Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016 Andrew Rhodes[1*], Laura E. Evans[2], Waleed Alhazzani[3], Mitchell M. Levy[4], Massimo Antonelli[5], Ricard Ferrer[6], Anand Kumar[7], Jonathan E. Sevransky[8], Charles L. Sprung[9], Mark E. Nunnally[2], Bram Rochwerg[3], Gordon D. Rubenfeld[10], Derek C. Angus[11], Djillali Annane[12], Richard J. Beale[13], Geoffrey J. Bellinghan[14], Gordon R. Bernard[15], Jean-Daniel Chiche[16], Craig Coopersmith[8], Daniel P. De Backer[17], Craig J. French[18], Seitaro Fujishima[19], Herwig Gerlach[20], Jorge Luis Hidalgo[21], Steven M. Hollenberg[22], Alan E. Jones[23], Dilip R. Karnad[24], Ruth M. Kleinpell[25], Younsuk Koh[26], Thiago Costa Lisboa[27], Flavia R. Machado[28], John J. Marini[29], John C. Marshall[30], John E. Mazuski[31], Lauralyn A. McIntyre[32], Anthony S. McLean[33], Sangeeta Mehta[34], Rui P. Moreno[35], John Myburgh[36], Paolo Navalesi[37], Osamu Nishida[38], Tiffany M. Osborn[31], Anders Perner[39], Colleen M. Plunkett[25], Marco Ranieri40, Christa A. Schorr[22], Maureen A. Seckel[41], Christopher W. Seymour[42], Lisa Shieh43, Khalid A. Shukri[44], Steven Q. Simpson[45], Mervyn Singer[46], B. Taylor Thompson[47], Sean R. Townsend[48], Thomas Van der Poll[49], Jean-Louis Vincent[50], W. Joost Wiersinga[49], Janice L. Zimmerman[51] and R. Phillip Dellinger[22]

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ABSTRACT

Objective: To provide an update to "Surviving Sepsis Campaign Guidelines for Management of Sepsis and Septic Shock: 2012".

Design: A consensus committee of 55 international experts representing 25 international organizations was convened. Nominal groups were assembled at key international meetings (for those committee members attending the conference). A formal conflict-of-interest (COI) policy was developed at the onset of the process and enforced throughout. A stand-alone meeting was held for all panel members in December 2015. Teleconferences and electronic-based discussion among subgroups and among the entire committee served as an integral part of the development.

Methods: The panel consisted of five sections: hemodynamics, infection, adjunctive therapies, metabolic, and ventilation. Population, intervention, comparison, and outcomes (PICO) questions were reviewed and updated as needed, and evidence profiles were generated. Each subgroup generated a list of questions, searched for best available evidence, and then followed the principles of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to assess the quality of evidence from high to very low, and to formulate recommendations as strong or weak, or best practice statement when applicable.

Results: The Surviving Sepsis Guideline panel provided 93 statements on early management and resuscitation of patients with sepsis or septic shock. Overall, 32 were strong recommendations, 39 were weak recommendations, and 18 were best-practice statements. No recommendation was provided for four questions.

Conclusions: Substantial agreement exists among a large cohort of international experts regarding many strong recommendations for the best care of patients with sepsis. Although a significant number of aspects of care have relatively weak support, evidence-based recommendations regarding the acute management of sepsis and septic shock are the foundation of improved outcomes for these critically ill patients with high mortality.

Keywords: Evidence-based medicine, Grading of Recommendations Assessment, Development, and Evaluation criteria, Guidelines, Infection, Sepsis, Sepsis bundles, Sepsis syndrome, Septic shock, Surviving Sepsis Campaign

INTRODUCTION

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection [1–3]. Sepsis and septic shock are major healthcare problems, affecting millions of people around the world each year, and killing as many as one in four (and often more) [4–6]. Similar to polytrauma, acute myocardial infarction, or stroke, early identification and appropriate management in the initial hours after sepsis develops improves outcomes.The recommendations in this document are intended to provide guidance for the clinician caring for adult patients with sepsis or septic shock. Recommendations from these guidelines cannot replace the clinician's decision-making capability when presented with a patient's unique set of clinical variables. These guidelines are appropriate for the sepsis patient in a hospital setting. These guidelines are intended to be best practice (the committee considers this a goal for clinical practice) and not created to represent standardof care.

METHODOLOGY

Below is a summary of the important methodologic considerations for developing these guidelines.

Definitions

As these guidelines were being developed, new definitions for sepsis and septic shock (Sepsis-3) were published. Sepsis is now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality [3]. The Sepsis-3 definition also proposed clinical criteria to operationalize the new definitions; however, in the studies used to establish the evidence for these guidelines, patient populations were primarily characterized by the previous definition of sepsis, severe sepsis, and septic shock stated in the 1991 and 2001 consensus documents [7].

History of the guidelines

These clinical practice guidelines are a revision of the 2012 Surviving Sepsis Campaign (SSC) guidelines for the management of severe sepsis and septic shock [8, 9]. The initial SSC guidelines were first published in 2004 [10], and revised in 2008 [11, 12] and 2012 [8, 9]. The current iteration is based on updated literature searches incorporated into the evolving manuscript through July 2016. A summary of the 2016 guidelines appears in "Appendix 1". A comparison of recommendations from 2012 to 2016 appears in "Appendix 2". Unlike previous editions, the SSC pediatric guidelines will appear in a separate document, also to be published by the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM).

Sponsorship Funding for the development of these guidelines was provided by SCCM and ESICM. In addition, sponsoring organizations provided support for their members' involvement.

Selection and organization of committee members

The selection of committee members was based on expertise in specific aspects of sepsis. Co-chairs were appointed by the SCCM and ESICM governing bodies. Each sponsoring organization appointed a representative who had sepsis expertise. Additional committee members were appointed by the co-chairs and the SSC Guidelines Committee Oversight

Group to balance continuity and provide new perspectives with the previous committees' membership as well as to address content needs. A patient representative was appointed by the co-chairs. Methodologic expertise was provided by the GRADE Methodology Group.

Question development

The scope of this guideline focused on early management of patients with sepsis or septic shock. The guideline panel was divided into five sections (hemodynamics,infection, adjunctive therapies, metabolic, and ventilation). The group designations were the internal work structure of the guidelines committee. Topic selection was the responsibility of the co-chairs and group heads, with input from the guideline panel in each group. Prioritization of the topics was completed by discussion through e-mails, teleconferences, and face-to-face meetings. All guideline questions were structured in PICO format, which described the population, intervention, control, and outcomes.

Questions from the last version of the SSC guidelines were reviewed; those that were considered important and clinically relevant were retained. Questions that were considered less important or of low priority to clinicians were omitted, and new questions that were considered high priority were added. The decision regarding question inclusion was reached by discussion and consensus among the guideline panel leaders with input from panel members and the methodology team in each group. GRADE methodology was applied in selecting only outcomes that were considered critical from a patient's perspective [13]. All PICO questions with supporting evidence are presented in Supplemental Digital Content 1 (ESM 1).

Search strategy

With the assistance of professional librarians, an independent literature search was performed for each defined question. The panel members worked with group heads, methodologists, and librarians to identify pertinent search terms that included, at a minimum, sepsis, severe sepsis, septic shock, sepsis syndrome, and critical illness, combined with appropriate key words specific to the question posed.

For questions addressed in the 2012 SSC guidelines, the search strategy was updated from the date of the last literature search. For each of the new questions, an electronic search was conducted of a minimum of two major databases (e.g., Cochrane Registry, MEDLINE, or EMBASE) to identify relevant systematic reviews and randomized clinical trials (RCTs).

Grading of recommendations

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system principles guided assessment of quality of evidence from high to very low and were used to determine the strength of recommendations (Tables 1, 2) [14]. The GRADE methodology is based on assessment of evidence according to six categories: (1) risk of bias, (2) inconsistency, (3) indirectness, (4) imprecision, (5) publication bias, and (6) other criteria, followed by assessment of the balance between benefit and harm, patients' values and preferences, cost and resources, and feasibility and acceptability of the intervention. The final recommendations formulated by the guideline panel are based on the assessment of these factors. The GRADE assessment of the quality of evidence is presented in Table 1.

RCTs begin as high-quality evidence that could be downgraded due to limitations in any of the afore-mentioned categories. While observational (nonrandomized) studies begin as low-quality evidence, the quality level could be upgraded on the basis of a large magnitude of effect or other factors. The GRADE methodology classifies recommendations as strong or weak. The factors influencing this determination are presented in Table 2. The guideline committee assessed whether the desirable effects of adherence would outweigh the undesirable effects, and the strength of a recommendation reflects the group's degree of confidence in that balance assessment. Thus, a strong recommendation in favor of an intervention reflects the panel's opinion that the desirable effects of adherence to a recommendation will clearly outweigh the undesirable effects. A weak recommendation in favour of an intervention indicates the judgment that the desirable effects of adherence to a recommendation probably will outweigh the undesirable effects, but the panel is not confident about these trade-offs—either because some of the evidence is low quality (and thus uncertainty remains regarding the benefits and risks) or the benefits and downsides are closely balanced. A strong recommendation is worded as "we recommend" and a weak recommendation as "we suggest". An alphanumeric scheme was used in previous editions of the SSC guidelines. Table 3 provides a comparison to the current grading system.

The implications of calling a recommendation strong are that most patients would accept that intervention and that most clinicians should use it in most situations. Circumstances may exist in which a strong recommendation cannot or should not be followed for an individual because of that patient's preferences or clinical characteristics that make the recommendation less applicable. These are described in Table 4. A strong recommendation does not imply standard of care.

A number of best practice statements (BPSs) appear throughout the document; these statements represent ungraded strong recommendations and are used under strict criteria. A BPS would be appropriate, for example, when the benefit or harm is unequivocal, but the evidence is hard to summarize or assess using GRADE methodology. The criteria suggested by the GRADE Working Group in Table 5 were applied in issuing BPSs [15].

Voting process

Following formulation of statements through discussion in each group and deliberation among all panel members during face-to-face meetings at which the groups presented their draft statements, all panel members received links to polls created using SurveyMonkey, Inc. (Palo Alto, CA) to indicate agreement or disagreement with the statement, or abstention. Acceptance of a statement required votes from 75% of the panel members with an 80% agreement threshold. Voters could provide feedback for consideration in revising statements that did not receive consensus in up to three rounds of voting.

Conflict of interest policy

No industry input into guidelines development occurred, and no industry representatives were present at any of the meetings. No member of the guidelines committee received honoraria for any role in the guidelines process. The process relied solely on personal disclosure, and no attempt was made by the group to seek additional confirmation. The co-chairs, COI chair, and group heads adjudicated this to the best of their abilities. On initial review, 31 financial COI disclosures and five nonfinancial disclosures were submitted by

committee members; others reported no COI. Panelists could have both financial and nonfinancial COI. Declared COI disclosures from 11 members were determined by the COI subcommittee to be not relevant to the guidelines content process. Fifteen who were determined to have COI (financial and nonfinancial) were adjudicated by a management plan that required adherence to SSC COI policy limiting discussion or voting at any committee meetings during which content germane to their COI was discussed. Five were judged as having conflicts that were managed through reassignment to another group as well as the described restrictions on voting on recommendations in areas of potential COI. One individual was asked to step down from the committee. All panellists with COI were required to work within their group with full disclosure when a topic for which they had relevant COI was discussed, and they were not allowed to serve as group head. At the time of final approval of the document, an update of the COI statement was required. No additional COI issues were reported that required further adjudication.

A summary of all statements determined by the guidelines panel appears in "Appendix 1". All evidence summaries and evidence profiles that informed the recommendations and statements appear in ESM 2. Links to specific tables and figures appear within the relevant text.

INITIAL RESUSCITATION

1. Sepsis and septic shock are medical emergencies, and we recommend that treatment and resuscitation begin immediately (BPS).
2. We recommend that, in the resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid be given within the first 3 h (strong recommendation, low quality of evidence).
3. We recommend that, following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status (BPS).

