showing higher blood pressure at early and later time points [339], higher static filling pressures [340], and lower net fluid balance [339] with albumin. Limited data precludes a cutoff value for crystalloid infusion above which albumin might be considered as part of resuscitation.

In the 2016 SSC guidelines, a strong recommendation was issued against using hydroxyethyl starch (HES) [12]. No new data were identified. A previous meta-analysis of RCTs in septic patients showed a higher risk of RRT with the use of HES 130/0.38–0.45 (RR 1.36; 95% CI 1.08–1.72) and a higher risk of death in a pre-defined analysis of low risk of bias trials (RR 1.11; 95% CI 1.0–1.2) [343]. A network meta-analysis of patients with sepsis or septic shock also demonstrated a higher risk of death (OR 1.1; 95% CI 0.99–1.30) and need for RRT (OR 1.39; 95% CI 1.17–1.66) [331] with starches in a direct comparison with crystalloids. Therefore, the 2016 recommendation against the use of HES in resuscitation of patients with sepsis or septic shock did not change [331, 343].

Gelatin is a synthetic colloid used as a resuscitation fluid; there is a lack of powered well-designed studies supporting its administration in sepsis and septic shock. Included studies are generally small and include mostly post-operative, non-critically ill patients. In an indirect comparison, a 4-node network meta-analysis conducted in patients with sepsis, showed no clear effect on mortality when compared to crystalloids (OR 1.24; 95% credible interval [CrI] 0.61–2.55) [331]. Similarly, another RCT did not find an effect on mortality with gelatin use (RR 0.87; 95% CI 0.66–1.12) [344]. Adverse effects of gelatin have been reviewed in a network meta-analysis, which demonstrated higher risk of RRT with gelatin use compared to normal saline (OR 1.27; 95% CrI 0.44–3.64) and balanced crystalloids (OR 1.50; 95% CrI 0.56–3.96) [345]. Overall, the quality of evidence was moderate, due to imprecision and indirectness. In a systematic review of RCTs including patients with hypovolemia, gelatin use increased the risk of anaphylaxis (RR 3.01; 95% CI 1.27–7.14) in comparison with crystalloids use [346]. Furthermore, gelatins may affect haemostasis and the effect on blood transfusions was unclear (RR 1.10; 95% CI 0.86–1.41). Therefore, in the face of inconclusive effect on mortality, increased adverse effects, and higher costs, the panel issued a weak recommendation against the use of gelatin for acute resuscitation. More high-quality studies are needed to inform future guideline updates.

Vasoactive agents

Recommendations

37. For adults with septic shock, we **recommend** using norepinephrine as the first-line agent over other vasopressors. *Strong recommendation*

Dopamine. H*igh quality evidence*
Vasopressin. Moderate-quality evidence
Epinephrine. Low-quality evidence
Selepressin. *Low-quality evidence*
Angiotensin II. *Very low-quality evidence*

Remark

In settings where norepinephrine is not available, epinephrine or dopamine can be used as an alternative, but we encourage efforts to improve the availability of norepinephrine. Special attention should be given to patients at risk for arrhythmias when using dopamine and epinephrine

38. For adults with septic shock on norepinephrine with inadequate MAP levels, we **suggest** adding vasopressin instead of escalating the dose of norepinephrine

Weak recommendation, moderate-quality evidence

Remark

In our practice, vasopressin is usually started when the dose of norepinephrine is in the range of 0.25–0.5 μg/kg/min

39. For adults with septic shock and inadequate MAP levels despite norepinephrine and vasopressin, we **suggest** adding epinephrine

Weak recommendation, low-quality evidence

40. For adults with septic shock, we **suggest against** using terlipressin

Weak recommendation, low quality of evidence

Rationale

Norepinephrine is a potent α-1 and β-1 adrenergic receptors agonist, which results in vasoconstriction and increased MAP with minimal effect on heart rate. Dopamine acts in a dose-dependent fashion on dopamine-1, α-1 and β-1 adrenergic receptors. At lower dosages, dopamine causes vasodilation via dopamine-1 receptor activity in the renal, splanchnic, cerebral, and coronary beds. With higher dosages, dopamine's α-adrenergic receptor activity predominates resulting in vasoconstriction and increased systemic vascular resistance (SVR); its β-1 adrenergic receptor activity can lead to dose-limiting arrhythmias. Norepinephrine is more potent than

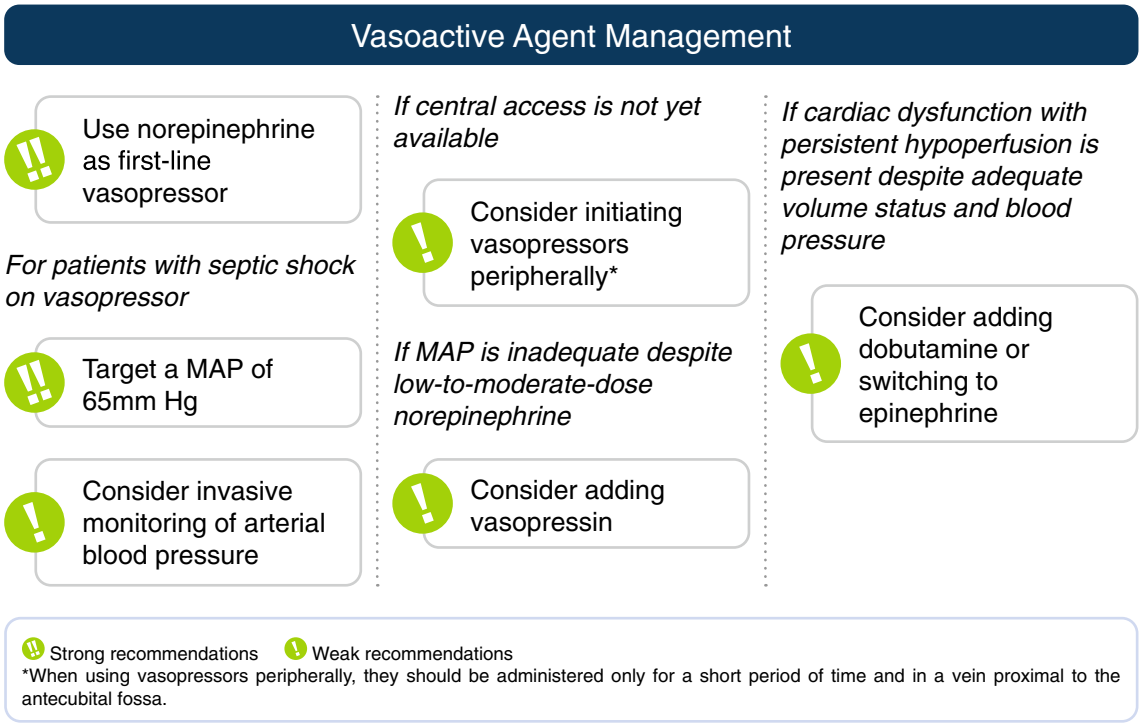

Fig. 2 Summary of vasoactive agents recommendations

dopamine as a vasoconstrictor. In a systematic review and meta-analysis of 11 RCTs, norepinephrine resulted in a lower mortality (RR 0.89; 95% CI 0.81–0.98) and lower risk of arrhythmias (RR 0.48; 95% CI 0.40–0.58) compared with dopamine [347]. Although the β-1 activity of dopamine may be useful in patients with myocardial dysfunction, the higher risk of arrhythmias limits its use [348].

Epinephrine's action is also dose-dependent with potent β-1 adrenergic receptor activity and moderate β-2 and α-1 adrenergic receptor activity. The activity of epinephrine, at low doses, is primarily driven by its action on β-1 adrenergic receptors, resulting in increased cardiac output (CO), decreased systemic vascular resistance (SVR) and variable effects on MAP. At higher doses, however, epinephrine administration results in increased SVR and CO. Potential adverse effects of epinephrine include arrhythmias and impaired splanchnic circulation [349]. Epinephrine may increase aerobic lactate production via stimulation of skeletal muscle β-2 adrenergic receptors, making the use of serum lactate to guide resuscitation challenging [350]. A randomised blinded study comparing epinephrine with norepinephrine in patients with shock showed no difference in 90-day mortality (HR 0.88; 95% CI 0.63–1.25) and vasopressor-free days [351]. The panel issued a strong recommendation for norepinephrine as the first-line agent over other vasopressors (Fig. 2).

Vasopressin is an endogenous peptide hormone produced in the hypothalamus and stored and released by the posterior pituitary gland. Its mechanism for vasoconstrictive activity is multifactorial and includes binding of V_1 receptors on vascular smooth muscle resulting in increased arterial blood pressure. Studies show that vasopressin concentration is elevated in early septic shock but decreases to normal range in the majority of patients between 24 and 48 h as shock continues [352, 353]. This finding has been called "relative vasopressin deficiency" as, in the presence of hypotension, vasopressin would be expected to be elevated. The significance of this finding is unknown. Unlike most vasopressors, vasopressin is not titrated to response, but it is usually administered at a fixed dose of 0.03 units/min for the treatment of septic shock. In clinical trials, vasopressin was used up to 0.06 units/min [354]. Higher doses of vasopressin have been associated with cardiac, digital, and splanchnic ischaemia [355].

The VANISH trial directly compared the use of vasopressin versus norepinephrine by randomizing patients with septic shock in a factorial 2 × 2 design aiming to also assess the role of hydrocortisone. There was no significant difference between the vasopressin and norepinephrine groups in 28-day mortality [30.9% vs 27.5%; RR

1.13 (95% CI 0.85–1.51). Although there was no difference with respect to kidney injury (RR 0.89; 95% CI 0.72–1.11), vasopressin use reduced the risk of RRT (RR 0.71; 95% CI 0.53–0.97) [354].

As for combination therapy, the main study (the VASST trial) comparing norepinephrine alone to norepinephrine plus vasopressin (0.01–0.03 U/min) showed no improvement in 28-day mortality (39.3% vs 35.4%, $p = 0.26$) [356]. However, in a subgroup analysis, patients with less severe shock receiving norepinephrine < 15 μg/min had improved survival with the addition of vasopressin (26.5% vs. 35.7%, $p = 0.05$). Both VANISH and VASST demonstrated a catecholamine-sparing effect of vasopressin; as such, the early use of vasopressin in combination with norepinephrine may help reduce the adrenergic burden associated with traditional vasoactive agents [357]. In our systematic review of 10 RCTs, vasopressin with norepinephrine reduced mortality as compared to norepinephrine alone (RR 0.91; 95% CI 0.83–0.99) but did not reduce the need for RRT (RR 0.79; 95% CI 0.57–1.10). There was no difference in the risks of digital ischaemia (RR 1.01; 95% CI 0.33–9.84) or arrhythmias (RR 0.88; 95% CI 0.63–1.23). The threshold for adding vasopressin varied among studies and remains unclear. Starting vasopressin when norepinephrine dose is in the range of 0.25–0.5 μg/kg/min seems sensible [354]. Another meta-analysis of RCTs on distributive shock showed a lower risk of atrial fibrillation with the combination of vasopressin and norepinephrine compared to norepinephrine alone [358]. However, a recent individual patient data meta-analysis of patients with septic shock from 4 RCTs showed that vasopressin alone or in combination with norepinephrine led to higher risk of digital ischaemia (risk difference [RD] 1.7%; 95% CI 0.3–3.2) but lower risk of arrhythmia (RD −2.8%; 95% CI −0.2 to −5.3) compared to norepinephrine alone [359].

The evidence regarding the optimal therapeutic strategy for shock requiring high dose vasopressors is scant [360]. Epinephrine has been suggested as second or third-line vasopressor for patients with septic shock. With the use of norepinephrine at elevated concentrations, the α1 receptors may already be saturated and downregulated [361]. Thus, the use of another drug such as epinephrine that targets the same receptors may be of limited utility and vasopressin could be more adequate in this scenario. In an indirect comparison, a network meta-analysis did not find any significant difference between epinephrine and vasopressin in terms of mortality (RR 0.94; 95% CI 0.47–1.88) [362]. Epinephrine might be useful in refractory septic shock patients with myocardial dysfunction.

Thus, we considered the desirable and undesirable consequences of these vasopressors and issued a strong recommendation to use norepinephrine as a first line agent instead of dopamine, vasopressin, epinephrine and selepressin and angiotensin II in patients with septic shock as a first-line agent, and a weak recommendation over selepressin and angiotensin II. Although some evidence suggests that vasopressin might be superior to norepinephrine in terms of clinical outcomes, the panel took into consideration its higher costs and lower availability and have issued a strong recommendation to use norepinephrine as first line agent instead of vasopressin. We also consider the potential benefit and undesirable consequences of using the combination of norepinephrine and vasopressin and issue a weak recommendation for adding vasopressin instead of escalating the dose of norepinephrine. Further evidence is needed to properly address the role of combination therapy of vasopressors in septic shock.

The panel also recognised that availability of, and experience with, norepinephrine may vary. As part of the global campaign for universal healthcare, the World Health Organisation (WHO) essential medicines and health products programme works to increase global access to essential, high-quality, safe, effective, and affordable medical products. If norepinephrine is unavailable, either dopamine or epinephrine can be used with special attention given to the risk of arrhythmias.