Remarks Reassessment should include a thorough clinical examination and evaluation of available physiologic variables (heart rate, blood pressure, arterial oxygen saturation, respiratory rate, temperature, urine output, and others, as available) as well as other noninvasive or invasive monitoring, as available.

4. We recommend further hemodynamic assessment (such as assessing cardiac function) to determine the type of shock if the clinical examination does not lead to a clear diagnosis (BPS).
5. We suggest that dynamic over static variables be used to predict fluid responsiveness, where available (weak recommendation, low quality of evidence).
6. We recommend an initial target mean arterial pressure (MAP) of 65 mm Hg in patients with septic shock requiring vasopressors (strong recommendation, moderate quality of evidence).
7. We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion (weak recommendation, low quality of evidence).

Rationale: Early effective fluid resuscitation is crucial for stabilization of sepsis-induced tissue hypoperfusion or septic shock. Sepsis-induced hypoperfusion may be manifested by acute organ dysfunction and/ or ± decreased blood pressure and increased serum lactate. Previous iterations of these guidelines have recommended a protocolized quantitative resuscitation, otherwise known as early goal-directed therapy (EGDT), which was based on the protocol published by Rivers [16]. This recommendation described the use of a series of "goals" that included central venous pressure (CVP) and central venous oxygen saturation ($ScvO_2$). This approach has now been challenged following the failure to show a mortality reduction in three subsequent large multicenter RCTs [17–19]. No harm was associated with the interventional strategies; thus, the use of the previous targets is still safe and may be considered. Of note, the more recent trials included less severely ill patients (lower baseline lactate levels, $ScvO_2$ at or above the target value on admission, and lower mortality in the control group). Although this protocol cannot now be recommended from its evidence base, bedside clinicians still need guidance as to how to approach this group of patients who have significant mortality and morbidity. We recommend, therefore, that these patients be viewed as having a medical emergency that necessitates urgent assessment and treatment. As part of this, we recommend that initial fluid resuscitation begin with 30 mL/kg of crystalloid within the first 3 h. This fixed volume of fluid enables clinicians to initiate resuscitation while obtaining more specific information about the patient and while awaiting more precise measurements of hemodynamic status. Although little literature includes controlled data to support this volume of fluid, recent interventional studies have described this as usual practice in the early stages of resuscitation, and observational evidence supports the practice [20, 21]. The average volume of fluid pre-randomization given in the PROCESS and ARISE trials was approximately 30 mL/kg, and approximately 2 L in the PROMISE trial [17 –19]. Many patients will require more fluid than this, and for this group we advocate that further fluid be given in accordance with functional hemodynamic measurements.

One of the most important principles to understand in the management of these complex patients is the need for a detailed initial assessment and ongoing reevaluation of the response to treatment. This evaluation should start with a thorough clinical examination and evaluation of available physiologic variables that can describe the patient's clinical state (heart rate, blood pressure, arterial oxygen saturation, respiratory rate, temperature, urine output, and others as available). Echocardiography in recent years has become available to many bedside clinicians and enables a more detailed assessment of the causes of the hemodynamic issues [22]. The use of CVP alone to guide fluid resuscitation can no longer be justified [22] because the ability to predict a response to a fluid challenge when the CVP is within a relatively normal range (8–12 mmHg) is limited [23]. The same holds true for other static measurements of right or left heart pressures or volumes. Dynamic measures of assessing whether a patient requires additional fluid have been proposed in an effort to improve fluid management and have demonstrated better diagnostic accuracy at predicting those patients who are likely to respond to a fluid challenge by increasing stroke volume. These techniques encompass passive leg raises, fluid challenges against stroke volume measurements, or the variations in systolic pressure, pulse pressure, or stroke volume to changes in intrathoracic pressure induced by mechanical ventilation [24]. Our review of five studies of the use of pulse pressure variation to predict fluid responsiveness in patients with sepsis or septic shock demonstrated a sensitivity of 0.72 (95% CI 0.61–0.81) and a specificity

of 0.91 (95% CI 0.83–0.95); the quality of evidence was low due to imprecision and risk of bias (ESM 3) [24]. A recent multicentre study demonstrated limited use of cardiac function monitors during fluid administration in the ICUs. Even though data on the use of these monitors in the emergency department are lacking, the availability of the devices and applicability of the parameters to all situations may influence the routine use of dynamic indices [22, 25].

MAP is the driving pressure of tissue perfusion. While perfusion of critical organs such as the brain or kidney may be protected from systemic hypotension by autoregulation of regional perfusion, below a threshold MAP, tissue perfusion becomes linearly dependent on arterial pressure. In a single-center trial [26], dose titration of norepinephrine from 65 to 75 and 85 mmHg raised cardiac index (from 4.7 ± 0.5 to 5.5 ± 0.6 L/min/m^2) but did not change urinary flow, arterial lactate levels, oxygen delivery and consumption, gastric mucosal PCO_2, RBC velocity, or skin capillary flow. Another single-center [27] trial compared, in norepinephrine-treated septic shock, dose titration to maintain MAP at 65 mmHg versus achieving 85 mmHg. In this trial, targeting high MAP increased cardiac index from 4.8 (3.8–6.0) to 5.8 (4.3–6.9) L/min/m^2 but did not change renal function, arterial lactate levels, or oxygen consumption. A third single-center trial [28] found improved microcirculation, as assessed by sublingual vessel density and the ascending slope of thenar oxygen saturation after an occlusion test, by titrating norepinephrine to a MAP of 85 mmHg compared to 65 mm Hg. Only one multicenter trial that compared norepinephrine dose titration to achieve a MAP of 65 mm Hg versus 85 mm Hg had mortality as a primary outcome [29]. There was no significant difference in mortality at 28 days (36.6% in the high-target group and 34.0% in the low-target group) or 90 days (43.8% in the high-target group and 42.3% in the low-target group). Targeting a MAP of 85 mm Hg resulted in a significantly higher risk of arrhythmias, but the subgroup of patients with previously diagnosed chronic hypertension had a reduced need for renal replacement therapy (RRT) at this higher MAP. A recent pilot trial of 118 septic shock patients [30] suggested that, in the subgroup of patients older than 75 years, mortality was reduced when targeting a MAP of 60–65 versus 75–80 mm Hg. The quality of evidence was moderate (ESM 4) due to imprecise estimates (wide confidence intervals). As a result, the desirable consequences of targeting MAP of 65 mm Hg (lower risk of atrial fibrillation, lower doses of vasopressors, and similar mortality) led to a strong recommendation favoring an initial MAP target of 65 mm Hg over higher MAP targets. When a better understanding of any patient's condition is obtained, this target should be individualized to the pertaining circumstances.

Serum lactate is not a direct measure of tissue perfusion [31]. Increases in the serum lactate level may represent tissue hypoxia, accelerated aerobic glycolysis driven by excess beta-adrenergic stimulation, or other causes (e.g., liver failure). Regardless of the source, increased lactate levels are associated with worse outcomes [32]. Because lactate is a standard laboratory test with prescribed techniques for its measurement, it may serve as a more objective surrogate for tissue perfusion as compared with physical examination or urine output. Five randomized controlled trials (647 patients) have evaluated lactate-guided resuscitation of patients with septic shock [33–37]. A significant reduction in mortality wasseen in lactate-guided resuscitation compared to resuscitation without lactate monitoring (RR 0.67; 95% CI 0.53–0.84; low quality). There was no evidence for difference in ICU length of stay (LOS) (mean difference − 1.51 days; 95% CI − 3.65 to 0.62; low quality).

Two other meta-analyses of the 647 patients who were enrolled in these trials demonstrate moderate evidence for reduction in mortality when an early lactate clearance strategy was used, compared with either usual care (nonspecified) or with a $ScvO_2$ normalization strategy [38, 39].

B. SCREENING FOR SEPSIS AND PERFORMANCEIMPROVEMENT

1. We recommend that hospitals and hospital systems have a performance improvement program for sepsis, including sepsis screening for acutely ill, high-risk patients (BPS).

Rationale Performance improvement efforts for sepsis are associated with improved patient outcomes [40]. Sepsis performance improvement programs should optimally have multiprofessional representation (physicians, nurses, affiliate providers, pharmacists, respiratory therapists, dietitians, administrators) with stakeholders from all key disciplines represented in their development and implementation. Successful programs should include protocol development and implementation, targeted metrics to be evaluated, data collection, and ongoing feedback to facilitate continuous performance improvement [41].In addition to traditional continuing education efforts to introduce guidelines into clinical practice, knowledge translation efforts can be valuable in promoting the use of high-quality evidence in changing behavior [42]. Sepsis performance improvement programs can be aimed at earlier recognition of sepsis via a formal screening effort and improved management of patients once they are identified as being septic. Because lack of recognition prevents timely therapy, sepsis screening is associated with earlier treatment [43, 44].

Notably, sepsis screening has been associated with decreased mortality in several studies [20, 45]. The implementation of a core set of recommendations (bundle) has been a cornerstone of sepsis performance improvement programs aimed at improving management [46]. Note that the SSC bundles have been developed separately from the guidelines in conjunction with an educational and improvement partnership with the Institute for Healthcare Improvement [46]. The SSC bundles that are based on previous guidelines have been adopted by the U.S.-based National Quality Forum and have also been adapted by the U.S. healthcare system's regulatory agencies for public reporting. To align with emerging evidence and U.S. national efforts, the SSC bundles were revised in 2015. While specifics vary widely among different programs, a common theme is the drive toward improvement in compliance with sepsis bundles and practice guidelines suchas SSC [8]. A meta-analysis of 50 observational studies demonstrated that performance improvement programs were associated with a significant increase in compliancewith the SSC bundles and a reduction in mortality (OR 0.66; 95% CI 0.61–0.72) [47]. The largest study to date examined the relationship between compliance with the SSC bundles (based on the 2004 guidelines) and mortality. A total of 29,470 patients in 218 hospitals in the United States, Europe, and South America were examined over a 7.5-year period [21]. Lower mortality was observed in hospitals with higher compliance. Overall hospital mortality decreased 0.7% for every 3 months a hospital participated in the SSC, associated with a 4% decreased LOS for every 10% improvement in compliance with bundles. This benefit has also been shown across a wide geographic spectrum. A study of 1794 patients from 62 countries with severe sepsis (now termed "sepsis" after the Sepsis-3 definition [1] or septic shock demonstrated a

36–40% reduction of the odds of dying in the hospital with compliance with either the 3- or 6-h SSC bundles [48]. This recommendation met the prespecified criteria for a BPS. The specifics of performance improvement methods varied markedly between studies; thus, no single approach to performance improvement could be recommended (ESM 5).

DIAGNOSIS

1. We recommend that appropriate routine microbiologic cultures (including blood) be obtained before starting antimicrobial therapy in patients with suspected sepsis or septic shock if doing so results in no substantial delay in the start of antimicrobials (BPS).

Remarks Appropriate routine microbiologic cultures always include at least two sets of blood cultures (aerobic and anaerobic).

Rationale Sterilization of cultures can occur within minutes to hours after the first dose of an appropriate antimicrobial [49, 50]. Obtaining cultures prior to the administration of antimicrobials significantly increases the yield of cultures, making identification of a pathogen more likely. Isolation of an infecting organism(s) allows for de-escalation of antimicrobial therapy first at the point of identification and then again when susceptibilities are obtained. De-escalation of antimicrobial therapy is a mainstay of antibiotic stewardship programs and is associated with less resistant microorganisms, fewer side effects, and lower costs [51]. Several retrospective studies have suggested that obtaining cultures prior to antimicrobial therapy is associated with improved outcome [52, 53]. Similarly, de-escalation has also been associated with improved survival in several observational studies [54, 55]. The desire to obtain cultures prior to initiating antimicrobial therapy must be balanced against the mortality risk of delaying a key therapy in critically ill patients with suspected sepsis or septic shock who are at significant risk of death [56, 57].