Selepressin is a highly selective V1 agonist, inducing vasoconstriction via stimulation of vascular smooth muscle. It does not share the typical V1b and V2 receptor effects of vasopressin (increased pro-coagulant factors, salt, and water retention, nitric oxide, and corticosteroid release) and has, therefore, been postulated as a potentially attractive non-catecholamine vasopressor alternative to norepinephrine. Selepressin has been studied in two randomised trials in septic shock. The first, a double-blind, randomised, placebo-controlled phase IIa trial, compared three ascending doses of selepressin (1.25, 2.5 and 3.75 ng/kg/min) in maintaining blood pressure, with open-label norepinephrine [363]. Selepressin at a dose of 2.5 ng/kg/min was demonstrated to be effective in maintaining MAP > 60 mmHg without norepinephrine in about 50% of patients at 12 h and about 70% of patients at 24 h. A follow-on phase IIb/phase III trial using an adaptive design, initially comparing three doses (1.7, 2.5 and 3.5 ng/kg/min) with the potential to add a further 5 ng/kg/min dose group [364]. The study was stopped for futility after enrolment of 828 patients, with no significant differences between any of the key endpoints [ventilator- and vasopressor-free days, 15.0 (selepressin) versus

14.5 (placebo), $p = 0.30$; 90-day all-cause mortality, 40.6% vs 39.4%, $p = 0.77$; 30-day RRT-free days, 18.5 vs 18.2, $p = 0.85$; 30-day ICU-free days, 12.6 vs 12.2, $p = 0.41$]; adverse event rates were also similar between groups. The meta-analysis of the two studies did not show significant difference in mortality [selepressin: 41.8% vs norepinephrine: 40.45%; RR 0.99 (95% CI 0.84–1.18)]. As selepressin failed to demonstrate clinical superiority over norepinephrine, we considered the desirable and undesirable consequences to be in favour of norepinephrine and issued a weak recommendation against the use of selepressin as a first-line therapy. Furthermore, it is not currently commercially available.

Angiotensin II is a naturally occurring hormone with marked vasoconstrictor effects, triggered through stimulation of the renin-angiotensin system. A synthetic human preparation has recently become available for clinical use and has been studied in two clinical trials. After a small, short-term pilot of 20 patients with vasodilatory (septic) shock 10 patients in each group which showed physiological efficacy without obvious safety issues [365], a larger RCT of 344 patients was performed in patients with vasodilatory shock (approximately 90% confirmed or presumed sepsis) [366]. The primary endpoint, an increase of MAP of at least 10 mmHg or to at least 75 mmHg, was achieved in 114 of 163 patients in the angiotensin II group and in 37 of 158 patients in the placebo group (69.9% vs 23.4%, $p < 0.001$). A meta-analysis found no difference in mortality rates between angiotensin II and norepinephrine (46.2% vs 54.2%; RR 0.85 (95% CI 0.69–1.06); very low quality). There was no clear increase in adverse events with the use of angiotensin II. As the available evidence is of very low quality, and clinical experience in sepsis and, therefore, demonstration of safety remains limited, the panel considered that angiotensin should not be used as a first-line agent, but having demonstrated physiological effectiveness, it may have a role as an adjunctive vasopressor therapy.

Terlipressin is a prodrug and is converted to lysine vasopressin by endothelial peptidases, producing a "slow release" effect and giving an effective half-life of around 6 h. Terlipressin is more specific for the V1 receptors and it has been studied in 9 clinical trials of patients with sepsis, with or without cirrhosis, involving 950 patients in total. Our meta-analysis showed no difference in mortality (terlipressin: 42.9% vs 49.0%; RR 0.89 (95% CI 0.70–1.13); low quality) but an increase in adverse events. The largest of these studies enrolled 617 patients with septic shock, in a randomised, blinded fashion, with terlipressin (or placebo) added at a dose of between 20 to 160 mcg/h to a standard norepinephrine-based approach, to achieve a MAP of 65–75 mmHg [367]. The primary outcome was death from any cause at 28 days. The 28-day mortality in the two groups was 40% for terlipressin and 38% for norepinephrine (OR 0.93; 95% CI 0.55–1.56, $p = 0.80$), and there were no differences in SOFA score at day 7 or vasopressor free days. More patients who received terlipressin had serious adverse events; 33 of 260 (12%) patients experienced digital ischaemia after receiving terlipressin, versus only one patient who received norepinephrine ($p < 0.0001$); diarrhea was also more common in the terlipressin group (2.7% versus 0.35%, $p = 0.037$). There were three cases of mesenteric ischaemia in the terlipressin group versus one in the norepinephrine group. Therefore, the panel considered that the undesirable consequences are higher with the use of terlipressin and issued a weak recommendation against its use in patients with septic shock.

Inotropes

Recommendations
41. For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we **suggest** either adding dobutamine to norepinephrine or using epinephrine alone *Weak recommendation, low quality of evidence*
42. For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we **suggest against** using levosimendan *Weak recommendation, low quality of evidence*

Rationale

Sepsis-induced myocardial dysfunction is recognised as a major contributor to the haemodynamic instability and is associated with worse outcomes of patients with septic shock [368]. Inotropic therapy can be used in patients with persistent hypoperfusion after adequate fluid resuscitation, and in patients with myocardial dysfunction, based on suspected or measured low CO and elevated cardiac filling pressures. Dobutamine and epinephrine are the most commonly used inotropes. Physiologic studies demonstrate that dobutamine increases CO and oxygen transport, increases splanchnic perfusion and tissue oxygenation, improves intramucosal acidosis and hyperlactatemia [369]. However, these effects may not be predictable [370]. Dobutamine infusion may produce severe vasodilation and result in lower MAP. In addition, the inotropic response may be blunted in sepsis with a preserved chronotropic effect causing tachycardia without an increase in stroke volume (SV) [370]. No

RCTs compared dobutamine to placebo in this population. Indirect comparison from network meta-analysis showed that dobutamine with norepinephrine had no clear impact on mortality when compared to no inotropic agents (OR 0.69; 95% CI 0.32–1.47) [362]. None of the trials directly compared dobutamine combined with norepinephrine to norepinephrine alone. In an observational study of 420 patients with septic shock, the use of an inotropic agent (dobutamine, levosimendan, epinephrine, or milrinone) was independently associated with increased 90-day mortality (OR 2.29; 95% CI 1.33–3.94) even after propensity score adjustment [371]. However, the analysis adjusted only to baseline characteristics, without accounting for time-varying confounders including the patient condition at the time of initiating inotropes which may explain the association with mortality. The panel considered the network meta-analysis as a higher quality than observational studies and issued a suggestion to use inotropes only in selected situations.

No evidence supports the superiority of dobutamine over epinephrine. Epinephrine is commonly available especially in low-resource settings [372]. In an indirect comparison of dobutamine versus epinephrine, a network meta-analysis showed no clear effect on mortality (OR 1.18; 95% CI 0.47–3.97) [362]. Therefore, we considered the desirable and undesirable consequences to be comparable for both drugs and issued a weak recommendation to use either one for patients with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate fluid status and MAP. Both should be discontinued in the absence of improvement in hypoperfusion or in the presence of adverse events. Further evidence derived from high quality RCTs is needed to properly address the role of inotropes in sepsis.

Levosimendan is a calcium-sensitizing drug with inotropic and vasodilatory properties. It has been evaluated in septic shock [373]. A meta-analysis of three RCTs ($n=781$) showed that levosimendan, compared to no inotropic agents, did not impact mortality (RR 0.87; 95% CI 0.59–1.28). Data from the LeoPARDS trial ($n=515$) showed that levosimendan versus no inotropic agents was associated with a lower likelihood of successful weaning from mechanical ventilation and a higher risk of supraventricular tachyarrythmia [373]. A meta-analysis of seven RCTs comparing levosimendan with dobutamine showed that levosimendan was not superior to dobutamine in adults with sepsis in terms of mortality (OR 0.80; 95% CI 0.48, 1.33; $p=0.39$) [374]. Thus, the panel issued a weak recommendation against the use of levosimendan based on the lack of benefit, in addition to the safety profile, cost and the limited availability of the drug.

Monitoring and intravenous access

Recommendations

43. For adults with septic shock, we **suggest** using invasive monitoring of arterial blood pressure over non-invasive monitoring, as soon as practical and if resources are available

Weak recommendation, very low quality of evidence

44. For adults with septic shock, we **suggest** starting vasopressors peripherally to restore MAP rather than delaying initiation until a central venous access is secured

Weak recommendation, very low quality of evidence

Remark

When using vasopressors peripherally, they should be administered only for a short period of time and in a vein in or proximal to the antecubital fossa

Rationale

Estimation of blood pressure using a non-invasive cuff tends to be inaccurate and the discrepancy more pronounced in shock states [375–379]. Insertion of an arterial catheter permits safe, reliable and continuous measurement of arterial pressure and allows real time analysis so that therapeutic decisions can be based on immediate and accurate blood pressure information [380]. A systematic review of observational studies showed that the risk of limb ischaemia and bleeding was less than 1% for radial catheters, and the risk of limb ischaemia and bleeding was less than 1% and 1.58%, respectively, for femoral catheters. The most common complication was localised haematoma, 14% for radial and 6% for femoral catheters [381]. Ultrasound guidance may increase the first attempt success rate and decrease the complication rate [382, 383]. A systematic review showed higher risk of infections when femoral arterial catheters were used compared to radial artery catheters (RR 1.93; 95% CI 1.32–2.84), and the overall pooled incidence of bloodstream infection was 0.96 per 1000 catheter days [384]. In the previous version of these guidelines, a weak recommendation was issued for using invasive monitoring of arterial blood pressure over non-invasive monitoring [12]. Since then, no new relevant evidence became available. Large, randomised trials that compare arterial blood pressure monitoring versus non-invasive methods are still lacking. In view of the low complication rate and likely higher accuracy of blood pressure measurement, the benefits of arterial catheters probably outweigh the risks. However, the potentially limited resources in some countries and the lack of high-quality studies need to be considered. Therefore, the panel issued a weak recommendation in favour of arterial catheter placement. Arterial catheters should be removed as soon as continuous haemodynamic monitoring is no longer required to minimise the risk of complications.

The prompt initiation of vasopressors to restore blood pressure is an integral component of the management

of septic shock. Vasopressors have been traditionally administered via a central venous access due to concerns of extravasation, local tissue ischaemia and injury if administered peripherally. However, the process of securing central venous access can be time consuming and requires specialised equipment and training that may not be available in under resourced settings even in high income countries, leading to a delayed initiation of vasopressors [385]. Large randomised trials that compare central and peripheral catheters for initial infusion of vasopressor are lacking. A small study ($n=263$) randomly allocated patients to receive peripheral vascular access or a central access [386]. The need for vasopressor was the indication for venous access in 70% of the patients. The incidence of major catheter-related complications was higher in those randomised to peripheral venous lines with no significant difference in the incidence of minor catheter-related complication. The most common peripheral venous line complication was difficulty in placement. Almost half of the patients assigned to the peripheral access group did not need a central line throughout their ICU stay. Other authors also showed that central lines could be avoided by peripheral line insertion [387]. The administration of vasopressors through peripheral IV catheters is generally safe. A recent systematic review showed that extravasation occurred in 3.4% (95% CI 2.5–4.7%) of patients with no reported episodes of tissue necrosis or limb ischaemia [388]. Most of the studies reported no need for active treatment of the extravasation, and a systematic review concluded that most patients who experience extravasation events have no long-term sequelae [389]. Extravasation may occur more frequently if vasopressors are infused distally to the antecubital fossa; a meta-analysis showed that 85% of reported extravasation events occurred when vasopressors were infused by a catheter that was located distal to the antecubital fossa [389]. The occurrence of local tissue injury may be more likely with prolonged administration of vasopressors. Administration of vasopressors for a short period of time (<6 h) in a well-placed peripheral catheter proximal to the antecubital fossa is unlikely to cause local tissue injury [389].

The time to initiation of vasopressors may be shorter if peripheral access is used. A post-hoc analysis of the ARISE trial showed that 42% of patients had vasopressors initiated via a peripheral catheter with a shorter time to initiation of vasopressors (2.4 [1.3–3.9] vs. 4.9 h [3.5–6.6], $p<0.001$) [385]. Moreover, most patients who had vasopressors started peripherally achieved a MAP > 65 mmHg within 1 h. Delay in vasopressor initiation and achieving MAP of 65 is associated with increased mortality [390, 391].

Given the low complication rate of peripheral vasopressors and the possibility of restoring blood pressure faster, the benefits of initiating vasopressors for a short period of time in a vein proximal to the antecubital fossa probably outweigh the risks. Therefore, we issued a weak recommendation in favour of the rapid initiation of vasopressors peripherally. If the infusion of vasopressors is still needed after a short period of time, as soon as practical and if resources are available, they should be infused through a central venous access to minimise the risk of complications. The lack of availability and expertise in placement of central venous catheters in different settings is an important consideration [55]. Though data are generally sparse on the latter, a study of mostly senior resident doctors in Nigeria concluded that knowledge of central venous catheter placement was limited [392]. Though the panel suggests peripheral administration of norepinephrine as a temporizing measure until a central venous catheter can be placed, its longer-term central administration may not be possible in some settings. Larger prospective studies are needed to provide better evidence on the adequacy and safety of peripheral lines in this scenario.

Fluid balance

Recommendation
45. There is **insufficient evidence to make a recommendation** on the use of restrictive versus liberal fluid strategies in the first 24 h of resuscitation in patients with sepsis and septic shock who still have signs of hypoperfusion and volume depletion after initial resuscitation
Remarks
Fluid resuscitation should be given only if patients present with signs of hypoperfusion

Rationale

The current literature does not provide clear guidance about the best fluid strategy following the initial resuscitation bolus of fluids. The four largest clinical trials in sepsis resuscitation used moderate to large amounts of fluids in the first 72 h. Although Rivers [393] administered over 13 L of fluids, ProCESS[64], ARISE [65] and ProMISe [66] administered approximately 7–8 L in the usual care groups with a reported low mortality rate. However, recent evidence suggests that IV fluids used to restore organ perfusion may damage vascular integrity and lead to organ dysfunction [394]. Data from observational studies have shown an association of high-volume fluid resuscitation and increased mortality, but these studies are likely affected by unmeasured variables (i.e. the administration of higher amounts of fluids to sicker patients) [395, 396]. Recent data emerging from Africa showed that higher volume fluid resuscitation in adults was associated with

increased mortality, but the generalizability of these data is limited due to the high prevalence of HIV/AIDS and malnutrition in the patients enrolled and the resource-scarce conditions with limited access to ICUs [69].