We recommend that blood cultures be obtained prior to initiating antimicrobial therapy if cultures can be obtained in a timely manner. However, the risk/benefit ratio favors rapid administration of antimicrobials if it is not logistically possible to obtain cultures promptly. Therefore, in patients with suspected sepsis or septic shock, appropriate routine microbiologic cultures should be obtained before initiation of antimicrobial therapy from all sites considered to be potential sources of infection if it results in no substantial delay in the start of antimicrobials. This may include blood, cerebrospinal fluid, urine, wounds, respiratory secretions, and other body fluids, but does not normally include samples that require an invasive procedure such as bronchoscopy or open surgery. The decision regarding which sites to culture requires careful consideration from the treatment team. “Pan culture” of all sites that could potentially be cultured should be discouraged (unless the source of sepsis is not clinically apparent), because this practice can lead to inappropriate antimicrobial use [58]. If history or clinical examination clearly indicates a specific anatomic site of infection, cultures of other sites (apart from blood) are generally unnecessary. We suggest 45 min as an example of what may be considered to be no substantial delay in the initiation of antimicrobial therapy while cultures are being obtained.

Two or more sets (aerobic and anaerobic) of blood cultures are recommended before initiation of any new antimicrobial in all patients with suspected sepsis [59]. All necessary

blood cultures may be drawn together on the same occasion. Blood culture yield has not been shown to be improved with sequential draws or timing to temperature spikes [60, 61]. Details on appropriate methods to draw and transport blood culture samples are enumerated in other guidelines [61, 62].
In potentially septic patients with an intravascular catheter (in place >48 h) in whom a site of infection is not clinically apparent or a suspicion of intravascular catheter-associated infection exists, at least one blood culture set should be obtained from the catheter (along with simultaneous peripheral blood cultures). This is done to assist in the diagnosis of a potential catheter-related bloodstream infection. Data are inconsistent regarding the utility of differential time to blood culture positivity (i.e., equivalent volume blood culture from the vascular access device positive more than 2 h before the peripheral blood culture) in suggesting that the vascular access device is the source of the infection [63 –65]. It is important to note that drawing blood cultures from an intravascular catheter in case of possible infection of the device does not eliminate the option of removing the catheter (particular nontunneled catheters) immediately afterward.

In patients without a suspicion of catheter-associated infection and in whom another clinical infection site is suspected, at least one blood culture (of the two or more that are required) should be obtained peripherally. However, no recommendation can be made as to where additional blood cultures should be drawn. Options include: (a) all cultures drawn peripherally via venipuncture, (b) cultures drawn through each separate intravascular device but not through multiple lumens of the same intravascular catheter, or (c) cultures drawn through multiple lumens in an intravascular device [66 –70]. In the near future, molecular diagnostic methods may offer the potential to diagnose infections more quickly and more accurately than current techniques. However, varying technologies have been described, clinical experience remains limited, and additional validation is needed before recommending these methods as an adjunct to or replacement for standard blood culture techniques [71 –73]. In addition, susceptibility testing is likely to require isolation and direct testing of viable pathogens for the foreseeable future.

D. ANTIMICROBIAL THERAPY

1. We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and within 1 h for both sepsis and septic shock (strong recommendation, moderate quality of evidence; grade applies to both conditions).

Rationale The rapidity of administration is central to the beneficial effect of appropriate antimicrobials. In the presence of sepsis or septic shock, each hour delay in administration of appropriate antimicrobials is associated with a measurable increase in mortality [57, 74]. Further, several studies show an adverse effect on secondary endpoints (e.g., LOS [75], acute kidney injury [76], acute lung injury [77], and organ injury assessed by Sepsis-Related Organ Assessment score [78] with increasing delays. Despite a meta-analysis of mostly poor-quality studies that failed to demonstrate a benefit of rapid antimicrobial therapy, the largest and highest-quality studies support giving appropriate antimicrobials as soon as possible in patients with sepsis with or without septic shock [57, 74, 79-81]. The majority of studies within the meta-analysis were of low quality due to a number of deficiencies, including small study size, using an initial index time of an arbitrary time point such as

emergency department arrival, and indexing of outcome to delay in time to the first antimicrobial (regardless of activity against the putative pathogen) [82, 83]. Other negative studies not included in this meta-analysis are compromised by equating bacteremia with sepsis (as currently defined to include organ failure) and septic shock [84 –87]. Many of these studies are also compromised by indexing delays to easily accessible but nonphysiologic variables such as time of initial blood culture draw (an event likely to be highly variable in timing occurrence). While available data suggest that the earliest possible administration of appropriate IV antimicrobials following recognition of sepsis or septic shock yields optimal outcomes, 1 h is recommended as a reasonable minimal target. The feasibility of achieving this target consistently, however, has not been adequately assessed. Practical considerations, for example, challenges with clinicians' early identification of patients or operational complexities in the drug delivery chain, represent poorly studied variables that may affect achieving this goal. A number of patient and organizational factors appear to influence antimicrobial delays [88]. Accelerating appropriate antimicrobial delivery institutionally starts with an assessment of causes of delays [89]. These can include an unacceptably high frequency of failure to recognize the potential existence of sepsis or septic shock and of inappropriate empiric antimicrobial initiation (e.g., as a consequence of lack of appreciation of the potential for microbial resistance or recent previous antimicrobial use in a given patient). In addition, unrecognized or underappreciated administrative or logistic factors (often easily remedied) may be found. Possible solutions to delays in antimicrobial initiation include use of "stat" orders or including a minimal time element in antimicrobial orders, addressing delays in obtaining blood and site cultures pending antimicrobial administration, and sequencing antimicrobial delivery optimally or using simultaneous delivery of key antimicrobials, as well as improving supply chain deficiencies. Improving communication among medical, pharmacy, and nursing staff can also be highly beneficial.

Most issues can be addressed by quality improvement initiatives, including defined order sets. If antimicrobial agents cannot be mixed and delivered promptly from the pharmacy, establishing a supply of premixed drugs for urgent situations is an appropriate strategy for ensuring prompt administration. Many antimicrobials will not remain stable if premixed in a solution. This issue must be taken into consideration in institutions that rely on premixed solutions for rapid antimicrobial availability. In choosing the antimicrobial regimen, clinicians should be aware that some antimicrobial agents (notably β-lactams) have the advantage of being able to be safely administered as a bolus or rapid infusion, while others require a lengthy infusion. If vascular access is limited and many different agents must be infused, drugs that can be administered as a bolus or rapid infusion may offer anadvantage for rapid achievement of therapeutic levels for the initial dose.

While establishing vascular access and initiating aggressive fluid resuscitation are very important when managing patients with sepsis or septic shock, prompt IV infusion of antimicrobial agents is also a priority. This may require additional vascular access ports. Intraosseous access, which can be quickly and reliably established (even in adults), can be used to rapidly administer the initial doses of any antimicrobial [90, 91]. In addition, intramuscular preparations are approved and available for several first-line β-lactams, including imipenem/ cilastatin, cefepime, ceftriaxone, and ertapenem. Several additional first-line β-lactams can also be effectively administered intramuscularly in emergency

situations if vascular and intraosseous access is unavailable, although regulatory approval for intramuscular administration for these drugs is lacking [92 –94]. Intramuscular absorption and distribution of some of these agents in severe illness has not been studied; intramuscular administration should be considered only if timely establishment of vascular access is not possible.

2. 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) (strong recommendation, moderate quality of evidence).
3. We recommend that empiric antimicrobial therapy be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted (BPS).

Rationale The initiation of appropriate antimicrobial therapy (i.e., with activity against the causative pathogen or pathogens) is one of the most important facets of effective management of life-threatening infections causing sepsis and septic shock. Failure to initiate appropriate empiric therapy in patients with sepsis and septic shock is associated with a substantial increase in morbidity and mortality [79, 95 –97]. In addition, the probability of progression from gram-negative bacteremic infection to septic shock is increased [98]. Accordingly, the initial selection of antimicrobial therapy must be broad enough to cover all likely pathogens. The choice of empiric antimicrobial therapy depends on complex issues related to the patient's history, clinical status, and local epidemiologic factors. Key patient factors include the nature of the clinical syndrome/site of infection, concomitant underlying diseases, chronic organ failures, medications, indwelling devices, the presence of immunosuppression or other form of immunocompromise, recent known infection or colonization with specific pathogens, and the receipt of antimicrobials within the previous three months. In addition, the patient's location at the time of infection acquisition (i.e., community, chronic care institution, acute care hospital), local pathogen prevalence, and the susceptibility patterns of those common local pathogens in both the community and hospital must be factored into the choice of therapy. Potential drug intolerances and toxicity must also be considered.

The most common pathogens that cause septic shock are gram-negative bacteria, gram-positive, and mixed bacterial microorganisms. Invasive candidiasis, toxic shock syndromes, and an array of uncommon pathogens should be considered in selected patients. Certain specific conditions put patients at risk for atypical or resistant pathogens. For example, neutropenic patients are at risk for an especially wide range of potential pathogens, including resistant gram-negative bacilli and Candida species. Patients with nosocomial acquisition of infection are prone to sepsis with methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococci.Historically, critically ill patients with overwhelming infection have not been considered a unique subgroup comparable to neutropenic patients for purposes of selection of antimicrobial therapy. Nonetheless, critically ill patients with severe and septic shock are, like neutropenic patients, characterized by distinct differences from the typical infected patient that impact on the optimal antimicrobial management strategy. Primary among these differences are a predisposition to infection with resistant organisms and a marked increase in frequency of

death and other adverse outcomes if there is a failure of rapid initiation of effective antimicrobial therapy.

Selection of an optimal empiric antimicrobial regimen in sepsis and septic shock is one of the central determinants of outcome. Survival may decrease as much as fivefold for septic shock treated with an empiric regimen that fails to cover the offending pathogen [95]. Because of the high mortality associated with inappropriate initial therapy, empiric regimens should err on the side of over-inclusiveness. However, the choice of empiric antimicrobial regimens in patients with sepsis and septic shock is complex and cannot be reduced to a simple table. Several factors must be assessed and used in determining the appropriate antimicrobial regimen at each medical center and for each patient. These include:(a) The anatomic site of infection with respect to the typical pathogen profile and to the properties of individual antimicrobials to penetrate that site.(b) Prevalent pathogens within the community, hospital, and even hospital ward.(c) The resistance patterns of those prevalent pathogens.(d) The presence of specific immune defects such as neutropenia, splenectomy, poorly controlled HIV infection and acquired or congenital defects of immunoglobulin, complement or leukocyte function or production.(e) Age and patient comorbidities including chronic illness (e.g., diabetes) and chronic organ dysfunction (e.g., liver or renal failure), the presence of invasive devices (e.g., central venous lines or urinary catheter) that compromise the defense to infection.In addition, the clinician must assess risk factors for infection with multidrug-resistant pathogens including prolonged hospital/chronic facility stay, recent antimicrobial use, prior hospitalization, and prior colonization or infection with multidrug-resistant organisms. The occurrence of more severe illness (e.g., septic shock) may be intrinsically associated with a higher probability of resistant isolates due to selection in failure to respond to earlier antimicrobials.

Given the range of variables that must be assessed, the recommendation of any specific regimen for sepsis and septic shock is not possible. The reader is directed to guidelines that provide potential regimens based on anatomic site of infection or specific immune defects [67, 99 –109]. However, general suggestions can be provided. Since the vast majority of patients with severe sepsis and septic shock have one or more forms of immunocompromise, the initial empiric regimen should be broad enough to cover most pathogens isolated in healthcare-associated infections. Most often, a broad-spectrum carbapenem (e.g., meropenem, imipenem/cilastatin or doripenem) or extended-range penicillin/β-lactamase inhibitor combination (e.g., piperacillin/tazobactam or ticarcillin/ clavulanate) is used. However, several third- or higher generation cephalosporins can also be used, especially as part of a multidrug regimen. Of course, the specific regimen can and should be modified by the anatomic site of infection if it is apparent and by knowledge of local microbiologic flora.