The current evidence evaluating a restrictive IV fluid strategy in the management of septic patients varies with respect to the inclusion criteria, the definition of restrictive and liberal fluid strategies, the criteria guiding the administration of additional IV fluids (e.g., perfusion parameters vs. haemodynamic variables), and the duration of the interventions [397–401]. Moreover, the primary outcomes were mostly related to IV fluid volumes administered during the study period and given the small sample sizes, they were not powered to identify differences in patient-centered outcomes. The ongoing Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) trial and the Conservative vs liberal fluid therapy in septic shock (CLASSIC) trial will shed some light to this matter [402, 403]. Given the quality of the evidence and the variability among existing studies, the panel issued no recommendation for either restrictive or liberal fluid management in the first 24 h of resuscitation after the initial fluid bolus in patients with sepsis and septic shock. However, it is important to emphasise this discussion does not affect the recommendation for the initial IV fluid bolus and that the administration of IV fluids after the initial fluid bolus should be guided by perfusion parameters and not only by a response in haemodynamic variables.

Ventilation

Oxygen targets

Recommendation
46. There is **insufficient evidence to make a recommendation** on the use of conservative oxygen targets in adults with sepsis-induced hypoxemic respiratory failure

Rationale

Patients who are undergoing mechanical ventilation in the ICU often receive a high fraction of inspired oxygen and have a high arterial oxygen tension. The conservative use of oxygen may reduce oxygen exposure and diminish lung and systemic oxidative injury. The evidence for the use of conservative oxygen targets (generally defined as PaO_2 55–70 mmHg; SpO_2 88–92%) and therapy in patients with sepsis is limited, with three randomised trials in the critically ill population [404–406]. In the 1000-participant ICU-ROX trial [405], conservative oxygen therapy did not significantly affect the primary outcome, which was the number of ventilator-free days, compared with liberal oxygen therapy for ventilated adults in ICU. Mortality at 90 and 180 days did not differ. These findings are at variance with the results of a previous single-centre trial, which was stopped early after an unplanned interim analysis. In that trial, conservative oxygen therapy in the ICU was associated with a markedly lower rate of death than usual oxygen therapy [404]. In a recent systematic review and meta-analysis of multiple clinical syndromes, investigators found that a conservative oxygen strategy was associated with a lower rate of death in acutely ill adults than a liberal oxygen strategy [407]. However, in a post hoc analysis of the ICU-ROX trial including adults with sepsis, point estimates for the treatment effect of conservative oxygen therapy on 90-day mortality raise the possibility of clinically important harm [408]. The LOCO-2 study was terminated early by the data safety and monitoring board and reported no difference in 28-day survival in ARDS patients managed with a conservative oxygenation strategy [409]. There are several ongoing trials of conservative oxygen targets that will inform clinical practice in the future. At this point in time, there is insufficient evidence to make an evidence-based recommendation.

High-flow nasal oxygen therapy

Recommendation
47. For adults with sepsis-induced hypoxemic respiratory failure, we **suggest** the use of high flow nasal oxygen over non-invasive ventilation *Weak recommendation, low quality of evidence*

Rationale

Acute hypoxemic respiratory failure can result from causes of sepsis such as pneumonia or non-pulmonary infections resulting in ARDS. Patients presenting with hypoxia without hypercapnia are treated with high concentrations of inhaled oxygen which may be delivered conventionally with interfaces including nasal prongs, facemask with reservoir or Venturi mask.

Advanced interventions for patients with severe hypoxia requiring escalation of support include non-invasive ventilation (NIV) or high flow oxygen. Both therapies avoid the complications of intubation and invasive mechanical ventilation and promote patient interaction. In addition to improving gas exchange, NIV may help to reduce work of breathing in select patients. However, NIV use can be associated with development of complications including increased risk of gastric insufflation and aspiration, facial skin breakdown, excessively high tidal volumes as well as patient discomfort related to inability to eat or effectively phonate during therapy.

High flow nasal cannula (HFNC) is a non-invasive, high concentration oxygen delivery interface that confers warming and humidification of secretions, high flow rates to better match patient demand, washout of nasopharyngeal dead space, and modest positive airway pressure

effect. The single inspiratory limb of HFNC allows for airflows as high as 60 L per minute to achieve inspired oxygen fractions (FiO_2) as high as 95–100%. However, HFNC is less effective at reducing work of breathing and supplying a moderate or higher level of PEEP [410]. Complications with HFNC are possible; however, they are usually self-limited and do not require discontinuing therapy.

When comparing the strategies of NIV versus HFNC for acute hypoxemic respiratory failure *despite conventional oxygen*, a single, large randomised trial has been conducted for direct comparison [411]. Although the primary outcome of intubation rate at 28 days was not different, this study demonstrated improved 90-day survival with HFNC compared with NIV (OR 0.42; 95% CI 0.21–0.85) and HFNC patients experienced significantly more days free of mechanical ventilation during a 28-day study period [411]. In a post hoc analysis of patients with severe hypoxemia ($PaO_2/FiO_2 \leq 200$ mmHg) from the above trial, HFNC resulted in lower intubation rates compared with NIV (35 versus 58 percent, respectively). A systematic review and meta-analysis of nine RCTs [2] showed that HFNC reduces intubation compared with conventional oxygen (RR 0.85; 95% CI 0.74–0.99) but does not affect the risk of death or ICU length of stay [412–414]. However, the NIV technique was not standardised and the experience of the centers varied.

Although the quality of evidence is low, the benefits of a trial of HFNC for the sepsis patient with non-hypercapnic progressive hypoxia over NIV seems justified. Patients requiring HFNC for acute hypoxemic respiratory failure are at high risk of requiring intubation; therefore, such trials must be accompanied by careful surveillance for ventilatory failure.

Non-invasive ventilation

Recommendation
48. There is **insufficient evidence to make a recommendation** on the use of non-invasive ventilation in comparison to invasive ventilation for adults with sepsis-induced hypoxemic respiratory failure

Rationale

When directly compared to invasive positive pressure ventilation, NIV may be able to achieve similar physiologic benefits including improved gas exchange and reduced work of breathing in select patients, while avoiding complications associated with intubation, invasive ventilation, and accompanying sedation. In contrast, NIV can cause mask-related discomfort, unrecognised patient-ventilator asynchrony due to leaks, and gastric insufflation. The main risk of NIV for the indication of acute respiratory failure is the potential for delaying needed intubation and increasing the risk of an interval aspiration events. Studies have suggested that NIV failure is an independent risk factor for mortality specifically in this population, although careful patient selection may reduce this risk [415, 416].

Patients with sepsis-induced hypoxemic respiratory failure may or may not have a competing chronic respiratory disease (ex. COPD, obesity) and the use of NIV for the rescue of patients with exclusively acute hypoxic respiratory failure ("de novo respiratory failure") is less well studied, but not uncommon. For example, the LUNG SAFE trial demonstrated that NIV was used in 15% of patients with ARDS with varying failure and mortality rates, depending on ARDS severity [417].

A few small RCTs have shown benefit with NIV for early or mild ARDS or de novo hypoxic respiratory failure [418, 419]. Since the last guideline distribution, only one additional study was added for analysis [420]. Due to small number of patients studied, low quality of evidence, uncertainty regarding whether clinicians can identify hypoxic patients in respiratory failure in whom NIV might be beneficial, and observational data that suggest the potential for harm with NIV in this setting, no clear recommendation can be made. If NIV is used for patients with sepsis-associated hypoxic respiratory failure, we suggest monitoring for an early reduction in work of breathing and close monitoring of tidal volumes [421].

Protective ventilation in acute respiratory distress syndrome (ARDS)

Recommendation
49. For adults with sepsis-induced 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 quality of evidence

Rationale

This recommendation is the same as that of the previous guidelines. Of note, the studies that guide the recommendations in this section enrolled patients using criteria from the American-European Consensus Criteria Definition for Acute Lung Injury and ARDS [422]. For the current document, we used the 2012 Berlin definition and the terms mild, moderate, and severe ARDS ($PaO_2/FiO_2 \leq 300$, ≤ 200, and ≤ 100 mm Hg, respectively) [423]. Several multicentre RCTs have been performed in patients with established ARDS to evaluate the effects of limiting inspiratory pressure through moderation of tidal volume [424–427]. These studies showed differing results, which may have been caused by differences in airway pressures in the treatment and control groups [423, 424, 428].

Several meta-analyses suggest decreased mortality in patients with a pressure- and volume-limited strategy for established ARDS [353, 354]. The largest trial of a volume- and pressure-limited strategy showed 9% absolute decrease in mortality in ARDS patients ventilated with tidal volumes of 6 mL/kg compared with 12 mL/ kg predicted body weight (PBW), and aiming for plateau pressure ≤ 30 cm H_2O [424].

The use of lung-protective strategies for patients with ARDS is supported by clinical trials and has been widely accepted; however, the precise tidal volume for an individual ARDS patient requires adjustment for factors such as the plateau pressure, the selected positive end-expiratory pressure (PEEP), thoracoabdominal compliance, and the patient's breathing effort. Patients with profound metabolic acidosis, high minute ventilation, or short stature may require additional manipulation of tidal volumes. Some clinicians believe it may be safe to ventilate with tidal volumes > 6 mL/kg PBW as long as plateau pressure can be maintained ≤ 30 cm H_2O [429, 430]. The plateau pressure is only truly valuable if the patient is passive during the inspiratory hold. Conversely, patients with very stiff chest/ abdominal walls and high pleural pressures may tolerate plateau pressures > 30 cm H_2O because transpulmonary pressures will be lower. A retrospective study suggested that tidal volumes should be lowered even with plateau pressures ≤ 30 cm H_2O [431] because lower plateau pressures were associated with reduced hospital mortality [432]. A recent patient-level mediation analysis suggested that a tidal volume that results in a driving pressure (plateau pressure minus set PEEP) below 12–15 cm H_2O may be advantageous in patients without spontaneous breathing efforts [433]. Prospective validation of tidal volume titration by driving pressure is needed before this approach can be recommended. Tidal volumes > 6 cc/kg coupled with plateau pressures > 30 cm H_2O should be avoided in ARDS. Clinicians should use as a starting point the objective of reducing tidal volume over 1–2 h from its initial value toward the goal of a "low" tidal volume (≈ 6 mL/kg PBW) achieved in conjunction with an end-inspiratory plateau pressure ≤ 30 cm H_2O. If plateau pressure remains > 30 cm H_2O after reduction of tidal volume to 6 mL/kg PBW, tidal volume may be further reduced to as low as 4 mL/kg PBW. The clinician should keep in mind that very low tidal volumes may result in significant patient-ventilatory dyssynchrony and patient discomfort. Respiratory rate should be increased to a maximum of 35 breaths/min during tidal volume reduction to maintain minute ventilation. Volume- and pressure-limited ventilation may lead to hypercapnia even with these maximum-tolerated set respiratory rates; this appears to be tolerated and safe in the absence of contraindications (e.g., high intracranial pressure, sickle cell crisis). No single mode of ventilation (pressure control, volume control) has consistently been shown to be advantageous when compared with any other that respects the same principles of lung protection.

Recommendation

50. For adults with sepsis-induced severe ARDS, we **recommend** using an upper limit goal for plateau pressures of 30 cm H_2O, over higher plateau pressures

Strong recommendation, moderate quality of evidence

Rationale

This recommendation is unchanged from the previous guidelines, as no new trials evaluating plateau pressure have been published since then. Of note, the 3 RCTs that guide this recommendation [424, 426, 427] enrolled patients using the criteria from the American-European Consensus Criteria Definition for Acute Lung Injury and ARDS [422] whereas the current document use the 2012 Berlin definition and the terms mild, moderate, and severe ARDS (PaO_2/FiO_2 ≤ 300, ≤ 200, and ≤ 100 mm Hg, respectively) [423]. These three RCTS compared a strategy of low tidal volume and limited plateau pressure with a strategy using higher tidal volume and plateau pressure; pooled data suggest reduced mortality (RR 0.83; 95% CI 0.70–0.97) and more ventilator-free days (MD 1.8 days; 95% CI 0.35–3.25) in patients managed with low plateau pressures.

A recent systematic review which included five RCTs also identified a strong relationship between plateau pressure and mortality [434]. The recommendation is also supported by observational data. LUNGSAFE, a large international observational study, which reported that plateau pressure correlated with mortality; however, the relationship between the two was not evident when plateau pressure was below 20 cm H_2O [435]. A secondary analysis of five observational studies identified a plateau pressure cut-off value of 29 cm H_2O, above which an ordinal increment was accompanied by an increment of risk of death [436]. We therefore recommend that the upper limit goal for plateau pressure should be less than 30 cm H_2O.

Recommendation

51. For adults with moderate to severe sepsis-induced ARDS, we **suggest** using higher PEEP over lower PEEP

Weak recommendation, moderate quality of evidence

Rationale

The recommendation is unchanged from 2016. Two RCTs [437, 438] were published since the 2016 Guidelines [12, 13], but we did not include these trials in the meta-analyses because both studies applied recruitment maneuvers to titrate PEEP levels. Our conclusions did not change in a sensitivity analysis which includes these two trials.