Multidrug therapy is often required to ensure a sufficiently broad spectrum of empiric coverage initially. Clinicians should be cognizant of the risk of resistance to broad-spectrum β-lactams and carbapenems among gram-negative bacilli in some communities and healthcare settings. The addition of a supplemental gram-negative agent to the empiric regimen is recommended for critically ill septic patients at high risk of infection with such multidrug-resistant pathogens (e.g., Pseudomonas, Acinetobacter, etc.) to increase the probability of at least one active agent being administered [110]. Similarly, in situations of a

more-than-trivial risk for other resistant or atypical pathogens, the addition of a pathogen-specific agent to broaden coverage is warranted. Vancomycin, teicoplanin, or another anti-MRSA agent can be used when risk factors for MRSA exist. A significant risk of infection with Legionella species mandates the addition of a macrolide or fluoroquinolone. Clinicians should also consider whether Candida species are likely pathogens when choosing initial therapy. Risk factors for invasive Candida infections include immunocompromised status (neutropenia, chemotherapy, transplant, diabetes mellitus, chronic liver failure, chronic renal failure), prolonged invasive vascular devices (hemodialysis catheters, central venous catheters), total parenteral nutrition, necrotizing pancreatitis, recent major surgery (particularly abdominal), prolonged administration of broad-spectrum antibiotics, prolonged hospital/ICU admission, recent fungal infection, and multisite colonization [111, 112]. If the risk of Candida sepsis is sufficient to justify empiric antifungal therapy, the selection of the specific agent should be tailored to the severity of illness, the local pattern of the most prevalent Candida species, and any recent exposure to antifungal drugs. Empiric use of an echinocandin (anidulafungin, micafungin, or caspofungin) is preferred in most patients with severe illness, especially in those patients with septic shock, who have recently been treated with other antifungal agents, or if Candida glabrata or Candida krusei infection is suspected from earlier culture data [100, 105]. Triazoles are acceptable in hemodynamically stable, less ill patients who have not had previous triazole exposure and are not known to be colonized with azole-resistant species. Liposomal formulations of amphotericin B are a reasonable alternative to echinocandins in patients with echinocandin intolerance or toxicity [100, 105]. Knowledge of local resistance patterns to antifungal agents should guide drug selection until fungal susceptibility test results, if available, are received. Rapid diagnostic testing using β-d-glucan or rapid polymerase chain reaction assays to minimize inappropriate anti-Candida therapy may have an evolving supportive role. However, the negative predictive value of such tests is not high enough to justify dependence on these tests for primary decision-making. Superior empiric coverage can be obtained using local and unit-specific antibiograms [113, 114] or an infectious diseases consultation [115-117]. Where uncertainty regarding appropriate patient-specific antimicrobial therapy exists, infectious diseases consultation is warranted. Early involvement of infectious diseases specialists can improve outcome in some circumstances (e.g., S. aureus bacteremia) [113-115].

Although restriction of antimicrobials is an important strategy to reduce both the development of pathogen resistance and cost, it is not an appropriate strategy in the initial therapy for this patient population. Patients with sepsis or septic shock generally warrant empiric broad-spectrum therapy until the causative organism and its antimicrobial susceptibilities are defined. At that point, the spectrum of coverage should be narrowed by eliminating unneeded antimicrobials and replacing broad-spectrum agents with more specific agents [118]. However, if relevant cultures are negative, empiric narrowing of coverage based on a good clinical response is appropriate. Collaboration with antimicrobial stewardship programs is encouraged to ensure appropriate choices and rapid availability of effective antimicrobials for treating septic patients.

In situations in which a pathogen is identified, de-escalation to the narrowest effective agent should be implemented for most serious infections. However, approximately one-third of patients with sepsis do not have a causative pathogen identified [95, 119]. In some

cases, this may be because guidelines do not recommend obtaining cultures (e.g., community-acquired abdominal sepsis with bowel perforation) [108]. In others, cultures may have followed antimicrobial therapy. Further, almost half of patients with suspected sepsis in one study have been adjudicated in post hoc analysis to lack infection or represent only “possible” sepsis [120]. Given the adverse societal and individual risks to continued unnecessary antimicrobial therapy, we recommend thoughtful de-escalation of antimicrobials based on adequate clinical improvement even if cultures are negative. When infection is found not to be present, antimicrobial therapy should be stopped promptly to minimize the likelihood that the patient will become infected with an antimicrobial-resistant pathogen or develop a drug-related adverse effect. Thus, the decisions to continue, narrow, or stop antimicrobial therapy must be made on the basis of clinician judgment and clinical information.

4. We recommend against sustained systemic antimicrobial prophylaxis in patients with severe inflammatory states of noninfectious origin (e.g., severe pancreatitis, burn injury) (BPS).

Rationale A systemic inflammatory response without infection does not mandate antimicrobial therapy. Examples of conditions that may exhibit acute inflammatory signs without infection include severe pancreatitis and extensive burn injury. Sustained systemic antimicrobial therapy in the absence of suspected infection should be avoided in these situations to minimize the likelihood that the patient will become infected with an antimicrobial-resistant pathogen or will develop a drug-related adverse effect.

Although the prophylactic use of systemic antimicrobials for severe necrotizing pancreatitis has been recommended in the past, recent guidelines have favoured avoidance of this approach [121]. The current position is supported by meta-analyses that demonstrate no clinical advantage of prophylactic antibiotics that would outweigh their long-term adverse effects [122]. Similarly, prolonged systemic antimicrobial prophylaxis has been used in the past for patients with severe burns. However, recent meta-analyses suggest questionableclinical benefit with this approach [123,124]. Current guidelines for burn management do not support sustained antimicrobial prophylaxis [101]. Summarizing the evidence is challenging due to the diversity of the population. The quality of evidence was low for mortality in pancreatitis [122] and low for burns; therefore, we believe this recommendation is better addressed as a BPS, in which the alternative of administering antibiotics without indicators of infection is implausible [122–124]. Despite our recommendation against sustained systemic antimicrobial prophylaxis generally, brief antibiotic prophylaxis for specific invasive procedures may be appropriate. In addition, if there is a strong suspicion of concurrent sepsis or septic shock in patients with a severe inflammatory state of noninfectious origin (despite overlapping clinical presentations), antimicrobial therapy is indicated.

5. We recommend that dosing strategies of antimicrobials be optimized based on accepted pharmacokinetic/pharmacodynamic principles and specific drug properties in patients with sepsis or septic shock (BPS).

Rationale Early optimization of antimicrobial pharmacokinetics can improve the outcome of patients with severe infection. Several considerations should be made when determining optimal dosing for critically ill patients with sepsis and septic shock. These patients have distinct differences from the typical infected patient that affect the optimal antimicrobial management strategy. These differences include an increased frequency of hepatic and renal dysfunction, a high prevalence of unrecognized immune dysfunction, and a predisposition to infection with resistant organisms. Perhaps most importantly with respect to initial empiric antimicrobial dosing is an increased volume of distribution for most antimicrobials, in part due to the rapid expansion of extracellular volume as a consequence of aggressive fluid resuscitation. This results in an unexpectedly high frequency of suboptimal drug levels with a variety of antimicrobials in patients with sepsis and septic shock [125–128]. Early attention to appropriate antimicrobial dosing is central to improving outcome given the marked increase in mortality and other adverse outcomes if there is a failure of rapid initiation of effective therapy. Antimicrobial therapy in these patients should always be initiated with a full, high end-loading dose of each agent used.

Different antimicrobials have different required plasma targets for optimal outcomes. Failure to achieve peak plasma targets on initial dosing has been associated with clinical failure with aminoglycosides [129]. Similarly, inadequate early vancomycin trough plasma concentrations (in relation to pathogen minimum inhibitory concentration [MIC]) have been associated with clinical failure for serious MRSA infections [130] (including nosocomial pneumonia [131] and septic shock [132]. The clinical success rate for treatment of serious infections correlates with higher peak blood levels (in relation to pathogen MIC) of fluoroquinolones (nosocomial pneumonia and other serious infections) [133–135] and aminoglycosides (gram-negative bacteremia, nosocomial pneumonia, and other serious infections) [129, 136]. For β-lactams, superior clinical and microbiologic cures appear to be associated with a longer duration of plasma concentration above the pathogen MIC, particularly in critically ill patients [137–140]. The optimal dosing strategy for aminoglycosides and fluoroquinolones involves optimizing peak drug plasma concentrations. For aminoglycosides, this can most easily be attained with once daily dosing (5–7 mg/kg daily gentamicin equivalent). Once-daily dosing yields at least comparable clinical efficacy with possibly decreased renal toxicity compared to multiple daily dosing regimens [141, 142]. Once-daily dosing of aminoglycosides is used for patients with preserved renal function. Patients with chronically mildly impaired renal function should still receive a once-daily-equivalent dose but would normally have an extended period (up to 3 days) before the next dose. This dosing regimen should not be used in patients with severe renal function in whom the aminoglycoside is not expected to clear within several days. Therapeutic drug monitoring of aminoglycosides in this context is primarily meant to ensure that trough concentrations are sufficiently low to minimize the potential for renal toxicity. For fluoroquinolones, an approach that optimizes the dose within a nontoxic range (e.g., ciprofloxacin, 600 mg every 12 h, or levofloxacin, 750 mg every 24 h, assuming preserved renal function) should provide the highest probability of a favorable microbiologic and clinical response [127, 143, 144]. Vancomycin is another antibiotic whose efficacy isat least partially concentration-dependent. Dosing to a trough target of 15–20 mg/L is recommended by several authorities to maximize the probability of achieving appropriate pharmacodynamic targets, improve tissue penetration, and optimize clinical outcomes [145–147]. Pre-dose monitoring of trough concentrations is recommended. For sepsis and septic

shock, an IV loading dose of 25–30 mg/kg (based on actual body weight) is suggested to rapidly achieve the target trough drug concentration. A loading dose of 1 g of vancomycin will fail to achieve early therapeutic levels for a significant subset of patients. In fact, loading doses of antimicrobials with low volumes of distribution (teicoplanin, vancomycin, colistin) are warranted in critically ill patients to more rapidly achieve therapeutic drug levels due to their expanded extracellular volume related to volume expansion following fluid resuscitation [148 –152].

Loading doses are also recommended for β-lactams administered as continuous or extended infusions to accelerate accumulation of drug to therapeutic levels [153]. Notably, the required loading dose of any antimicrobial is not affected by alterations of renal function, although this may affect frequency of administration and/or total daily dose. For β-lactams, the key pharmacodynamics correlate to microbiologic and clinical response is the time that the plasma concentration of the drug is above the pathogen MIC relative to the dosing interval (T > MIC). A minimum T > MIC of 60% is generally sufficient to allow a good clinical response in mild to moderate illness. However, optimal response in severe infections, including sepsis, may be achieved with a T > MIC of 100% [139]. The simplest way to increase T > MIC is to use increased frequency of dosing (given an identical total daily dose). For example, piperacillin/tazobactam can be dosed at either 4.5 g every 8 h or 3.375 g every 6 h for serious infections; all things being equal, the latter would achieve a higher T > MIC. We suggested earlier that initial doses of β-lactams can be given as a bolus or rapid infusion to rapidly achieve therapeutic blood levels. However, following the initial dose, an extended infusion of drug over several hours (which increases T > MIC) rather than the standard 30 min has been recommended by some authorities [154, 155]. In addition, some meta-analyses suggest that extended/continuous infusion of β-lactams may be more effective than intermittent rapid infusion, particularly for relatively resistant organisms and in critically ill patients with sepsis [140, 156 –158]. A recent individual patient data meta-analysis of randomized controlled trials comparing continuous versus intermittent infusion of β-lactam antibiotics in critically ill patients with severe sepsis demonstrated an independent protective effect of continuous therapy after adjustment for other correlatesof outcome [140].While the weight of evidence supports pharmacokinetically optimized antimicrobial dosing strategies in critically ill patients with sepsis and septic shock, this is difficult to achieve on an individual level without a broader range of rapid therapeutic drug monitoring options than currently available (i.e., vancomycin, teicoplanin and aminoglycosides). The target group of critically ill, septic patients exhibit a variety of physiologic perturbations that dramatically alter antimicrobial pharmacokinetics. These include unstable hemodynamics, increased cardiac output, increased extracellular volume (markedly increasing volume of distribution), variable kidney and hepatic perfusion (affecting drug clearance) and altered drug binding due to reduced serum albumin [159]. In addition, augmented renal clearance is a recently described phenomenon that may lead to decreased serum antimicrobial levels in the early phase of sepsis [160-162]. These factors make individual assessment of optimal drug dosing difficult in critically ill patients. Based on studies with therapeutic drug monitoring, under-dosing (particularly in the early phase of treatment) is common in critically ill, septic patients, but drug toxicity such as central nervous system irritation with β-lactams and renal injury with colistin is also seen [163–166]. These problems mandate efforts to expand access to therapeutic drug monitoring for multiple antimicrobials for critically ill patients with sepsis.