Applying higher PEEP in patients with ARDS may open lung units to participate in gas exchange and may increase PaO_2. We included three multicentre RCTs [439–441] and one pilot RCT [442], investigating use of higher PEEP versus lower PEEP strategies *in conjunction with low tidal volumes* for the management of patients with ARDS. Among patients with ARDS receiving lower VTs, we did not identify a significant benefit for use of a higher PEEP versus lower PEEP strategy for improving mortality (RR = 0.93; 95% CI 0.83–1.03), days on mechanical ventilation (RR = 0.00; 95% CI − 1.02 to 1.02), or ventilator-free days (RR = 1.48; 95% CI 0.19–2.76); and there was no increase in the risk of barotrauma (RR = 1.49; 95% CI 0.99–2.23).

A patient-level meta-analysis showed no benefit of higher PEEP in *all patients* with ARDS; however, patients with moderate or severe ARDS ($PaO_2/FiO_2 \leq 200$ mmHg) had decreased mortality with the use of higher PEEP, whereas those with mild ARDS did not [443]. A patient-level analysis of two of the randomised PEEP trials [440, 441] suggested that patients with ARDS who respond to increased PEEP with improved oxygenation have a lower risk of death; this association was stronger in patients with more severe ARDS ($PaO_2/FiO_2 < 150$ mmHg) compared with patients with less severe ARDS [444].

The optimal method of selecting a higher PEEP level is not clear. One option is to titrate PEEP according to bedside measurements of thoracopulmonary compliance with the objective of obtaining the best compliance or lowest driving pressure, reflecting a favourable balance of lung recruitment and overdistension [445]. The second option is to titrate PEEP upward while the patient is receiving a tidal volume of 6 mL/kg PBW, until the plateau airway pressure is 28 cm H_2O [441]. A third option is to use a PEEP/FiO_2 titration table that titrates PEEP based on the combination of FiO_2 and PEEP required to maintain adequate oxygenation [439–441]. A PEEP > 5 cm H_2O is usually required to avoid lung collapse [446]. Esophageal pressure guided PEEP titration has been evaluated in two trials [447, 448]. While the pilot study suggested benefit [448], the subsequent 200 patient multicentre RCT that compared PEEP titration guided by esophageal (P_{ES}) measurement versus empirical high PEEP-FiO_2 titration, showed no significant difference in a composite outcome of death and days free from mechanical ventilation through day 28 [449].

Low tidal volume in non-ARDS respiratory failure

Recommendation

52. For adults with sepsis-induced respiratory failure (without ARDS), we **suggest** using low tidal volume as compared to high tidal volume ventilation

Weak recommendation, low quality of evidence

Rationale

Previous versions of SSC guidelines issued a strong recommendation with a moderate-quality evidence for using low tidal volume (Vt) ventilation (Vt 4–8 mL/kg of predicted body weight), over higher tidal volumes (Vt > 8 mL/kg) in the management of patients with ARDS [12, 13, 226]. There is not as strong an evidence base, however, for the patients presenting with acute respiratory failure requiring mechanical ventilation who do not fulfil the criteria for ARDS. A 2015 systematic review and meta-analysis found a reduction in the risk of a composite endpoint of ARDS or pneumonia during the hospital stay in the low tidal volume ventilation group compared to the high tidal volume ventilation group (RR 0.72; 95% CI 0.52–0.98) [450]. Our analysis of three RCTs (1129 patients) showed no difference in mortality with low V_t ventilation (RR 1.07; 95% CI 0.91–1.26), with a trend towards lower risk of developing ARDs (RR 0.59; 95% CI 0.34–1.02) (Supplementary Appendix 4).

There are limited data on ventilation strategies for patients with sepsis-induced respiratory failure who do not meet criteria for ARDS. However, sepsis is an independent risk factor for the development of ARDS, and delays in diagnosing ARDS may result in delayed use of low tidal volumes. We therefore suggest that low tidal volume ventilation be used in all patients with sepsis who are receiving mechanical ventilation in order to avoid underuse or delayed use of this intervention. Furthermore, the use of low tidal volume ventilation avoids the risk of promoting ventilator induced lung injury in septic patients in whom the diagnosis of ARDS has been missed.

Recruitment manoeuvres

Recommendations

53. For adults with sepsis-induced moderate-severe ARDS, we **suggest** using traditional recruitment maneuvers

Weak recommendation, moderate quality of evidence

54. When using recruitment maneuvers, we **recommend against** using incremental PEEP titration/strategy

Strong recommendation, moderate quality of evidence

Rationale

Many strategies exist for treating refractory hypoxemia in patients with severe ARDS [451]. Temporarily raising

transpulmonary pressure may facilitate opening atelectatic alveoli to permit gas exchange [446], but could also over distend aerated lung units leading to ventilator-induced lung injury and transient hypotension. Since the publication of the previous SSC Guidelines, two important RCTs were published both of which utilised a "non-traditional" approach to recruitment maneuvers. Instead of the "traditional" recruitment maneuver which consists of the application of sustained continuous positive airway pressure (e.g., 30–40 cm H_2O for 30–40 s), both trials conducted lung recruitment with incremental PEEP levels, followed by a decremental PEEP titration according to either best respiratory-system static compliance [452] or oxygen saturation [437]. When the incremental PEEP recruitment studies are analysed separately from studies utilizing traditional recruitment maneuvers, recruitment with incremental PEEP is associated with increased 28-day mortality RR 1.12; 95% CI 1.00–1.25), which justifies the strong recommendation against using incremental PEEP titration for recruitment. Traditional recruitment maneuvers appear to improve 28-day mortality (RR 0.79; 95% CI 0.64–0.96) in patients with ARDS (Supplementary Appendix 4). Although the effects of recruitment maneuvers improve oxygenation initially, the effects can be transient [453]. Selected patients with severe hypoxemia may benefit from recruitment maneuvers in conjunction with higher levels of PEEP, but little evidence supports the routine use in all ARDS patients, so we have focused our recommendations to patients with moderate-to-severe ARDS [453]. Any patient receiving recruitment maneuvers should be monitored closely and recruitment maneuvers should be discontinued if deterioration in clinical status is observed.

Prone ventilation

Recommendation
55. For adults with sepsis-induced moderate-severe ARDS, we **recommend** using prone ventilation for more than 12 h daily
Strong recommendation, moderate quality of evidence

Rationale

There were no new randomised, controlled trials evaluating the use of prone ventilation in sepsis induced severe ARDS published since the 2016 guidelines. Therefore, no change in the recommendation was made. In 2017, a meta-analysis was published [454] that was updated from a previous meta-analysis published in 2010 [455], to which only 1 study, the PROSEVA trial, published in 2013 [456] was added. This repeat meta-analysis confirmed the results from the previous published work: In patients with ARDS and a PaO_2/FiO_2 ratio < 200, the use of prone compared with supine position within the first 36 h of intubation, when performed for > 12 h a day, showed improved survival. Meta-analysis including this study demonstrated reduced mortality in severe ARDS patients treated with prone compared with supine position (RR 0.74; 95% CI 0.56–0.99) as well as improved oxygenation as measured by change in PaO_2/FiO_2 ratio (median 23.5 higher; 95% CI 12.4–34.5 higher) [454]. Most patients respond to the prone position with improved oxygenation and may also have improved lung compliance [457–459]. While prone position may be associated with potentially life-threatening complications including accidental removal of the endotracheal tube, this was not evident in pooled analysis (RR 1.09; 95% CI 0.85–1.39). However, prone position was associated with an increase in pressure sores (RR 1.22; 95% CI 1.05–1.41) [460, 461], and some patients have contraindications to the prone position [460, 461].

Neuromuscular blocking agents

Recommendation
56. For adults with sepsis induced moderate-severe ARDS, we **suggest** using intermittent NMBA boluses, over NMBA continuous infusion
Weak recommendation, moderate quality of evidence

Rationale

The most common indication for neuromuscular blocking agents (NMBAs) use in the ICU is to facilitate mechanical ventilation [462]. These drugs may improve chest wall compliance, prevent respiratory dyssynchrony, and reduce peak airway pressures [463]. In addition, use of NMBA may reduce oxygen consumption by decreasing the work of breathing [464]. In the SSC 2016 guidelines, we issued a weak recommendation for using NMBA infusion for 48 h in sepsis-induced moderate to severe ARDS [12, 13]. This recommendation was based on a meta-analysis of 3 trials that examined the role of NMBAs in ARDS [465–467], showing reduced risks of death (RR 0.72; 95% CI 0.58–0.91) and barotrauma (RR 0.43; 95% CI 0.20–0.90) with the use of cisatracurium infusion [468].

Since then, several RCTs have been published [469–471], the largest of which is the ROSE Trial [471]. Due to the presence of significant statistical and clinical heterogeneity, a meta-analysis of all seven trials was not appropriate. A continuous NMBA infusion did not improve mortality when compared to a light sedation strategy with as needed NMBA boluses but no continuous infusion (RR 0.99; 95% CI 0.86–1.15). On the other

hand, continuous NMBA infusion reduced mortality when compared to deep sedation with as needed NMBA boluses (RR 0.71; 95% CI 0.57–0.89). Overall, continuous NMBA infusion reduced the risk of barotrauma (RR 0.55; 95% CI 0.35–0.85), but the effect on ventilator-free days, duration of mechanical ventilation, and ICU-acquired weakness was unclear [472, 473].

Given the uncertainty that still exists pertaining to these important outcomes and the balance between benefits and potential harms, the panel issued a weak recommendation favouring intermittent NMBA boluses over a continuous infusion. Importantly, if NMBAs are used, clinicians must ensure adequate patient sedation and analgesia [191, 474]. Recently updated clinical practice guidelines are also available for specific guidance [472].

Extracorporeal membrane oxygenation (ECMO)

Recommendation

57. For adults with sepsis-induced severe ARDS, we **suggest** using veno-venous (VV) ECMO when conventional mechanical ventilation fails in experienced centers with the infrastructure in place to support its use

Weak recommendation, low quality of evidence

Rationale

Venovenous (VV) extracorporeal membrane oxygenation (ECMO) is used in patients with severe acute respiratory failure to facilitate gas exchange in the setting of refractory hypoxaemia or hypercapnic respiratory acidosis [475]. It may also be used to facilitate a reduction in the intensity of mechanical ventilation. The evidence for the use of VV-ECMO in sepsis-induced ARDS is limited, with two RCTs completed in the last 10 years to assess the potential efficacy of VV ECMO for severe ARDS [476, 477]. The inclusion criteria of the trials were strict and focused on a very sick population of patients with severe ARDS refractory to conventional ventilation strategies and other rescue therapies such as prone position. The evidence in this guideline was downgraded to very low quality due to indirectness.

There were methodological limitations of the included studies. In one trial, all intervention participants were treated at one centre, which may have inflated the effect size because the centre specialised in ECMO management [477]. In addition, some of the participants in this trial did not receive the intervention [477]. However, one recent systematic review found that VV ECMO delivered at expert centers reduced mortality for patients with severe ARDS [475]. In clinical practice, patient selection is important and usually discussed prior to initiation of ECMO at an ECMO centre. Cost and equity are substantial issues; and registry data will be very important to document longer-term outcomes in these patients outside of the clinical trial context.

Additional therapies

Corticosteroids

Recommendation

58. For adults with septic shock and an ongoing requirement for vasopressor therapy we **suggest** using IV corticosteroids

Weak recommendation; moderate quality of evidence

Remark

The typical corticosteroid used in adults with septic shock is IV hydrocortisone at a dose of 200 mg/day given as 50 mg intravenously every 6 h or as a continuous infusion. It is suggested that this is commenced at a dose of norepinephrine or epinephrine ≥ 0.25 mcg/kg/min at least 4 h after initiation

Rationale

In the 2016 guidance, the accumulated evidence did not support a recommendation for their use if adequate fluid resuscitation and vasopressor therapy were able to restore haemodynamic stability [12, 13] Since then, three large RCTs have been published [354, 478, 479]. An updated meta-analysis [480] found systemic corticosteroid to accelerate resolution of shock (MD 1.52 days; 95% CI 1.71–1.32). A meta-analysis conducted for this guideline revision (Supplementary Appendix 5) found an increase vasopressor-free days (MD 1.5 days; 95% CI 0.8–3.11 days); however, corticosteroid use increased neuromuscular weakness (RR 1.21; 95% CI 1.01–1.45), without a clear effect on short- or long-term mortality.

The overall quality of evidence was moderate. The panel judged the desirable effects (shock resolution, vasopressor free days) to outweigh the undesirable effects of low dose corticosteroid. This observation, when taken into consideration with the resources required, cost of the intervention, and feasibility supported a weak recommendation in favour of using low dose corticosteroid therapy in septic shock.

The optimal dose, timing of initiation, and duration of corticosteroids remain uncertain; recent RCTs used 200 mg per day of IV hydrocortisone in divided doses [354, 479]. The three trials [354, 478, 479] also used different inclusion criteria: in ADRENAL [479] eligible patients were those on any dose of vasopressor or inotrope for ≥ 4 h to maintain a MAP > 60 mmHg, and present at the time of randomisation. In APROCCHSS [478] the dose of vasopressor was ≥ 0.25 μg/kg/min or ≥ 1 mg/h of norepinephrine or epinephrine, or any other vasopressor for at least 6 h to maintain a MAP ≥ 65 mmHg. In the ADRENAL [479] study, hydrocortisone was administered for a maximum of seven days or until ICU discharge or death; in APROCCHSS [478] hydrocortisone was administered for seven days; in VANISH [354] 200 mg of hydrocortisone was administered daily for 5 days and then tapered over further 6 days.