6. We suggest empiric combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of septic shock (weak recommendation, low quality of evidence).

Remarks Readers should review Table 6 for definitions of empiric, targeted/definitive, broad-spectrum, combination, and multidrug therapy before reading this section.

7. We suggest that combination therapy not be routinely used for ongoing treatment of most other serious infections, including bacteremia and sepsis without shock (weak recommendation, low quality of evidence).

Remarks This does not preclude the use of multidrug therapy to broaden antimicrobial activity.

8. We recommend against combination therapy for the routine treatment of neutropenic sepsis/bacteremia (strong recommendation, moderate quality of evidence).

Remarks This does not preclude the use of multidrug therapy to broaden antimicrobial activity.

9. If combination therapy is initially used for septic shock, we recommend de-escalation with discontinuation of combination therapy within the first few days in response to clinical improvement and/or evidence of infection resolution. This applies toboth targeted (for culture-positive infections) and empiric (for culture-negative infections) combination therapy (BPS).

Rationale In light of the increasing frequency of pathogen resistance to antimicrobial agents in many parts of the world, the initial use of multidrug therapy is often required to ensure an appropriately broad-spectrum range of coverage for initial empiric treatment. The use of multidrug therapy for this purpose in severe infections is well understood.

The phrase “combination therapy” in the context of this guideline connotes the use of two different classes of antibiotics (usually a β-lactam with a fluoroquinolone, aminoglycoside, or macrolide) for a single putative pathogen expected to be sensitive to both, particularly for purposes of accelerating pathogen clearance. The term is not used where the purpose of a multidrug strategy is to strictly broaden the range of antimicrobial activity (e.g., vancomycin added to ceftazidime, metronidazole added to an aminoglycoside or an echinocandin added to a β-lactam).A propensity-matched analysis and a meta-analysis/ meta-regression analysis have demonstrated that combination therapy produces higher survival in severely ill septic patients with a high risk of death, particularly in those with septic shock [167, 168]. A meta-regression study [167] suggested benefit with combination therapy in patients with a mortality risk greater than 25%. Several observational studies have similarly shown a survival benefit in very ill patients [169–172]. However, the afore-mentioned meta-regression analysis also suggested the possibility of increased mortality risk with combination therapy in low-risk (<15% mortality risk) patients without septic shock [167]. One controlled trial suggested that, when using a carbapenem as empiric therapy in a

population at low risk for infection with resistant microorganisms, the addition of a fluoroquinolone does not improve patients' outcomes [173]. A close examination of the results, however, demonstrates findings consistent with the previously mentioned meta-regression (trend to benefit in septic shock with an absence of benefit in sepsis without shock). Despite the overall favorable evidence for combination therapy in septic shock, direct evidence from adequately powered RCTs is not available to validate this approach definitively. Nonetheless, in clinical scenarios of severe clinical illness (particularly septic shock), several days of combination therapy is biologically plausible and is likely to be clinically useful [152, 167, 168] even if evidence has not definitively demonstrated improved clinical outcome in bacteremia and sepsis without shock [174, 175]. Thus, we issue a weak recommendation based on low quality of evidence.

A number of other recent observational studies and some small, prospective trials also support initial combination therapy for selected patients with specific pathogens (e.g., severe pneumococcal infection, multidrug-resistant gram-negative pathogens) [172, 176–182]. Unfortunately, in most cases and pending the development of rapid bedside pathogen detection techniques, the offending pathogen is not known at the time of presentation. Therefore, specifying combination therapy to specific identified pathogens is useful only if more prolonged targeted combination therapy is contemplated. In addition, with respect to multidrug-resistant pathogens, both individual studies and meta-analyses yield variable results depending on the pathogen and the clinical scenario [179–184]. Infectious diseases consultation may be advisable if multidrug-resistant pathogens are suspected. One area of broad consensus on the use of a specific form of combination therapy is for streptococcal toxic shock syndrome, for which animal models and uncontrolled, clinical experience demonstrate a survival advantage with penicillin and clindamycin, the latter as a transcriptional inhibitor to pyrogenic exotoxin superantigens [109, 185, 186].Despite evidence suggesting benefit of combination therapy in septic shock, this approach has not been shown to be effective for ongoing treatment of most other serious infections, including bacteremia and sepsis without shock [168, 174, 175]. The term "ongoing treatment" includes extended empiric therapy for culture-negative infections and extended definitive/targeted therapy where a pathogen is identified. In the case of neutropenia in the absence of septic shock, studies using modern broad-spectrum antibiotics consistently suggest that, while multidrug therapy to broaden pathogen coverage (e.g., to include Candida species) may be useful, combination therapy using a β-lactam and an aminoglycoside for purposes of accelerating pathogen clearance is not beneficial for less severely ill "low-risk" patients [187]. Combination therapy of this sort for even "high-risk" neutropenic patients (inclusive of hemodynamic instability and organ failure) with sepsis is inconsistently supported by several international expert groups [106, 188]. This position against combination therapy for a single pathogen in any form of neutropenic infection emphatically does not preclude the use of multidrug therapy for the purpose of broadening the spectrum of antimicrobial treatment.

High-quality data on clinically driven de-escalation of antimicrobial therapy for severe infections are limited [189]. Early de-escalation of antimicrobial therapy in the context of combination therapy as described here has not been studied. However, observational studies have shown that early de-escalation of multidrug therapy is associated with equivalent or superior clinical outcomes in sepsis and septic shock [54, 190-192]; despite

this, at least one study has indicated an increased frequency of superinfection and longer ICU stay [192].In addition to institutional benefit with respect to limiting a driver of antimicrobial resistance, early de-escalation can also benefit the individual patient [193-195]. Although the data are not entirely consistent, on balance, an approach that emphasizes early de-escalation is favored when using combination therapy.

While substantial consensus on the need for early de-escalation of combination therapy exists, agreement is lacking on precise criteria for triggering de-escalation. Among approaches used by panel members are de-escalation based on: (a) clinical progress (shock resolution, decrease in vasopressor requirement, etc.), (b) infection resolution as indicated by biomarkers (especially procalcitonin), and (c) a relatively fixed duration of combination therapy. This lack of consensus on de-escalation criteria for combination therapy reflects the lack of solid data addressing this issue (notwithstanding procalcitonin data relating to general de-escalation).

10. We suggest that an antimicrobial treatment duration of 7–10 days is adequate for most serious infections associated with sepsis and septic shock (weak recommendation, low quality of evidence).
11. We suggest that longer courses are appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with S. aureus, some fungal and viral infections, or immunologic deficiencies, including neutropenia (weak recommendation, low quality of evidence).
12. We suggest that shorter courses are appropriate in some patients, particularly those with rapid clinical resolution following effective source control of intra-abdominal or urinary sepsis and those with anatomically uncomplicated pyelonephritis (weak recommendation, low quality of evidence).
13. We recommend daily assessment for de-escalation of antimicrobial therapy in patients with sepsis and septic shock (BPS).

Rationale Unnecessarily prolonged administration of antimicrobials is detrimental to society and to the individual patient. For society, excessive antimicrobial use drives antimicrobial resistance development and dissemination [196]. For individual patients, prolonged antibiotic therapy is associated with specific illnesses such as Clostridium difficile colitis [195] and, more broadly, an increased mortality risk [54]. The basis of the increased mortality with unnecessarily prolonged and broad antimicrobial therapy has not been convincingly demonstrated, although cumulative antimicrobial toxicity; the occurrence of antimicrobial-associated secondary infections (e.g., C. difficile colitis); and selection of, and superinfection with, multidrug-resistant pathogens are all potential contributors.Although patient factors will influence the length of antibiotic therapy, a treatment duration of 7–10 days (in the absence of source control issues) is generally adequate for most serious infections [103, 197-199]. Current guidelines recommend a 7-day course of therapy for nosocomial pneumonia [both hospital-acquired and ventilator-associated pneumonia (VAP)] [103]. Recent data suggest that some serious infections may be treated with shorter courses especially if there is a need for and successful provision of source control [200, 201].Subgroup analysis of the most critically ill subjects [Acute Physiologic and Chronic Health Evaluation (APACHE) II score greater than either 15 or 20] in the short course of antimicrobials in the intra-abdominal sepsis study of Sawyer et al. demonstrated no

difference in outcome based on the duration of therapy (as with the overall group) [200, 202]. A treatment duration of 3–5 days or fewer was as effective as a duration of up to 10 days. Similarly, studies have shown that a treatment duration of <7 days is as effective as longer durations in the management of acute pyelonephritis with or without bacteremia [201], uncomplicated cellulitis [203], and spontaneous bacterial peritonitis [204]. Some conditions are generally thought to require more prolonged antimicrobial therapy. These include situations in which there is a slow clinical response, undrainable foci of infection, bacteremia with S. aureus (particularly MRSA) [67, 104], candidemia/invasive candidiasis [105] and other fungal infections, some viral infections (e.g., herpes, cytomegalovirus), and immunologic deficiencies, including neutropenia [188].

Assessment of the required duration of therapy in critically ill patients should include host factors, particularly immune status. For example, patients with neutropenic infection and sepsis usually require therapy for at least the duration of their neutropenia. The nature of the infecting pathogen also plays a role.

In particular, uncomplicated *S. aureus* bacteremia requires at least 14 days of therapy, while complicated bacteremia requires treatment as an endovascular infection with 6 weeks of therapy. Uncomplicated bacteremia has been defined as: (1) exclusion of endocarditis, (2) no implanted prostheses, (3) negative results of follow-up blood cultures drawn 2–4 days after the initial set, (4) defervescence within 72 h after the initiation of effective antibiotic therapy, and (5) no evidence of metastatic infection [104].Patients with candidemia (whether or not catheter-associated) and deep Candida infections, whether or not associated with sepsis, require more prolonged therapy [105, 205]. Highly resistant gram-negative pathogens with marginal sensitivity to utilized antimicrobials maybe slow to clear and represent another example. The nature and site of infection may also affect duration of therapy. Larger abscesses and osteomyelitis have limited drug penetration and require longer therapy. Although it is well known that endocarditis requires prolonged antimicrobial therapy, severe disease more typically presents as cardiac failure/cardiogenic shock and emboli rather than as sepsis or septic shock [206, 207]. A variety of other factors may play a role in determining the optimal duration of therapy, particularly in critically ill infected patients. If the clinician is uncertain, infectious diseases consultation should be sought. Few of the studies noted focused on patients with septic shock, sepsis with organ failure, or even critical illness. To an extent, standard recommendations on duration of therapy in this document depend on inferences from less ill cohorts. Therefore, decisions to narrow or stop antimicrobial therapy must ultimately be made on the basis of sound clinical judgment.