Our recommendation focuses on adults with septic shock and ongoing requirement for vasopressor therapy. We defined ongoing requirement as a dose of norepinephrine or epinephrine ≥ 0.25 mcg/kg/min for at least 4 h after initiation to maintain the target MAP. The dose of hydrocortisone is typically 200 mg/day. No dose response benefit was seen in a prior systematic review and meta-analysis [480].

Blood Purification

Recommendations

59. For adults with sepsis or septic shock, we **suggest against** using polymyxin B haemoperfusion
Weak recommendation; low quality of evidence

60. There is **insufficient evidence to make a recommendation** on the use of other blood purification techniques

Rationale

Haemoperfusion refers to the circulation of blood through an extracorporeal circuit that contains an adsorbent containing cartridge. The previous guidelines made no recommendation regarding the use of blood purification techniques [12, 13]. The updated literature search for guideline identified one new relevant RCT [481].

The most widely investigated technique involves the use of polymyxin B-immobilised polystyrene-derived fibers. Randomised trials of this technique have been previously summarised in a systematic review and meta-analysis [482]. An updated meta-analysis of all available RCTs (Supplementary Appendix 5) demonstrated a possible reduction in mortality (RR 0.87; 95% CI 0.77–0.98, low quality), however this finding was challenged by sensitivity analyses: after excluding high risk of bias trials the risk ratio is 1.14 (95% CI 0.96–1.36); and after excluding trials published prior to 2010 we observed higher mortality with haemoperfusion (RR 1.23; 95% CI 1.04–1.46). Overall, the quality of evidence is judged as low (Supplementary Appendix 5).

Substantial uncertainty as to any beneficial effect exists and the frequency of undesirable effects is reported in few trials. Polymyxin B haemoperfusion is expensive, resource intensive, potentially reduces health equity, and is infeasible in low-income economies. All considered, the panel issued a weak recommendation against the use of polymyxin B haemoperfusion therapy.

We did not identify new evidence on other modalities such as haemofiltration, combined haemoperfusion and haemofiltration or plasma exchange. Accordingly, no recommendation regarding the use of these modalities is made. This is unchanged from the 2016 guidelines. Since the analysis new data has emerged, but at this stage was not sufficient for us to re-consider the recommendation [483].

Further research is needed to determine the effect of various blood purification techniques on patient outcomes.

Red blood cell (RBC) transfusion targets

Recommendation

61. For adults with sepsis or septic shock, we **recommend** using a restrictive (over liberal) transfusion strategy
Strong recommendation; moderate quality of evidence

Remark

A restrictive transfusion strategy typically includes a haemoglobin concentration transfusion trigger of 70 g/L; however, RBC transfusion should not be guided by haemoglobin concentration alone. Assessment of a patient's overall clinical status and consideration of extenuating circumstances such as acute myocardial ischaemia, severe hypoxemia or acute haemorrhage is required

Rationale

The previous guidance was informed by two RCTs [484, 485]. The Transfusion Requirements in Septic Shock (TRISS) trial addressed a transfusion threshold of 70 g/L versus 90 g/L in 1000 septic shock patients after admission to the ICU. The results showed similar 90-day mortality, ischaemic events, and use of life support in the two treatment groups with fewer transfusions in the lower-threshold group. The Transfusion requirements in in Critical Care trial (TRICC), which compared a restrictive transfusion threshold of 70 g/L versus 100 g/L in 838 euvolemic ICU patients, demonstrated no difference in the primary outcome (30-day mortality). In the subgroup of 218 patients with sepsis or septic shock 30-day mortality was similar in the two groups (22.8% in the restrictive group vs. 29.7% in the liberal group, $p = 0.36$).

Our literature search identified a recent systematic review and meta-analysis of RCTs [486] and one new RCT: The Transfusion Requirements in Critically Ill Oncologic Patients (TRICOP) trial [487]. This trial randomised 300 adult cancer patients with septic shock to either a liberal (haemoglobin threshold, < 90 g/L) or restrictive strategy (haemoglobin threshold, < 70 g/L) of RBC transfusion. At 28 days after randomisation, the mortality rate in the liberal group was 45% 67 patients versus 56% 84 patients in the restrictive group (HR 0.74; 95% CI 0.53–1.04; $p = 0.08$) with no differences in ICU and hospital length of stay. At 90 days after randomisation, mortality rate in the liberal group was lower (59% vs 70%) than in the restrictive group (hazard ratio, 0.72; 95% CI 0.53–0.97).

Our update of the meta-analysis showed no difference in 28-day mortality (OR 0.99 95% CI 0.67–1.46, moderate quality). This is due to the inclusion of the TRICOP study where lower 28 mortality was observed with a liberal

strategy. Overall, the quality of evidence was judged moderate.

The overall balance of effects is uncertain and does not favour either the intervention or comparator. However, a restrictive strategy was determined likely beneficial with regards to resources required, cost effectiveness, and health equity considerations. A restrictive strategy is feasible in low- and middle-income countries. The 2016 strong recommendation favouring a restrictive strategy is unchanged; however, the overall quality of evidence changed from strong to moderate.

Immunoglobulins

Recommendation
62. For adults with sepsis or septic shock, we **suggest against** using intravenous immunoglobulins
Weak recommendation, low quality of evidence

Rationale

Patients with sepsis and septic shock may have evidence of hyper-inflammation and immunosuppression [488]. There are no high-quality studies examining the effect of intravenous (IV) immunoglobulins on the outcomes of patients with sepsis or septic shock. The previous guidance was a weak recommendation against their use [12, 13].

Our literature search identified two new RCTs [489, 490] and three meta-analyses [350, 491, 492] evaluating the effects of polyclonal IV immunoglobulins (IVIG) and immunoglobulin M-enriched polyclonal Ig (IVIGM) in patients with sepsis. The updated meta-analyses demonstrated reduced mortality with IVIG (RR 0.73; 95% CI 0.51–0.91) and IVIGM (RR 0.69; 95% CI 0.55–0.85), however the quality of evidence is low with many of the included studies at high risks of bias including single-centre trials with small sample size, undefined randomisation, allocation and blinding procedures, different dosing regimens and durations of treatment, different controls and few studies reported adverse events. Furthermore, after excluding high risk of bias studies, the significant reduction in mortality is no longer apparent.

Overall, the balance of effects (beneficial and undesirable) remains uncertain. Intravenous immunoglobulin is also relatively expensive, possibly not cost-effective and may reduce health equity. Its cost also limits its feasibility in countries with low- and middle-income economies. Based on these judgements, clinicians may consider avoiding the routine use of IV immunoglobulins in patients with sepsis and septic shock. Large, multicentre, well-designed, RCTs are needed to resolve the uncertainty regarding the role of immunoglobulin therapies in this patient population.

Stress ulcer prophylaxis

Recommendation
63. For adults with sepsis or septic shock, and who have risk factors for gastrointestinal (GI) bleeding, we **suggest** using stress ulcer prophylaxis
Weak recommendation, moderate quality of evidence

Rationale

Stress ulcers develop in the gastrointestinal (GI) tract of critically ill patients and can be associated with significant morbidity and mortality [493]. In 2016, this guideline recommended stress ulcer prophylaxis for patients with risk factors [12, 13].

Our literature search identified one new RCT [494] and the meta-analysis from the previous guideline was updated. This demonstrated no effect on mortality (RR 1.01 95% CI 0.93–1.10) and a reduction in GI haemorrhage (RR 0.52 95% CI 0.45–0.61). A sensitivity analysis including only trials at low risk of bias provided similar results. No increase in *Clostridoides difficile* colitis or pneumonia was observed. However, it was noted that the most recent (and largest) RCT did not demonstrate any effect of pantoprazole versus placebo on 90-day mortality and a composite outcome of clinically important events [494]. A recent meta-analysis published since the finalisation of the literature searches has suggested that there is a higher risk of recurrent *Clostridioides difficile* infections with proton pump inhibitors [495].

Overall, it was judged that the evidence probably favoured the administration of stress ulcer prophylaxis. This is driven by a modest reduction in gastrointestinal haemorrhage for which there is moderate quality of evidence (Supplementary Appendix 5). While no adverse effects were observed, the quality of evidence for these outcomes was low. Stress ulcer prophylaxis is relatively inexpensive, requires limited resources and is applicable to countries with low-income economies. These judgements support a weak recommendation for the use of stress ulcer prophylaxis in at-risk patients. This represents a downgrading of the strong recommendation based on low-quality evidence made in 2016.

A recent systematic review evaluated risk factors for clinically important GI bleeding [496]. After excluding high risk of bias studies, risk factors included: coagulopathy (relative effect (RE) 4.76; 95% CI 2.62–8.63), shock (RE 2.60; 95% CI 1.25–5.42), and chronic liver disease (RE 7.64; 95% CI 3.32–17.58). The effect of mechanical

ventilation on clinically important bleeding was unclear (RE 1.93, 0.57–6.50, very low certainty).

Venous thromboembolism (VTE) prophylaxis

Recommendations
64. For adults with sepsis or septic shock, we **recommend** using pharmacologic VTE prophylaxis unless a contraindication to such therapy exists *Strong recommendation, moderate quality of evidence*
65. For adults with sepsis or septic shock, we **recommend** using low molecular weight heparin (LMWH) over unfractionated heparin (UFH) for VTE prophylaxis *Strong recommendation, moderate quality of evidence*
66. For adults with sepsis or septic shock, we **suggest against** using mechanical VTE prophylaxis in addition to pharmacological prophylaxis, over pharmacologic prophylaxis alone *Weak recommendation, low quality of evidence*

Rationale

Critically ill patients are at risk for deep vein thrombosis (DVT) as well as pulmonary embolism (PE). The incidence of DVT acquired in the ICU may be as high as 10% [497], the incidence of acquired PE may be 2–4% [498, 499].

No new RCT evidence was identified. Our previous meta-analysis demonstrated a significant reduction in both DVT and PE and no increase in bleeding complications.

On balance, the effect favours the intervention with a moderate quality of evidence. The cost of intervention is not large, and it is likely feasible in countries with low- and middle-income economies. These judgements support a recommendation for the use of pharmacologic venous thromboembolism (VTE) prophylaxis unless a contraindication exists. The recommendation is unchanged from the 2016 guidelines.

Our literature review found no new RCT evidence comparing the administration of low molecular weight heparin (LMWH) to unfractionated heparin (UFH). The prior meta-analysis demonstrated significantly lower rates of DVT following the administration of LMWH compared to UFH (RR 0.84 95% CI 0.71–0.98). No difference in the rates of clinically significant bleeding, mortality or PE were observed. The overall quality of evidence was rated as moderate: it was downgraded for imprecision. It was determined that the balance of overall effects favoured LMWH over UFH. Any difference in resources required between the two interventions was considered to be negligible, and LMWH administration was feasible and applicable in countries with low- and middle-income economies. Further, LMWH may have greater consumer acceptance as it requires only one subcutaneous injection daily. These judgements support a recommendation for the use of LMWH over UFH for VTE prophylaxis in patients with sepsis or septic shock. This recommendation is unchanged from the 2016 guidelines.

Combined pharmacologic prophylaxis and mechanical prophylaxis with intermittent pneumatic compression (IPC) and/or graduated stockings may offer another option for patients with sepsis and septic shock. In the 2016 guidelines, a suggestion to use combination therapy whenever possible, was based on indirect and imprecise data [12, 13]. Our literature search identified one new RCT that compared the combination of mechanical and pharmacological prophylaxis to pharmacological prophylaxis alone [500].

The PREVENT study randomised 2003 critically ill patients to intermittent pneumatic calf compression alone or in combination with pharmacological prophylaxis [500]. No difference in mortality (RR 0.98 95% CI 0.84–1.13), or the rates of DVT and PE were observed. No difference in lower extremity ischaemia was demonstrated. The study was downgraded during the quality assessment for imprecision. For the outcome of mortality, the quality was assessed as moderate; for other outcomes it was further downgraded for risk of bias.

It was judged that any effects of the intervention (mechanical prophylaxis in addition to pharmacologic), either beneficial or undesirable, were likely trivial (Supplementary Appendix 5). However, there are resource implications and costs associated with the use of mechanical VTE prophylaxis. These, together with the lack of any effect on a patient centered outcome support a weak recommendation against the use of the combination of mechanical and pharmacologic prophylaxis.

It is acknowledged that in some patents with sepsis and septic shock pharmacologic prophylaxis may be contraindicated. These patients may benefit from mechanical VTE prophylaxis. No data for this population exist. Further research is indicated.

Renal replacement therapy

Recommendations
67. In adults with sepsis or septic shock and AKI who require renal replacement therapy, we **suggest** using either continuous or intermittent renal replacement therapy *Weak recommendation, low quality of evidence*
68. In adults with sepsis or septic shock and AKI, with no definitive indications for renal replacement therapy, we **suggest against** using renal replacement therapy *Weak recommendation, moderate quality of evidence*

Rationale

Two systematic reviews and meta-analyses [501, 502] summarised the total body of evidence: they do not show a difference in mortality between patients who receive continuous (CRRT) versus intermittent haemodialysis

(IHD). The results remained the same when the analysis is restricted to RCTs [502].

Our updated literature search identified no new RCTs but two meta-analysis comparing continuous and intermittent renal replacement therapies [503, 504]. The quality of evidence was judged as low. The balance of effects favoured neither (IHD) nor CRRT. It was acknowledged that the resources required for the interventions vary. In low- and middle-income economies, the specialised equipment, expertise and personal required for continuous modalities may not be available. The recommendation, for either intervention, is unchanged from the 2016 guidelines.

Timing of renal replacement therapy initiation is of importance. Prior research has suggested benefit [505] or harm [506] for "early" versus "delayed" initiation of RRT.

Our search identified a new RCT comparing early versus delayed RRT [507].This trial included 488 patients with AKI and septic shock. It was stopped early, after the second planned interim analysis, for futility. Eligible patients were those with septic shock (within 48 h of the onset of vasopressor therapy and AKI defined as oliguria (< 0.3 ml/kg/h for ≥ 24 h), anuria for 12 h or more, or a serum creatinine level 3 times baseline accompanied by a rapid increase of ≥ 0.5 mg/dl. Subsequent to the censor date for our literature search, the results of the STARRT-AKI trial were published. The trial, which randomised 3000 participants, demonstrated no difference in mortality in those allocated to an accelerated strategy of RRT compared to those allocated to a "standard" strategy. No differential effect was observed in the a priori sepsis subgroup of 1689 patients [508].

The results of this trial were included in an updated meta-analysis (Supplementary Appendix 5). No effect of the timing of initiation of renal replacement therapy on mortality and renal recovery was observed. The IDEAL-ICU trial [507] did not report central venous access device (CVAD) infections: the results for this outcome are unchanged from 2016. The certainty of evidence for the key outcomes of mortality, renal recovery and CVAD infection was a least moderate and was only downgraded for imprecision (Supplementary Appendix 5). Overall, the balance of effects favoured delayed rather than early initiation of RRT. This is principally driven by the higher rate of CVAD infection in the "early" initiation. Therefore, after considering of the resources required, cost and health equity issues, the panel issued a weak recommendation against the use of RRT in patients with sepsis and AKI for increases in creatinine or oliguria alone, and without other absolute indications for dialysis (uremic complications, refractory academia, refractory fluid overload or hyperkalemia).

Glucose control

Recommendation

69. 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 quality of evidence

Remark
Following initiation of an insulin therapy, a typical target blood glucose range is 144–180 mg/dL (8–10 mmol/L)

Rationale

Hyperglycemia (> 180 mg/dL), hypoglycemia and increased glycemic variability are associated with increased mortality in critically ill patients [509–511]. The *American Diabetes Association*, in its most recent recommendations for glycemic control of critically ill patients, recommended the initiation of insulin therapy for persistent hyperglycemia > 180 mg/dL and thereafter a target glucose range of 140–180 mg/dL [512].

In a single centre study, targeting blood glucose to 80-110 mg/dL reduced ICU mortality [513], however this finding was not reproduced in subsequent multi-centre RCTs [514, 515]. Meta-analyses also report a higher incidence of hypoglycemia (glucose < 40 mg/dL) in critically patients where blood glucose was targeted to 80–110 mg/dL [516, 517]. The previous recommendation to commence insulin when two consecutive blood glucose levels are > 180 mg/dL derives from the NICE-SUGAR trial [518]. A summary of the evidence for this trigger of > 180 mg/dL is found in the Supplementary Appendix 5. In this version of the guideline, we asked a new question: in adults with sepsis of septic shock, what level of glucose should trigger one to start an insulin infusion (> 180 or > 150 mg/dl)?

We identified a recent network meta-analysis of 35 RCTs [519]. The analysis compared four different blood glucose targets (< 110, 110–144, 144–180, and > 180 mg/dL). No significant difference in the risk of hospital mortality was observed between the four blood glucose ranges. Target concentrations of < 110 and 110–144 mg/dL were associated with a four to nine-fold increase in the risk of hypoglycemia compared with 144–180 and > 180 mg/dL. No significant difference in the risk of hypoglycemia comparing a target of 144–180 and > 180 mg/dL was demonstrated (OR 1.72; 95% CI 0.79–3.7).

The overall quality of evidence was rated as moderate (Supplementary Appendix 5). Overall, the balance of effects favoured initiation of insulin therapy at a glucose level of > 180 mg/dl. This was principally driven by the increased risk of hypoglycemia observed with lower targets. No significant differences existed between the

two-insulin initiation blood glucose levels evaluated. After considering the resources required, cost, health equity issues, and applicability to low- and middle-income economies, the panel made a strong recommendation for the initiation of insulin therapy at a glucose level of ≥ 180 mg/dL (10 mmol/L).

Further research is indicated to: (1) identify which technologies including electronic glucose management, continuous glucose monitoring, and closed loop systems, can more safely achieve better glycemic control and lower rates of hypoglycemia; and (2) determine the optimal glycemic control for different patient populations including diabetic and nondiabetic patients, medical and surgical patients.

Vitamin C

Recommendation
70. For adults with sepsis or septic shock, we **suggest against** using IV vitamin C *Weak recommendation, low quality of evidence*

Rationale

Vitamin C is known to have anti-inflammatory properties [520]. In 2017, a single centre before and after study reported shorter duration of vasopressor therapy and lower mortality following the administration of combination of high dose vitamin C, hydrocortisone, and thiamine to patients with sepsis and septic shock [521]. Our literature review found one systematic review and meta-analysis [522] (containing six RCTs) and one additional RCT [523].

Our updated analysis (Supplementary Appendix 5) included seven RCTs (416 critically ill patients). The use of vitamin C did not reduce mortality compared to usual care (RR 0.79; 95% CI 0.57–1.1, low quality). One study reported reduced vasopressor use at 168 h [523]. Of the patients alive at 7 days, 22% (16/72) administered vitamin C remained on vasopressor therapy compared to 10% (6/59) of controls.

Subsequent to the censor date for our literature search, the results of two additional RCTs of Vitamin C versus placebo were published [524, 525]. In the study by Fujii et al. [524], 211 adults with septic shock were randomised to the combination of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone. The authors reported no difference for the primary outcome of time alive and free of vasopressors up to 168 h between the intervention and control group (median 122.1 h [IQR 76.3–145.4 h] vs 124.6 h [IQR 82.1–147 h]; $p = 0.83$). Ninety-day mortality was 28.6% (30/105) in the vitamin C group, and 24.5% (25/102) in the control group (HR 1.18; 95% CI 0.69–2.0). In the study by Moskowitz et al. [525], 200 patients were randomised to a combination of vitamin C, hydrocortisone and thiamine vs placebo. No difference in the primary outcome of mean SOFA score change at 72 h post enrolment was observed. At 30 days, 34.7% (35/101) of patients randomised to combination therapy had died vs. 29.3% (29/99) randomised to placebo (HR, 1.3; 95% CI 0.8–2.2; $p = 0.26$). When these data are added to our meta-analysis, the point estimate for mortality becomes RR 0.9 (95% CI 0.69–1.18: low quality).

The overall size of any desirable effect was judged as small with a low quality of evidence (Supplementary Appendix 5). There are limited available data of any undesirable effects: it was noted that the point estimate of the HR for 90-day mortality in the largest RCT [524] was 1.18 (95% CI 0.69–2.00) i.e. favouring the control group. The balance of effects was accordingly judged as favouring neither the intervention nor the comparator. The intervention itself requires limited resources and is feasible in low- and middle-income economies.

The panel issued a weak recommendation against the use of vitamin C in patients with sepsis and septic shock. The results of ongoing RCTs may influence the quality of evidence and future updates of the guidelines.

Bicarbonate therapy

Recommendations
71. For adults with septic shock and hypoperfusion-induced lactic acidemia, we **suggest against** using sodium bicarbonate therapy to improve haemodynamics or to reduce vasopressor requirements *Weak recommendation, low quality of evidence*
72. For adults with septic shock, severe metabolic acidemia (pH ≤ 7.2) and AKI (AKIN score 2 or 3), we **suggest** using sodium bicarbonate therapy *Weak recommendation, low quality of evidence*

Rationale

The previous guidance was based on two small, blinded crossover RCTs that compared equimolar saline vs sodium bicarbonate in patients with lactic acidosis and failed to reveal any difference in haemodynamic variables or vasopressor requirements [526, 527]. A weak recommendation was made against the use of bicarbonate therapy to improve haemodynamics or to reduce vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH ≥ 7.15.

Our literature search identified one new RCT [528]. In this multicentre trial, 400 patients with severe metabolic acidemia (pH ≤ 7.20) were randomly allocated to receive IV 4.2% sodium bicarbonate with the aim of achieving an arterial pH of 7.3, or control (no bicarbonate). No between-group difference was observed in the primary outcome of a composite of 28-day mortality and organ failure at day 7. However, hypernatremia, hypocalcaemia, and metabolic alkalosis were observed more frequently in those randomised to bicarbonate. In the subgroup of patients with AKI defined as AKI Network (AKIN) stage 2 or 3 at randomisation (182/389–47%), lower mortality was observed with bicarbonate therapy: control 57/90 (63%), bicarbonate (42/92–46%), absolute risk reduction (ARR) −17.7% (−33.0 to −2.3), $p = 0.016$. There was a significant differential effect between patients with an AKIN score of 2 or 3 compared with those with a score of 0–1 (p value for heterogeneity = 0.023).

Sepsis was present in 61% (238/389) of patients at the time of randomisation. No differential effect was observed between patients with vs without sepsis. The outcomes of patients with both sepsis and AKI were not reported.

Overall, the quality of evidence is low (Supplementary Appendix 5). The summary of judgements supported a weak recommendation against the intervention. The 2016 recommendation is essentially unchanged. However, when considering the subset of patients with septic shock, severe metabolic acidosis and AKI, the balance of effects probably favours IV bicarbonate. A weak recommendation for the use of IV bicarbonate in this population was made.

Nutrition

Recommendation
73. For adult patients with sepsis or septic shock who can be fed enterally, we **suggest** early (within 72 h) initiation of enteral nutrition
Weak recommendation; very low quality of evidence

Rationale

The early administration of enteral nutrition in patients with sepsis and septic shock has potential physiologic advantages related to the maintenance of gut integrity and prevention of intestinal permeability, dampening of the inflammatory response, and modulation of metabolic responses that may reduce insulin resistance [529, 530]. Our literature search defined early enteral nutrition as enteral nutrition commenced within 72 h of ICU admission. The comparator was enteral nutrition commenced after 72 h.

The literature search identified one new RCT [531]. This multicentre trial conducted in 44 French ICUs randomised 2410 invasively mechanically ventilated patients with shock to early enteral nutrition vs early parenteral nutrition. 1504 (62%) of the participants had sepsis. The results of this trial were included in a meta-analysis with four relevant trials from the 2016 guidelines [532–535]. No significant effect favouring early enteral nutrition was observed for all outcomes evaluated. The quality of evidence was assessed low or very low: downgrades were for risk of bias, inconsistency, and imprecision.

The overall balance of effects did not favour either early enteral feeding (within 72 h) compared with enteral feeding commenced after that time. Although the available evidence is of low quality, it does not suggest harm following the institution of early enteral feeding. Neither intervention was considered more beneficial when considering resources utilisation, cost effectiveness, and equity issues. The institution of early enteral nutrition was also considered feasible in low- and middle-income economies.

Given the plausible possibility of benefit when considering the available physiological data, and the absence of any apparent harm, a weak recommendation to start feeding early in patients with sepsis and septic shock was made. Further research addressing this question in patients with sepsis and septic shock is required.

Long-term outcomes and goals of care

Patients who survive a protracted period of ICU care for sepsis typically face a long and complicated road to recovery. There will not only be physical rehabilitation challenges to overcome but also great uncertainty about the way to organize and coordinate care, both to promote recovery/avoid complications/recurrence and to ensure care is matched to patient and family goals of care.

There is broad consensus that the current healthcare system is likely falling short of what optimal care during the recovery period might look like for this patient population. However, generating a robust evidence base upon which to make concrete recommendations about changes in the care paradigm has proven to be extraordinarily difficult. Some of the difficulties relate to:

- not all patients are the same, and understanding which patients ought to receive which interventions is very poor;
- not all healthcare delivery systems are the same—even within one system, some patients may be very well-supported while others may not—really complicating what 'control' care looks like;
- lack of understanding about dosing and intensity of many of the proposed interventions, and when and whether they should be combined in packages is generally missing.

While these issues of patient heterogeneity, variable control care, and lack of understanding about ideal configuration of interventions are protean, they are exquisitely true in this setting: while two ICUs may be different, each ICU discharges patients into a broad and variable milieu of settings. The variation in both ICU and post-ICU management of critically ill patients increases the complexity of understanding and defining best practice.

Thus, putting all this together, there are some overarching conceptual features about 'best practice' that the panel endorses, recognising, however, that the nature, timing, and combination of these broad aspects of care may vary, and strong unambiguous evidence for the 'how to' for these things is often going to be lacking.

Goals of care

Recommendations
74. For adults with sepsis or septic shock, we **recommend** discussing goals of care and prognosis with patients and families over no such discussion *Best Practice Statement*
75. For adults with sepsis or septic shock, we **suggest** addressing goals of care early (within 72 h) over late [72] *Weak recommendation, low-quality evidence*
76. There is **insufficient evidence to make a recommendation** for any specific standardised criterion to trigger goals of care discussion

Rationale

Patients with sepsis or septic shock are at high risk of multi-organ failure, long-term functional sequelae, and death. Some patients may accept any and all treatment for their condition, but others may consider limitations depending on prognosis, invasiveness of interventions, and predicted quality of life (QoL). A discussion of goals of care and prognosis is essential to determine which treatments are acceptable and those interventions that are not desired [536].

No studies were identified that compared discussions of goals of care and prognosis versus no such discussion in critically ill or septic patients. While advance care planning in patients with life-limiting illness may reduce use of life-sustaining treatments, it may also increase use of hospice and palliative care, and improve concordance between treatment and patient values [537]. The relevance of advance care planning for future health needs to goals of care discussions at the time of a critical illness is unclear. Despite lack of evidence, the panel recognised that discussion of prognosis and exploration of goals of care with patients and/or family is a necessary precondition to determine patient treatment preferences and providing value-concordant care. Thus, the panel made a best practice recommendation to discuss goals of care and prognosis with patients and families.