There are many reasons for unnecessarily prolonged antimicrobial therapy. For complicated, critically ill patients admitted with serious infections, non-infectious concurrent illness and medical interventions may produce signs and symptoms consistent with active infection (even following control of infection). For example, pulmonary infiltrates and shortness of breath may be caused by pulmonary edema in addition to pneumonia; an elevated white cell count may occur as a consequence of corticosteroid administration or physiologic stress; fever may be associated with certain drugs, including β-lactams and phenytoin. In addition, there is a natural tendency to want to continue a therapy that is often seen as benign long enough to be confident of cure. However, as discussed, antimicrobials are not an entirely benign therapy. In low-risk patients, the

adverse effects can outweigh any benefit. Given the potential harm associated with unnecessarily prolonged antimicrobial therapy, daily assessment for de-escalation of antimicrobial therapy is recommended in patients with sepsis and septic shock. Studies have shown that daily prompting on the question of antimicrobial de-escalation is effective and may be associated with improved mortality rates [55, 208].

14. We suggest that measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients (weak recommendation, low quality of evidence).
15. We suggest that procalcitonin levels can be used to support the discontinuation of empiric antibiotics in patients who initially appeared to have sepsis, but subsequently have limited clinical evidence of infection (weak recommendation, low quality of evidence).

Rationale During the past decade, the role of biomarkers to assist in the diagnosis and management of infections has been extensively explored. The use of galactomannan and β-d-glucan to assist in the assessment of invasive aspergillus (and a broad range of fungal pathogens) has become well accepted [209, 210].

Similarly, measurement of serum procalcitonin is commonly used in many parts of the world to assist in the diagnosis of acute infection and to help define the duration of antimicrobial therapy. Various procalcitonin-based algorithms have been used to direct de-escalation of antimicrobial therapy in severe infections and sepsis [211-216]. However, it is not clear that any particular algorithm provides a clinical advantage over another. A large body of literature suggests that use of such algorithms can speed safe antimicrobial de-escalation compared to standard clinical approaches with reduced antimicrobial consumption without an adverse effect on mortality. Recently, a large randomized trial on procalcitonin use in critically ill patients with presumed bacterial infection demonstrated evidence of a reduction in duration of treatment and daily defined doses of antimicrobials [217]. However, given the design of the study, the reduction could have been related to a prompting effect as seen in other studies [55, 218]. In addition, the procalcitonin group showed a significant reduction in mortality. This finding is congruent with studies demonstrating an association between early antimicrobial de-escalation and survival in observational studies of sepsis and septic shock [54, 55].

This benefit is uncertain, though, because another meta-analysis of randomized controlled studies of de-escalation failed to demonstrate a similar survival advantage [219]. Meta-analyses also suggest that procalcitonin can also be used to assist in differentiating infectious and noninfectious conditions at presentation [211, 214, 216]. The strongest evidence appears to relate to bacterial pneumonia versus noninfectious pulmonary pathology [216, 220], where meta-analysis suggests that procalcitonin may assist in predicting the presence of bacteremia, particularly in ICU patients [221].

No evidence to date demonstrates that the use of procalcitonin reduces the risk of antibiotic-related diarrhea from C. difficile. However, the occurrence of C. difficile colitis is known to be associated with cumulative benefit is likely. In addition, although prevalence of antimicrobial resistance has not been shown to be reduced by the use of procalcitonin, the

emergence of antimicrobial resistance is known to be associated with total antimicrobial consumption in large regions [196]. It is important to note that procalcitonin and all other biomarkers can provide only supportive and supplemental data to clinical assessment. Decisions on initiating, altering, or discontinuing antimicrobial therapy should never be made solely on the basis of changes in any biomarker, including procalcitonin.

E. SOURCE CONTROL

1. We recommend that a specific anatomic diagnosis of infection requiring emergent source control be identified or excluded as rapidly as possible in patients with sepsis or septic shock, and that any required source control intervention be implemented as soon as medically and logistically practical after the diagnosis is made (BPS).
2. 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 (BPS).

Rationale The principles of source control in the management of sepsis and septic shock include rapid diagnosis of the specific site of infection and determination of whether that infection site is amenable to source control measures (specifically the drainage of an abscess, debridement of infected necrotic tissue, removal of a potentially infected device, and definitive control of a source of ongoing microbial contamination) [222]. Foci of infection readily amenable to source control include intra-abdominal abscesses, gastrointestinal perforation, ischemic 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. Infectious foci suspected to cause septic shock should be controlled as soon as possible following successful initial resuscitation [223, 224]. A target of no more than 6–12 h after diagnosis appears to be sufficient for most cases [223–229]. Observational studies generally show reduced survival beyond that point. The failure to show benefit with even earlier source control implementation may be a consequence of the limited number of patients in these studies. 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.

Clinical experience suggests that, without adequate source control, some more severe presentations will not stabilize or improve despite rapid resuscitation and provision of appropriate antimicrobials. In view of this fact, prolonged efforts at medical stabilization prior to source control for severely ill patients, particularly those with septic shock, are generally not warranted [108]. The selection of optimal source control methods must weigh the benefits and risks of the specific intervention, risks of transfer for the procedure, potential delays associated with a specific procedure, and the probability of the procedure's success. Source control interventions may cause further complications, such as bleeding, fistulas, or inadvertent organ injury. In general, the least invasive effective option for 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 or when the probability of success with a percutaneous procedure is uncertain and the mortality risk as a consequence of a failed procedure causing delays is

high. Specific clinical situations require consideration of available choices, the patient's preferences, and the clinician's expertise. Logistic factors unique to each institution, such a surgical or interventional staff availability, may also play a role in the decision. Intravascular devices such as central venous catheters can be the source of sepsis or septic shock. An intravascular device suspected to be a source of sepsis should generally be removed promptly after establishing another site for vascular access. In the absence of both septic shock and fungemia, some implanted, tunneled catheter infections may be able to be treated effectively with prolonged antimicrobial therapy if removal of the catheter is not practical [67]. However, catheter removal (with antimicrobial therapy) is definitive and is preferred where possible.

F. FLUID THERAPY

1. We recommend that a fluid challenge technique be applied where fluid administration is continued as long as hemodynamic factors continue to improve (BPS).
2. We recommend crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock (strong recommendation, moderate quality of evidence).
3. We suggest using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock (weak recommendation, low quality of evidence).
4. We suggest using albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock when patients require substantial amounts of crystalloids (weak recommendation, low quality of evidence).
5. We recommend against using hydroxyethyl starches (HESs) for intravascular volume replacement in patients with sepsis or septic shock (strong recommendation, high quality of evidence).
6. We suggest using crystalloids over gelatins when resuscitating patients with sepsis or septic shock (weak recommendation, low quality of evidence).

Rationale The use of IV fluids in the resuscitation of patients is a cornerstone of modern therapy. Despite this, there is little available evidence from RCTs to support its practice; this is an area in which research is urgently needed. One trial of children (mostly with malaria) in Africa, in a setting where escalation to mechanical ventilation and other organ support was limited, questioned this practice [230]. We believe that the extrapolation of these data to patients in better-resourced settings is not valid and thus recommend that clinicians restore euvolemia with IV fluids, more urgently initially, and then more cautiously as the patient stabilizes. There is some evidence that a sustained positive fluid balance during ICU stay is harmful [231–235]. We do not recommend, therefore, that fluid be given beyond initial resuscitation without some estimate of the likelihood that the patient will respond positively.The absence of any clear benefit following the administration of colloid compared to crystalloid solutions in the combined subgroups of sepsis, in conjunction with the expense of albumin, supports a strong recommendation for the use of crystalloid solutions in the initial resuscitation of patients with sepsis and septic shock.We were unable to recommend one crystalloid solution over another because no direct comparisons have been made between isotonic saline and balanced salt solutions in patients with sepsis. One before-after study in all ICU patients suggested increased rates of acute kidney injury and

RRT in patients managed with a chloride-liberal strategy compared to a chloride-restrictive strategy [236]. There is indirect low-quality evidence from a network meta-analysis suggesting improved outcome with balanced salt solutions as compared to saline in patients with sepsis [237] (ESM 6). In addition, the neutral result of the SPLIT cluster RCT in ICU patients (mainly surgical patients) in four New Zealand ICUs lowered our confidence in recommending one solution over the other [238].

No cost-effectiveness studies compare balanced and unbalanced crystalloid solutions. Therefore, we considered the desirable and undesirable consequences to be comparable for both solutions, and issued a weak recommendation to use either solution. Hyperchloremia should be avoided, however, and thus close scrutiny of serum chloride levels is advised, whichever fluid solutions are used.

The SAFE study indicated that albumin administration was safe and equally effective as 0.9% saline in ICU patients requiring fluid administration [239]. A meta-analysis aggregated data from 17 randomized trials (n = 1977) of albumin versus other fluid solutions in patients with sepsis or septic shock [240]; 279 deaths occurred among 961 albumin-treated patients (29%) versus 343 deaths among 1016 patients (34%) treated with other fluids, favoring albumin (OR 0.82; 95% CI 0.67–1.00). When albumin-treated patients were compared with those receiving crystalloids (seven trials, n = 144), the odds ratio of dying was significantly reduced for albumin-treated patients (OR 0.78; 95% CI 0.62-0.99).

Since the 2012 SSC guideline publication, six systematic reviews/meta-analyses [237, 241–245] were published assessing the use of albumin solutions in the management of patients with sepsis or septic shock. Each meta-analysis included different populations (adult/child, septic/nonseptic, and acute resuscitation/maintenance), different comparators and different duration of exposure to the intervention (hours, days), which made combining data challenging (ESM 7).

Xu et al. [242] evaluated albumin compared to crystalloid as a resuscitation fluid. Five studies, encompassing 3658 sepsis and 2180 septic shock patients, were included. Albumin use resulted in reduced septic shock 90-day mortality (OR 0.81; 95% CI 0.67–0.97) and trended toward reduced 90-day mortality in sepsis (OR 0.88; 95% CI 0.76–1.01; p = 0.08). Jiang et al. [245] evaluated albumin in a mixed population of sepsis severity including adults and children. Three septic shock studies, encompassing 1931 patients, were included. Albumin use resulted in decreased mortality (OR 0.89; 95% CI 0.80–0.99) with low heterogeneity (I2 = 0%). A mortality reduction trend was reported for albumin administration compared to crystalloids when given less than 6 h from identification (11 studies; n = 5515; OR 0.94; 95% CI 0.86–1.03).

Patel et al. [244] evaluated mixed populations, including resuscitation and maintenance. Additionally, a series of studies excluded from other meta-analyses due to accuracy concerns was included in this evaluation [246–248]. When comparing crystalloid and albumin, the authors report a combined mortality benefit of albumin as compared to crystalloid (seven studies, n = 3878; OR 0.93; 95% CI 0.86–1.00), but it was not consistent across individual severity subgroups. Use of albumin in septic shock trended toward mortality benefit (four studies; n = 1949; OR 0.91; 95% CI 0.82–1.01; p = 0.06), and the use

of albumin in sepsis was not significant (four studies; n = 1929; OR 0.96; 95% CI 0.83–1.10). Evaluation of treatment within 24 h also trended toward mortality benefit (four studies; n = 3832; RR 0.93; 95% CI 0.86–1.01). Rochwerg 2014 et al. [237] evaluated resuscitativefluid use in a network meta-analysis of 14 trials, encompassing 18,916 patients. When comparing albumin to crystalloid, there was no significant reduction in mortality with moderate quality of evidence in both the four- and six-node analyses (four-node: OR 0.83; credible interval [CrI] 0.65–1.04; six-node OR 0.82; CrI 0.65–1.04).The ALBIOS trial [249] showed no mortality benefit of albumin in combination with crystalloids compared to crystalloids alone in patients with sepsis or septic shock (RR 0.94; 95% CI 0.85–1.05); a subgroup analysis suggested that the albumin group was associated with lower 90-day mortality in patients with septic shock (RR 0.87; 95% CI 0.77–0.99). Fluid administration continued for 28 days or until discharge and was not targeted for acute resuscitation. In addition, the amount of 20% albumin was guided by serum albumin level with the ultimate goal of achieving levels >30 g/L. These results are limited by significant indirectness and imprecision, resulting in low quality of evidence.