The timing of discussions of goals of care and prognosis in the ICU was addressed in one study where 26% of patients had infection or sepsis as a primary diagnosis [538]. A multicomponent family support intervention included a meeting at 48 h after ICU admission that included discussion of goals of care and prognosis. The support intervention did not affect family psychological outcomes but did improve perceived quality of communication and perception of patient- and family-centeredness of care. A reduction in ICU length of stay was noted, yet it is unknown if the reduction is due to increased mortality. Based on this study, early (within 72 h of ICU admission) discussion of the goals of care is suggested.

We identified several studies exploring the use of specific criteria to trigger a goals of care discussion in critically ill patients, though none report the proportion of patients with sepsis or septic shock. Conflict over values-based treatment was used to trigger ethics consultation in the intervention group in three randomised ICU studies [539–541]. Reductions in ICU and ventilator days in intervention patients who died before hospital discharge were found in two studies [539, 540], and the third study found overall shorter ICU and hospital stay in the ethics consultation group [541]. Ethics consultation did not affect overall mortality in any study. Duration of mechanical ventilation and duration of ICU stay were used to trigger specific interventions in two randomised studies [542, 543]. The study by Carson et al. randomised patients after 7 days of mechanical ventilation to a group receiving an informational brochure and two family meetings with palliative care specialists to address goals of care or a group receiving an informational brochure and meetings led by the ICU team [543]. Palliative care meetings failed to show benefit in decreasing anxiety and depression in surrogate decision makers in the intervention group but did increase post-traumatic stress disorder (PTSD) symptoms. No benefit was demonstrated on family satisfaction, ICU days, or hospital days. Andereck et al. randomised patients after 5 days or more in a medical-surgical ICU to proactive ethics consultation versus usual care [542]. Ethics consultation did not result in a reduction in ICU stay, hospital stay, or life-sustaining treatments in patients who did not survive to discharge. Neither study demonstrated an effect of interventions on mortality. One study [544] investigated the use of an automated early warning system alert in patients hospitalised on medical units (27% with infection). The early warning system did not impact hospital mortality or hospital length of stay, but did reduce ICU transfers and ICU length of stay and increased documentation of advance directives and resuscitation status compared to the usual care group.

Given the variety of triggers used in these studies and the lack of superiority of any single trigger, no recommendation can be made for specific criteria to initiate a goals of care discussion. The timing of and triggers for such discussions should take into account the current condition of the patient, premorbid health and QoL, prognosis, response to treatment, interventions under consideration, anticipated QoL following treatment, availability of resources, and readiness and ability of the patient or family to engage in the discussion.

Public members judged it important to assess patient and family understanding of the information provided in goals of care discussion and for a member of the care team to check with them to determine if further explanations are needed. Additional input included the recommendation that a goals of care discussion should take into account chronic medical conditions in addition to sepsis.

Palliative care

Recommendations
77. For adults with sepsis or septic shock, we **recommend** integrating principles of palliative care (which may include palliative care consultation based on clinician judgement) into the treatment plan, when appropriate, to address patient and family symptoms and suffering *Best Practice Statement*
78. 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 *Weak recommendation, low-quality evidence*

Rationale

While the goal of treating most patients with sepsis or septic shock is to improve survival, some patients have significant comorbidities that may be life limiting or significantly impair QoL. Palliative (supportive) care may be particularly helpful in patients with sepsis who are not responding to treatment or for whom sepsis is an end-stage manifestation of their underlying chronic illness. Studies have evaluated palliative care interventions in the ICU but not specifically in patients with sepsis [543, 545–548]. However, indirect evidence from these studies was judged likely to apply to patients with sepsis.

Criteria for patient inclusion and the interventions in these studies demonstrate significant heterogeneity. Inclusion criteria for ICU patients consisted of mechanical ventilation for 7 days [543], high risk on a palliative care screen [548], physician determination that care should not be escalated or care should be withdrawn [545], physician belief that the patient would die in a few days [547], or death in the ICU or within 30 h of transfer out of the ICU [546]. Interventions comprised formal palliative care consultation [543, 545, 548], a complex quality improvement project to improve end-of-life care [546], and a planned end-of-life conference conducted by intensivists according to specific guidelines along with a bereavement brochure [547].

Various outcome measures are reported but none of the studies evaluated critical patient-centered outcomes such as QoL, physical or cognitive recovery, psychological outcomes, or symptoms. Only one study with a structured palliative care intervention [547] demonstrated a beneficial effect of lower prevalence of anxiety and depression symptoms and PTSD symptoms in family members 90 days after the patient's death. In contrast, Carson et al. found an increase in PTSD symptoms in family surrogate decision makers with palliative care consultation [543]. Palliative care interventions had no significant impact on family satisfaction with care, ICU length of stay [543, 545–548], hospital length of stay [543, 545, 548], or mortality [543, 545, 548].

Overall evidence for routine formal palliative care interventions in ICU patients is of low quality and provides mixed evidence of benefit. Thus, the panel suggests against routine formal palliative care consultation for all patients with sepsis or septic shock, instead using clinician judgment to determine which patients and families may benefit from a palliative care consultation.

Despite the lack of evidence for formal palliative care consultation, the panel and public members judged that the principles of palliative care, whether instituted by palliative care specialists, intensivists or other clinicians are essential to address symptoms and suffering in patients and their families. Therefore, the panel made a best practice statement recommending incorporation of palliative care principles in the care of patients with sepsis and septic shock.

Peer support groups

Recommendation
79. For adult survivors of sepsis or septic shock and their families, we **suggest** referral to peer support groups over no such referral *Weak recommendation, very low quality of evidence*

Rationale

Peer support groups have been used to enhance recovery from illness when survivors have long-lasting disability but have only recently been used in critical care and sepsis [549–551]. With increased recognition of post-intensive care syndrome (PICS) in survivors of critical illness and their families, peer support represents a patient-centered approach to improve long-term outcomes [552, 553]. Public members suggested that referral to an individual peer support person during the sepsis hospitalisation may provide a means of support and hope for recovery while referring sepsis survivors and their

families to a peer support group may help them regain functional and emotional health.

Models of peer support are numerous and include community-based in person or virtual peer support; outpatient ICU follow-up clinics (with or without psychologist support); within-ICU peer support; and individual peer mentors [551]. We did not identify sufficient studies to allow for meta-analysis. Four observational studies examined the impact of peer support groups on ICU patients, though they were not specific to sepsis patients. These studies evaluated the impact of peer support in ICU survivors from a surgical ICU [554], two general ICUs [555–557] and two cardiac ICUs [555, 558]. Group models varied, with facilitated in-person [554, 557], group-based integrated with rehabilitation [555, 556] or a "buddy" with a former patient-to-patient programme [558]. In several qualitative studies, ICU survivors described peer support as a helpful aid to recovery [559–563]. Three qualitative studies identified two common themes of peer support, (1) benefit of knowing that others shared similar experiences and (2) benefit of shared coping with others [564].

Overall quality of evidence was judged to be very low for the impact of peer support groups on outcomes. No studies described costs associated with support groups, which will vary given the model and resource availability. Research evaluating support groups is needed with at least two RCTs planned [564–566].

Despite the very low certainty of evidence, the panel made a weak recommendation in favour of referring patients and families to peer support, which will increase the equity of access to such services. As individuals who receive referral to peer support have the choice to participate or not (based on personal preference, timing, location, functional status, and resources required) a weak recommendation provides an opportunity to access support for sepsis survivors who otherwise may not know where to turn [552].

Transitions of care

Recommendations
80. 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 *Weak recommendation, very low-quality evidence*
81. There is **insufficient evidence to make a recommendation** for the use of any specific structured handoff tool over usual handoff processes

Rationale

Transitions of care are prone to communication errors, which have been identified as a barrier to the timely detection and management of sepsis [567]. Improving handoff at transitions in care represents an opportunity to improve patient outcomes across the entire spectrum of sepsis care, from hospitalisation to return to the community.

We did not identify any studies specifically evaluating patients with sepsis. Structured handoff interventions for critically ill patients have been evaluated at many transitions of patient care (ED/ICU, OR/ICU, ICU/ward, and hospital/home). The majority are observational pre-post studies and report process measures such as completeness and accuracy of communication rather than clinical outcomes. There were insufficient data to allow for meta-analysis.

A single RCT using a stepped-wedge design in 8 ICUs evaluated the impact of a standardised handoff process, finding no effect upon duration of mechanical ventilation, ICU length of stay or duration of handover [568]. Observational studies of structured handoff process have demonstrated mixed effects, with some finding reductions in unexpected clinical events [569], or ICU readmission [570, 571] and others without impact upon length of stay [572], mortality [572, 573] or hospital readmission [572, 573].

Overall quality of evidence was judged to be very low. While it is unclear whether structured handoffs impact important patient outcomes, many sepsis interventions and tests are time-dependent and communication failures may increase the chances of critical medical errors. Structured handoff processes appear to result in more complete and accurate transfer of information, without any undesirable effects. Thus, despite the low certainty of evidence, the panel made a weak recommendation in favour of structured handoff processes at transitions of care. Of the structured handover tools studied, none specifically applies to sepsis. Given the wide variety of hospital staffing models, medical records, and discharge processes, along with the lack of evidence to recommend any one tool over another, the panel chose to make no recommendation for a specific structured handover tool.

Screening for economic or social support

Recommendation
82. For adults with sepsis or septic shock and their families, we **recommend** screening for economic and social support (including housing, nutritional, financial, and spiritual support), and make referrals where available to meet these needs *Best Practice Statement*

Rationale

Non-medical social needs and potentially modifiable factors such as economic and social support largely influence health outcomes. While survival from sepsis is

improving, long-term health requires survivors to have the resources to recover and thrive. Notably, critically ill patients have a decline in socio-economic status (SES) after their illness [574]. Many observational studies describe the relationship between various socioeconomic supports and patient outcomes that suggest that low SES, substance abuse and poor nutritional status lead to poor outcomes, and that critical illness itself results in lower SES post-illness. Additionally, living in neighborhoods with low SES is associated with an increased risk of sepsis [575], community-acquired bacteremia [575] and death from bacteremia [576] and worse outcomes [577]. Racial disparities in sepsis [578] are at least partially explained by living in medically underserved neighborhoods [579].

Screening for economic and social support may help reduce these inequities. Although socioeconomic screening is considered part of standard clinical practice, all clinical teams in many settings may not do it. This may be particularly true in the critical care setting where patients are often unable to communicate, and social determinants of health may not be addressed during management of the acute illness.

No studies were identified comparing screening versus no screening for economic and social support. Furthermore, it is unlikely that many research studies would be conducted, since locally available social needs and supports vary. In LMIC where resources are limited, needs may be vast. Despite these variations, social and economic screening may identify challenges that sepsis survivors are experiencing, allowing clinicians to identify potential resources and referrals, which can assist to improve long-term health outcomes.

[582]. We identified six RCTs that evaluated educational interventions for critically ill patients and their families [583–588]. Only one specifically studied patients with sepsis [588], evaluating a complex intervention, which included education along with primary care follow-up and post-discharge monitoring. Varied education methods were employed, including delivery by trained nurses [586, 588], multimedia nursing education [585], information booklets developed by nurses [584], a family information leaflet [583], and informational videos with accompanying web-based content [587].

These studies provided limited data for review. ICU education did not appear to impact patients' anxiety and depression [584, 586, 588], but did improve families' satisfaction with care [583]. The panel judged that education would likely have variable acceptability, as a qualitative study showed that patients who survived sepsis had diverse viewpoints ranging from appreciating the education about sepsis to not being able to recall the education session, to even disliking it as a reminder of the severity of their condition [587]. Based on these data and feedback from the public panel, we suggest that multiple opportunities for education be offered prior to hospital discharge and in the follow-up setting, taking into account patients' and/or families' readiness to process information. Sepsis education is regarded as a low cost intervention and feasible, even in low-resource settings, as a number of online and published sepsis education resources exist [589]. Future studies are needed to better understand the effects, the cost-effectiveness, and the optimal approach for educating patients and families after sepsis.

Sepsis education for patients and families

Recommendation
83. For adults with sepsis or septic shock and their families, we **suggest** offering written and verbal sepsis education (diagnosis, treatment, and post-ICU/post-sepsis syndrome) prior to hospital discharge and in the follow-up setting
Weak recommendation, very low-quality evidence

Rationale

Almost 40% of sepsis survivors are re-hospitalised within 3 months, often for preventable conditions [580], contributing to increased healthcare costs [581]. Given the risk of post-sepsis morbidity, sepsis education may have a role in the timely healthcare seeking behavior in sepsis survivors who experience complications. In an international survey of sepsis survivors from 41 countries, 45% and 63% reported dissatisfaction with sepsis education at the acute and post-acute phase, respectively

Shared decision making

Recommendation
84. For adults with sepsis or septic shock and their families, we **recommend** the clinical team provide the opportunity to participate in shared decision making in post-ICU and hospital discharge planning to ensure discharge plans are acceptable and feasible
Best Practice Statement

Rationale

Shared decision making (SDM) is a process in which health professionals, patients and their caregivers collaborate in making decisions about a patient's care options [590]. This patient-centered approach may be less routinely used in post-ICU and hospital discharge planning than in other aspects of acute patient care. No studies were identified that compared SDM with other types of ICU or hospital discharge planning. Despite the lack of evidence, SDM in discharge planning as in other care decisions is more likely to result in decisions consistent

with the values and preferences of the patient and family. Patient and family involvement in discharge planning may also increase family satisfaction. A small study of ICU relatives found that anxiety and depression rates were lower in those who preferred an active role or shared responsibility in decision-making compared to those who preferred a passive role [591]. A family care conference with nursing staff at the time of discharge from the ICU resulted in lower anxiety scores for family members compared to a control group although it is not clear that families participated in SDM [592]. Family caregivers of critically ill patients discharged home felt overwhelmed and unprepared and had difficulty managing expectations [593]. Communication through SDM at the time of ICU or hospital discharge may improve support for family caregivers as communication was found to be important to decision-making for family surrogates of chronic critically ill patients [594]. Studies of tools employed to promote SDM in patients with other serious illnesses show improved patient knowledge and awareness of treatment options [595]. Due to the potential benefits of SDM and the current emphasis on patient-centered care, the opportunity for patients and/or family to participate in SDM for ICU and hospital discharge planning is recommended as a best practice statement.

Discharge planning

Recommendations
85. For adults with sepsis and septic shock and their families, we **suggest** using a critical care transition programme, compared to usual care, upon transfer to the floor *Weak recommendation, very low-quality evidence*
86. For adults with sepsis and septic shock, we **recommend** reconciling medications at both ICU and hospital discharge *Best Practice Statement*
87. For adult survivors of sepsis and septic shock and their families, we **recommend** including information about the ICU stay, sepsis and related diagnoses, treatments, and common impairments after sepsis in the written and verbal hospital discharge summary *Best Practice Statement*

Rationale

Transfer from ICU to general floor and discharge from the hospital are both vulnerable periods for patients, with high frequency of medication errors and information loss [596–602]. Sepsis patients, with longer than average hospitalisations and higher comorbidity burden, may be at particular risk for poor outcomes with transitions. Several studies, mostly before-and-after design, have examined the impact of critical care transition programmes on reducing ICU readmission or death among patients transferred from ICU to the ward [597, 601, 603–611]. These programmes have used varied models, but generally involve ICU clinicians (e.g., nurse, respiratory therapist, and/or physician) following patients daily on the wards after transferring out of the ICU for a few days or until clinically stable. Meta-analysis of these studies suggests that critical care transition programmes reduce risk of in-hospital mortality and potentially reduce risk of ICU readmission. Effects on ICU workload and workflow have not been systematically examined. Public panel members were supportive of such programmes, as they may provide reassurance and a sense of protection to patients after they leave the ICU.

Medication reconciliation is broadly recognised to be important during patient transitions. Hospitalisation and ICU admission are high-risk periods for unintentional medication error—both continuations of medications for temporary indications and unintentional discontinuations of chronic medications [596, 599, 600, 602]. Medication reconciliation has been associated with fewer medication errors [598, 612] and may help reduce hospital readmission [613, 614]. Given the frequency of medication changes during an ICU stay, we recommend reconciling medications at both ICU and hospital discharge. Medication reconciliation surrounding sepsis hospitalisation involves getting the correct list of medications and adjusting medication dosing regularly in response to dynamic physiologic changes during and after critical illness [580].

Key information from hospitalisation is often missing on hospital discharge documentation [615–618]. Information on post-intensive care syndrome (PICS) may be provided to only one in three ICU survivors [550, 618], mechanical ventilation, dialysis), and common impairments after sepsis. We recommend providing information about the ICU stay, sepsis diagnosis, key treatments (e.g. mechanical ventilation, dialysis), and post-ICU/post-sepsis syndrome." to replace sentence fragment "mechanical ventilation, dialysis) and common impairments after sepsis. Public panel members stressed the importance of providing information in both verbal and written form and assessing that the information was understood. There are a growing number of online resources and informational brochures regarding “post intensive care” / “post-sepsis syndrome" [580], but more research is needed to determine the optimal approaches to providing anticipatory guidance to patients and families after critical illness [582, 619].

Recommendations

88. For adults with sepsis or septic shock who developed new impairments, we **recommend** hospital discharge plans include follow-up with clinicians able to support and manage new and long-term sequelae

Best Practice Statement

89. There is **insufficient evidence to make a recommendation** on early post-hospital discharge follow-up compared to routine post-hospital discharge follow-up

Rationale

Many sepsis survivors experience short and/or long-term sequela such as cognitive and/or physical disability, with ongoing recovery persisting for months to years [620]. Public panelists rated cognitive and physical recovery, psychologic symptoms in survivors and their families, QoL and readmission to the hospital and/or ICU as critically important outcomes. These outcomes were consistent with a 2019 qualitative analysis of health related QoL domains identified by sepsis survivors [621]. Follow-up with a provider after hospital discharge is one-step in the recovery process.

Sepsis survivors are at risk for hospital readmission, which has been associated with increased mortality or discharge to hospice [622, 623]. Hospital readmission within 90 days of discharge occurs in approximately 40% of sepsis survivors and is associated with high costs [624]. In addition, sepsis survivors are at increased risk for recurrent infection, AKI and new cardiovascular events compared to patients hospitalised for other diagnoses [580]. Observational studies in patients with congestive heart failure have associated early (within 7–14 days) post-discharge follow-up with reduced hospital readmissions [625]. Among older adults, early post discharge follow-up (within 7 days) with a primary care physician was associated with lower risk of 30-day readmission [626, 627].

Three studies, one RCT [628] and two observational studies [629, 630] evaluated early post-hospital follow-up in patients with critical illness. None of the three studies specifically evaluated a sepsis population or reported the proportion of sepsis patients. The interventions and QoL measures varied among the three studies each with severe limitations. In an analysis of older adults with severe sepsis, one study found that the combination of early home health care and a visit with a medical provider was associated with a reduced readmission risk [631]. There were insufficient studies to allow meta-analysis and the limited evidence is of very low quality.

Despite these limitations, the panel recommends follow-up with a provider after hospital discharge to manage new impairments associated with sepsis. Due to the low quality and lack of evidence specific to sepsis, we are unable to make a recommendation for early (7–14 days) provider follow-up versus routine follow-up upon hospital discharge. Timely, coordinated resources and provider follow-up may lead to improved QoL for sepsis survivors, however further research on the impact of post-discharge follow-up is needed.

Cognitive therapy

Recommendation

90. There is **insufficient evidence to make a recommendation** on early cognitive therapy for adult survivors of sepsis or septic shock

Rationale

Sepsis is associated with newly acquired cognitive impairment and functional disability amongst survivors [620]. Long-term impairments in memory, attention, verbal fluency, decision-making and executive functioning may be linked to a variety of mechanisms such as metabolic derangements, cerebral ischaemia, overwhelming inflammation, disrupted blood–brain barrier, oxidative stress, and severe microglial activation, particularly within the limbic system [632]. A feasibility, pilot, randomised trial in general medical/surgical ICU survivors comparing usual care to an intervention of combined in-home cognitive, physical, and functional rehabilitation following discharge showed improved executive functioning at 3 months [633]. Some small single centre studies tested specific early cognitive therapies to enhance cognitive and overall functional recovery after critical illness [634, 635].

A proof-of-concept single-centre pilot study aimed to evaluate the efficacy and safety of the use of a multifaceted early intervention (cognitive therapy within ICU) in patients with respiratory failure and/or shock [634]. ICU patients were randomised to receive either combined cognitive and physical therapy or physical therapy alone. The results demonstrated that the intervention was feasible and safe, but the study was underpowered and therefore inconclusive regarding its clinical effects on cognitive function and health-related QoL outcomes at 3-month follow-up. In addition, a prospective cohort study testing a series of cognitive training sessions starting in the ICU and continued for up to 2 months, found overall minimal clinical relevance as Minimum Clinically Important Difference (MID) of Montreal Cognitive Assessment (MOCA) was small, with some meaningful results in younger patients, but not in the middle-aged or older population [635, 636].

In view of these findings, the panel judged there to be insufficient evidence to make a recommendation. In centers where cognitive therapy is used, it could reasonably be continued as it is likely acceptable and feasible,

but there is insufficient evidence to change practice in centers without such therapy. Further larger studies in patients with sepsis are required to determine the impact of early cognitive therapy, as well as costs and type of intervention.

Post-discharge follow-up

Recommendations
91. For adult survivors of sepsis or septic shock, we **recommend** assessment and follow-up for physical, cognitive, and emotional problems after hospital discharge Best Practice Statement
92. For adult survivors of sepsis or septic shock, we **suggest** referral to a post-critical illness follow-up programme if available *Weak recommendation, very low-quality evidence*
93. For adult survivors of sepsis or septic shock receiving mechanical ventilation for > 48 h or an ICU stay of > 72 h, we **suggest** referral to a post-hospital rehabilitation programme *Weak recommendation, very low-quality evidence*

Rationale

Given the prevalence of new or worsening physical, cognitive, and emotional problems experienced by sepsis survivors [580, 620], we recommend assessment and follow-up for these problems after hospital discharge. There are insufficient data to suggest any specific tool to assess for these problems, and the optimal approach will vary by patient and setting. At a minimum, physicians should ask patients and families about new problems in these domains.

Post-critical illness programmes have been developed as a means of screening for and addressing the multi-faceted issues faced by ICU survivors. These programmes vary in their structure, and are not consistently available worldwide [637]. Few randomised studies have assessed post-critical illness clinics [588, 628, 638, 639], and—consistent with a recent Cochrane review [640]—our meta-analysis found no differences from usual care in terms of mortality, QoL, physical function, or cognition, with possible small improvements in psychological symptoms (anxiety, depression, PTSD). More studies of post-sepsis follow-up programmes are in process [641, 642]. We suggest offering referral to post-critical illness clinics where available. While efficacy data are equivocal, these programmes are consistently well-liked by patients and offer an environment to learn about challenges sepsis survivors face, as well as to pilot and test interventions for enhancing recovery [637, 643]. Lessons learned in post-critical care clinics could be adapted to other, more-scalable interventions such as telehealth.

Several randomised studies have assessed physical rehabilitation programmes for survivors of critical illness [581, 606, 644–651]. These studies focused on critically ill patients, generally defined by days in ICU or days with mechanical ventilation and begin on the floor or post-hospital setting. Meta-analysis suggests possible small improvements in QoL and depressive symptoms, but no difference in mortality, physical function, or anxiety. Nonetheless, based on their strong rationale, and benefit in related populations [580] (e.g., older patients with cognitive impairment, patients following stroke or traumatic brain injury), we suggest referral to rehabilitation programmes in survivors of sepsis. This suggestion is consistent with the guidance of several expert panels [646, 652, 653]. Future research is needed to determine an optimal approach to functional rehabilitation (timing, dosing, intensity, duration) and patient selection [643].

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s00134-021-06506-y.

Electronic supplementary material
- Methodology
- Appendix 1. Screening and Early Treatment
- Appendix 2. Infection
- Appendix 3. Haemodynamic Management
- Appendix 4. Ventilation
- Appendix 5. Additional Therapies
- Appendix 6. Goals and Long Term Outcomes
- Appendix 7. Search Strategy

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Endorsements
This manuscript has been endorsed by the following societies: European Society of Intensive Care Medicine, Society of Critical Care Medicine, American Association of Critical Care Nurses, American College of Chest Physicians, American College of Emergency Physicians, American Thoracic Society, African Sepsis Alliance, Asia and Pacific Sepsis Alliance, Association De Medicina Intensiva Brasileira, Australian and New Zealand Intensive Care Society, Canadian Critical Care Society, Chinese Society of Critical Care Medicine, Chest, European Respiratory Society, European Society of Clinical Microbiology and Infectious Diseases, Indian Society of Critical Care Medicine, Infectious Diseases Society of North America, Japanese Society of Intensive Care Medicine, Latin American Sepsis Institute, Society for Academic Emergency Medicine, Scandinavian Critical Care Trials Group, Surgical Infection Society, World Federation of Critical Care Nurses, World Federation of Societies of Intensive and Critical Care Medicine.

Governance of surviving sepsis campaign
SSC Guidelines Committee Co-chairs: Andrew Rhodes, Laura Evans; SSC Guidelines Committee Co vice-chairs: Hallie Prescott, Marlies Ostermann; SSC Guidelines Committee Oversight Group: Andrew Rhodes, Laura Evans, Waleed Alhazzani; SSC Guidelines Committee Group-heads: Craig French, Flavia Machado, Mitchell Levy, Lauralyn McIntyre, Christa Schorr, Steven Simpson, Joost Wiersinga; SSC Conflicts of Interest Co-chairs: Massimo Antonelli, Craig Coopersmith; GUIDE Methodology group: Waleed Alhazzani (chair), Emilie Belley-Cote, Fayez Alshamsi, John Centofanti, Mark Nunnally, Morten Hylander-Moller, Simon Oczkowski.

Declarations

Conflicts of interest
Dr. Alhazzani is the Chair of the Guidelines Chapter for the Saudi Critical Care Society and is the chair of the guidelines in intensive care, development and evaluation (GUIDE) Group, McMaster University Canada. Dr. Antonelli received funding from GE, Toray-Estor, Baxter, Pfizer, Orion, Maquet, and Fisher and Paykel; he was on the board of Baxter and Pfizer, and is a member of the executive committee and past president of Società Italiana di Anestesia Rianimazione e Terapia Intensiva (SIAARTI). Dr. French contributed to the ANZICS Guidelines and the National COVID-19 Guidelines. Dr. Machado is a member of the Executive Committee for the Basics Study (for which Baxter provided the drugs and logistics) and AMIB. Dr. McIntyre is a member of the Canadian Critical Care Society and serves on the Surviving Sepsis Campaign Steering Committee. Dr. Ostermann is a council member of the Intensive Care Society UK and member of the Renal Association UK and World Sepsis Alliance. 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