HESs are colloids for which there are safety concerns in patients with sepsis. A meta-analysis of nine trials (3456 patients) comparing 6% HES 130/0.38–0.45 solutions to crystalloids or albumin in patients with sepsis showed no difference in all-cause mortality (RR 1.04; 95% CI 0.89–1.22) [250]. However, when low risk of bias trials were analyzed separately, HES use resulted in higher risk of death compared to other fluids (RR 1.11; 95% CI 1.01–1.22; high quality evidence), which translates to 34 more deaths per 1000 patients. Furthermore, HES use led to a higher risk of RRT (RR 1.36; 95% CI 1.08–1.72; high-quality evidence) [250]. A subsequent network meta-analysis focused on acute resuscitation of patients with sepsis or septic shock and found that HES resulted in higher risk of death (10 RCTs; OR 1.13; CrI, 0.99–1.30; high-quality evidence) and need for RRT (7 RCTs; OR 1.39; CrI, 1.17–1.66; high-quality evidence) compared to crystalloids. When comparing albumin to HES, albumin resulted in lower risk of death (OR 0.73; CrI, 0.56–0.93; moderate-quality evidence) and a trend toward less need for RRT (OR 0.74; CrI, 0.53–1.04; low quality evidence) [237]. Overall, the undesirable consequences of using HES (increased risk of death and need for RRT) along with moderate to high quality of available evidence resulted in a strong recommendation against the use of HES in resuscitation of patients with sepsis or septic shock.

Gelatin is another synthetic colloid that can be used for fluid resuscitation; however, high-quality studies comparing gelatins to other fluids in patients with sepsis or septic shock are lacking. Trials conducted in critically ill patients were summarized in a recent meta-analysis [251]. Gelatin use in critically ill adult patients did not increase mortality (RR 1.10; 95% CI 0.85–1.43; low-quality evidence) or acute kidney injury (RR 1.35; 95% CI 0.58–3.14; very low-quality evidence) compared to albumin or crystalloid. These results are limited by indirectness, since the studies did not focus on critically ill patients. The afore-mentioned network meta-analysis by Rochwerg et al. did not identify any RCTs comparing gelatins to crystalloids or albumin; therefore, the generated estimates were imprecise and were based on indirect comparisons [237]. Given the low quality of the available data and the cost associated with gelatin use, we issued a weak recommendation favouring the use of crystalloids over gelatins.

G. VASOACTIVE MEDICATIONS

1. We recommend norepinephrine as the first-choice vasopressor (strong recommendation, moderate quality of evidence).
2. We suggest adding either vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) or epinephrine (weak recommendation, low quality of evidence) to norepinephrine with the intent of raising MAP to target, or adding vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) to decrease norepinephrine dosage.
3. We suggest using dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (weak recommendation, low quality of evidence).
4. We recommend against using low-dose dopamine for renal protection (strong recommendation, high quality of evidence).
5. We suggest using dobutamine in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents (weak recommendation, low quality of evidence).

Remarks If initiated, vasopressor dosing should be titrated to an end point reflecting perfusion, and the agent reduced or discontinued in the face of worsening hypotension or arrhythmias.

Rationale The physiologic effects of vasopressors and combined inotrope/vasopressor selection in septic shock are outlined in an extensive number of literature reviews [252–261]. Norepinephrine increases MAP due to its vasoconstrictive effects, with little change in heart rate and less increase in stroke volume compared with dopamine. Dopamine increases MAP and cardiac output, primarily due to an increase in stroke volume and heart rate. Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in patients with septic shock. Dopamine may be particularly useful in patients with compromised systolic function but causes more tachycardia and may be more arrhythmogenic than norepinephrine [262]. It may also influence the endocrine response via the hypothalamic pituitary axis and may have immunosuppressive effects [263]. However, a recent systematic review and meta-analysis that included 11 randomized trials (n = 1710) comparing norepinephrine to dopamine does not support the routine use of dopamine in the management of septic shock [264]. Indeed, norepinephrine use resulted in lower mortality (RR 0.89; 95% CI 0.81–0.98, high-quality evidence) and lower risk of arrhythmias (RR 0.48; 95% CI 0.40–0.58; high-quality evidence) compared with dopamine (ESM 8).

Human and animal studies suggest that the infusion of epinephrine may have deleterious effects on the splanchnic circulation and produces hyperlactatemia. However, clinical trials do not demonstrate worsening of clinical outcomes. One RCT comparing norepinephrine to epinephrine demonstrated no difference in mortality but an increase in adverse drug-related events with epinephrine [265]. Similarly, a meta-analysis of four randomized trials (n = 540) comparing norepinephrine to epinephrine found no significant difference in mortality (RR 0.96; CI 0.77–1.21; low-quality evidence) (ESM 9) [264]. Epinephrine may increase aerobic lactate production via stimulation of skeletal muscle β2-adrenergic receptors and thus may preclude the use of lactate clearance to guide resuscitation.

Vasopressin levels in septic shock have been reported to be lower than anticipated for a shock state [266]. Low doses of vasopressin may be effective in raising blood pressure in patients refractory to other vasopressors and may have other potential physiologic benefits [266–271]. Terlipressin has similar effects, but is long-acting [272]. Studies show that vasopressin concentrations are elevated in early septic shock, but decrease to normal range in the majority of patients between 24 and 48 h as shock continues [273]. This finding has been called relative vasopressin deficiency because, in the presence of hypotension, vasopressin would be expected to be elevated. The significance of this finding is unknown. The VASST trial, an RCT comparing norepinephrine alone to norepinephrine plus vasopressin at 0.03 U/min, showed no difference in outcome in the intent-to-treat population [274]. An *a priori* defined subgroup analysis demonstrated improved survival among patients receiving <15 μg/min norepinephrine at randomization with the addition of vasopressin; however, the pretrial rationale for this stratification was based on exploring potential benefit in the population requiring ≥ 15 μg/min norepinephrine. Higher doses of vasopressin have been associated with cardiac, digital, and splanchnic ischemia and should be reserved for situations in which alternative vasopressors have failed [275]. In the VANISH trial, 409 patients with septic shock were randomized in a factorial (2 x 2) design to receive vasopressin with placebo or hydrocortisone, or norepinephrine with placebo or hydrocortisone. There was no significant difference in kidney failure-free days or death; however, the vasopressin group had less use of RRT [276]. We conducted an updated meta-analysis to include the results of the VANISH trial. Data from nine trials (n = 1324 patients with septic shock), comparing norepinephrine with vasopressin (or terlipressin) demonstrated no significant difference in mortality (RR 0.89; 95% CI 0.79–1.00; moderate-quality evidence) (ESM 10) [268, 271, 272, 277 –279]. Results were similar after excluding trials that used a combination of norepinephrine and vasopressin in the intervention arm (RR 0.89; 95% CI 0.77–1.02). Large studies comparing vasopressin to other vasopressors in septic shock are lacking; most of the data regarding vasopressin support a sparing effect on norepinephrine dose, and there is uncertainty about the effect of vasopressin on mortality. Norepinephrine, therefore, remains the first-choice vasopressor to treat patients with septic shock. We do not recommend the use of vasopressin as a first-line vasopressor for the support of MAP and would advocate caution when using it in patients who are not euvolemic or at doses higher than 0.03 U/min.Phenylephrine is a pure α-adrenergic agonist. Clinical trial data in sepsis are limited. Phenylephrine has the potential to produce splanchnic vasoconstriction [280]. A network meta-analysis resulted in imprecise estimates (wide confidence intervals) when phenylephrine was compared to other vasopressors [281]. Therefore, the impact on clinical outcomes is uncertain, and phenylephrine use should be limited until more research is available.

A large randomized trial and meta-analysis comparing low-dose dopamine to placebo found no difference in need for RRT, urine output, time to renal recovery, survival, ICU stay, hospital stay, or arrhythmias [282, 283]. Thus, the available data do not support administration of low doses of dopamine solely to maintain renal function.

Myocardial dysfunction consequent to infection occurs in a subset of patients with septic shock, but cardiac output is usually preserved by ventricular dilation, tachycardia, and reduced vascular resistance [284]. Some portion of these patients may have diminished cardiac reserve, and may not be able to achieve a cardiac output adequate to support

oxygen delivery. Recognition of such reduced cardiac reserve can be challenging; imaging studies that show decreased ejection fraction may not necessarily indicate inadequate cardiac output. Concomitant measurement of cardiac output along with a measure of the adequacy of perfusion is preferable. Routinely increasing cardiac output to predetermined "supranormal" levels in all patients clearly does not improve outcomes, as shown by two large prospective clinical trials of critically ill ICU patients with sepsis treated with dobutamine [285–287]. Some patients, however, may have improved tissue perfusion with inotropic therapy aimed at increasing oxygen delivery. In this situation, dobutamine is the first-choice inotrope for patients with measured or suspected low cardiac output in the presence of adequate left ventricular filling pressure (or clinical assessment of adequate fluid resuscitation) and adequate MAP. Monitoring the response of indices of perfusion to measured increases in cardiac output is the best way to target such a therapy [287].

The data supporting dobutamine are primarily physiologic, with improved hemodynamics and some improvement in indices of perfusion, which may include clinical improvement, decreasing lactate levels, and improvement in $Scvo_2$. No randomized controlled trials have compared the effects of dobutamine versus placebo on clinical outcomes. Mortality in patients randomized to dobutamine added to norepinephrine was no different compared to epinephrine [287], although the trial may have been underpowered. Dobutamine was used as the first-line inotrope as part of standard care in clinical trials of EGDT [16, 19, 288, 289], and adverse effects on mortality were not detected with its use.

Although there are only a few studies, alternative inotropic agents might be used to increase cardiac output in specific situations. Phosphodiesterase inhibitors increase intracellular cyclic AMP and thus have inotropic effects independent of β-adrenergic receptors. The phosphodiesterase inhibitor milrinone was shown to increase cardiac output in one small randomized trial of 12 pediatric patients, but the trial was underpowered for assessment of outcomes [290]. Levosimendan increases cardiac myocyte calcium responsiveness and also opens ATP-dependent potassium channels, giving the drug both inotropic and vasodilatory properties. Given the potential role for abnormal calcium handling in sepsis-induced myocardial depression, the use of levosimendan has been proposed in septic shock as well. In a trial of 35 patients with septic shock and acute respiratory distress syndrome (ARDS) randomized to levosimendan or placebo, levosimendan improved right ventricular performance and mixed venous oxygen saturation compared to placebo [291]. Trials comparing levosimendan with dobutamine are limited but show no clear advantage for levosimendan [292]. Levosimendan is more expensive than dobutamine and is not available in many parts of the world. Six small RCTs (116 patients in total) compared levosimendan to dobutamine; pooled estimates showed no significant effect on mortality (RR 0.83; 95% CI 0.66–1.05; low quality) (ESM 11). Given the low-quality evidence available and the higher cost associated with levosimendan, dobutamine remains the preferred choice in this population. An RCT enrolled 516 patients with septic shock who were randomized to receive either levosimendan or placebo; there was no difference in mortality. However, levosimendan led to significantly higher risk of supraventricular tachyarrhythmia than placebo (absolute difference, 2.7%; 95% CI 0.1–5.3%) [293]. The results of this trial question the systematic use of this agent in patients with septic shock. Of note, cardiac function was not evaluated in that trial, and inotropic stimulation may be of benefit in patients with a low cardiac output due to impaired cardiac function.

6. We suggest that all patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (weak recommendation, very low quality of evidence).

Rationale In shock states, estimation of blood pressure using a cuff, especially an automated measurement system, may be inaccurate. Use of an arterial cannula provides a more accurate and reproducible measurement of arterial pressure [287, 294] and also allows beat-to-beat analysis so that decisions regarding therapy can be based on immediate and reproducible blood pressure information [295]. Insertion of radial arterial catheters is generally safe; a systematic review of observational studies showed an incidence of limb ischemia and bleeding to be less than 1%, with the most common complication being localized hematoma (14%) [296]. Complication rates may be lower if an ultrasound-guided technique is used [297]. A recent 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 3.4 per 1000 catheters [298]. Large randomized trials that compare arterial blood pressure monitoring versus noninvasive methods are lacking.

In view of the low complication rate and likely better estimation of blood pressure but potentially limited resources in some countries, and the lack of high quality studies, the benefits of arterial catheters probably outweigh the risks. Therefore, we issued a weak recommendation in favor of arterial catheter placement. Arterial catheters should be removed as soon as continuous hemodynamic monitoring is not required to minimize the risk of complications.

H. CORTICOSTEROIDS

1. We suggest against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg per day (weak recommendation, low quality of evidence).

Rationale The response of septic shock patients to fluid and vasopressor therapy seems to be an important factor in selection of patients for optional hydrocortisone therapy. One French multicenter RCT of patients in vasopressor-unresponsive septic shock (systolic blood pressure <90 mm Hg despite fluid resuscitation and vasopressors for more than 1 h) showed significant shock reversal and reduction of mortality rate in patients with relative adrenal insufficiency [defined as a maximal postadrenocorticotropic hormone (ACTH) cortisol increase ≤9 μg/dL] [299]. Two smaller RCTs also showed significant effects on shock reversal with steroid therapy [300, 301]. In contrast, a large, European multicenter trial(CORTICUS) that enrolled patients with systolic blood pressure of <90 mm Hg despite adequate fluid replacement or need for vasopressors had a lower risk of deaththan the French trial and failed to show a mortality benefit with steroid therapy [302]. There was no difference in mortality in groups stratified by ACTH response.

Several systematic reviews have examined the use of low dose hydrocortisone in septic shock with contradictory results. Annane et al. [299] analyzed the results of 12 studies and calculated a significant reduction in 28-day mortality with prolonged low-dose steroid treatment in adult septic shock patients (RR 0.84; 95% CI 0.72–0.97; p = 0.02). In parallel, Sligl et al. [303] used a similar technique, but identified only eight studies for their meta-analysis, six of which had a high-level RCT design with low risk of bias. In contrast to the afore-mentioned review, this analysis revealed no statistically significant difference in mortality (RR 1.00; 95% CI 0.84–1.18). Both reviews, however, confirmed the improved shock reversal by using low-dose hydrocortisone. More recently, Annane et al. included 33 eligible trials (n = 4268) in a new systematic review [304]. Of these 33 trials, 23 were at low risk of selection bias; 22 were at low risk of performance and detection bias; 27 were at low risk of attrition bias; and 14 were at low risk of selective reporting. Corticosteroids reduced 28-day mortality (27 trials; n = 3176; RR 0.87; 95% CI 0.76–1.00). Treatment with a long course of low-dose corticosteroids significantly reduced 28-day mortality (22 trials; RR 0.87; 95% CI 0.78–0.97). Corticosteroids also reduced ICU mortality (13 trials; RR 0.82; 95% CI 0.68–1.00) and in hospital mortality (17 trials; RR 0.85; 95% CI 0.73–0.98). Corticosteroids increased the proportion of shock reversal by day 7 (12 trials; RR 1.31; 95% CI 1.14–1.51) and by day 28 (seven trials; n = 1013; RR 1.11; 95% CI 1.02–1.21). Finally, an additional systematic review by Volbeda et al. including a total of 35 trials randomizing 4682 patients has been published (all but two trials had high risk of bias) [305]. Conversely, in this review, no statistically significant effect on mortality was found for any dose of steroids versus placebo or for no intervention at maximal follow-up. The two trials with low risk of bias also showed no statistically significant difference (random-effects model RR 0.38; 95% CI 0.06–2.42). Similar results were obtained in subgroups of trials stratified according to hydrocortisone (or equivalent) at high (>500 mg) or low (≤ 500 mg) doses [RR 0.87; trial sequential analysis (TSA)-adjusted CI; 0.38–1.99; and RR 0.90; TSA-adjusted CI 0.49–1.67, respectively]. No statistically significant effects on serious adverse events other than mortality were reported (RR 1.02; TSA-adjusted CI 0.7–1.48). In the absence of convincing evidence of benefit, we issue a weak recommendation against the use of corticosteroids to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability.

In one study, the observation of a potential interaction between steroid use and ACTH test was not statistically significant [306]. Furthermore, no evidence of this distinction was observed between responders and nonresponders in a recent multicenter trial [302]. Random cortisol levels may still be useful for absolute adrenal insufficiency; however, for septic shock patients who have relative adrenal insufficiency (no adequate stress response), random cortisol levels have not been demonstrated to be useful. Cortisol immunoassays may over or underestimate the actual cortisol level, affecting the assignment of patients to responders or nonresponders [307]. Although the clinical significance is not clear, it is now recognized that etomidate, when used for induction for intubation, will suppress the hypothalamic–pituitary–adrenal axis [308, 309]. Moreover, a subanalysis of the CORTICUS trial revealed that the use of etomidate before application of low-dose steroids was associated with an increased 28-day mortality rate [302].

There has been no comparative study between a fixed duration and clinically guided regimen or between tapering and abrupt cessation of steroids. Three RCTs used a fixed

duration protocol for treatment [300, 302, 306], and therapy was decreased after shock resolution in two RCTs [301, 310]. In four studies, steroids were tapered over several days [300 –302, 310] and steroids were withdrawn abruptly in two RCTs [306, 311]. One crossover study showed hemodynamic and immunologic rebound effects after abrupt cessation of corticosteroids [312].

Further, one study revealed no difference in outcome of septic shock patients if low-dose hydrocortisone is used for 3 or 7 days; hence, we suggest tapering steroids when vasopressors are no longer needed [313]. Steroids may be indicated when there is a history ofsteroid therapy or adrenal dysfunction, but whetherlow-dose steroids have a preventive potency in reducingthe incidence of sepsis and septic shock in critically illpatients cannot be answered. A recent large multicenterRCT demonstrated no reduction in the development ofseptic shock in septic patients treated with hydrocortisone versus placebo [314]; steroids should not be used inseptic patients to prevent septic shock. Additional studies are underway that may provide additional information toinform clinical practice.

Several randomized trials on the use of low-dose hydrocortisone in septic shock patients revealed a significant increase of hyperglycemia and hypernatremia [306] as side effects. A small prospective study demonstratedthat repetitive bolus application of hydrocortisone leadsto a significant increase in blood glucose; this peak effectwas not detectable during continuous infusion. Further, considerable inter-individual variability was seen in thisblood glucose peak after the hydrocortisone bolus [315].

Although an association of hyperglycemia and hypernatremia with patient outcome measures could not beshown, good practice includes strategies for avoidanceand/or detection of these side effects.

I. BLOOD PRODUCTS

1. We recommend that RBC transfusion occur onlywhen hemoglobin concentration decreases to<7.0 g/dL in adults in the absence of extenuatingcircumstances, such as myocardial ischemia, severe hypoxemia, or acute hemorrhage (strongrecommendation, high quality of evidence).

Rationale Two clinical trials in septic patients evaluatedspecific blood transfusion thresholds. The Transfusion Requirements In Septic Shock (TRISS) trial addressed a transfusion threshold of 7 versus 9 g/dL in septic shock patients after admission to the ICU [316]. Results showed similar 90-day mortality, ischemic events, and use of life support in the two treatment groups with fewer transfusionsin the lower-threshold group. The hemoglobin targets in two of the three treatment arms in the Protocol-Based Care for Early Septic Shock (ProCESS) trial were a subpart of a more comprehensive sepsis management strategy [18]. The EGDT group received transfusion at a haematocrit <30% (hemoglobin 10 g/dL) when the $Scvo_2$ was <70% after initial resuscitation interventions compared to the protocol-based standard care group that received blood transfusion only when the hemoglobin was <7.5 g/dL. No significant differences were found between the twogroups for 60-day in-hospital mortality or 90-day mortality. Although the ProCESS trial is a less direct assessment of blood transfusion therapy, it does provide important information in regard to transfusion in the acute resuscitative phase of sepsis. We judge the evidence to be

high certainty that there is little difference in mortality, and, if there is, that it would favor lower hemoglobin thresholds.

2. We recommend against the use of erythropoietinfor treatment of anemia associated with sepsis (strong recommendation, moderate quality of evidence).

Rationale No specific information regarding erythropoietin use in septic patients is available, and clinical trials of erythropoietin administration in critically ill patients show a small decrease in red cell transfusion equirement with no effect on mortality [317, 318]. The effect of erythropoietin in sepsis and septic shock would not be expected to be more beneficial than in other criticalconditions. Erythropoietin administration may be associated with an increased incidence of thromboticevents in the critically ill. Patients with sepsis and septic shock may have coexisting conditions that meet indicationsfor the use of erythropoietin or similar agents.

3. We suggest against the use of fresh frozen plasmato correct clotting abnormalities in the absenceof bleeding or planned invasive procedures (weakrecommendation, very low quality of evidence).

Rationale No RCTs exist related to prophylactic fresh frozen plasma transfusion in septic or critically ill patientswith coagulation abnormalities. Current recommendations are based primarily on expert opinion that fresh frozen plasma be transfused when there is a documented deficiency of coagulation factors (increased prothrombin time, international normalized ratio, or partial thromboplastin time) and the presence of active bleeding or before surgicalor invasive procedures [319]. In addition, transfusion of fresh frozen plasma usually fails to correct the prothrombin time in nonbleeding patients with mild abnormalities. No studies suggest that correction of more severe coagulation abnormalities benefits patients who are not bleeding.

4. We suggest prophylactic platelet transfusion when counts are <10,000/mm^3 (10 x 109 /L) in the absence of apparent bleeding and when counts are<20,000/mm^3 (20 x 10^9 /L) if the patient has a significant risk of bleeding. Higher platelet counts [≥ 50,000/mm^3 (50 x 10^9 /L)] are advised for active bleeding, surgery, or invasive procedures (weak recommendation, very low quality of evidence).

Rationale No RCTs of prophylactic platelet transfusion in septic or critically ill patients exist. Current recommendationsand guidelines for platelet transfusion arebased on clinical trials of prophylactic platelet transfusionin patients with therapy-induced thrombocytopenia (usually leukemia and stem cell transplant) [320–327].Thrombocytopenia in sepsis is likely due to a different pathophysiology of impaired platelet production andincreased platelet consumption. Factors that may increasethe bleeding risk and indicate the need for a higher plateletcount are frequently present in patients with sepsis.

J. IMMUNOGLOBULINS

1. We suggest against the use of IV immunoglobulins in patients with sepsis or septic shock (weak recommendation, low quality of evidence).

Rationale There were no new studies informing this guideline recommendation. One larger multicenter RCT (n = 624) [328] in adult patients found no benefit for IV immunoglobulin (IVIg). The most recent Cochrane meta-analysis [329] differentiates between standard polyclonal IV immunoglobulins (IVIgG) and immunoglobulin M-enriched polyclonal Ig (IVIgGM). In ten studies withIVIgG (1430 patients), mortality between 28 and 180 days was 29.6% in the IVIgG group and 36.5% in the placebo group (RR 0.81; 95% CI 0.70–0.93), and for the sevenstudies with IVIgGM (528 patients), mortality between 28and 60 days was 24.7% in the IVIgGM group and 37.5% inthe placebo-group (RR 0.66; 95% CI 0.51–0.85). The certaintyof the studies was rated as low for the IVIgG trials, based on risk of bias and heterogeneity, and as moderatefor the IVIgGM trials, based on risk of bias. Comparable results were found in other meta-analyses [330]. However, after excluding low-quality trials, the recent Cochrane analysis [329] revealed no survival benefit.

These findings are in accordance with those of two older meta-analyses [331, 332] from other Cochrane authors. One systematic review [332] included a total of 21 trials and showed a reduction in death with immunoglobulin treatment (RR 0.77; 95% CI 0.68–0.88); however, theresults of only high-quality trials (total of 763 patients) did not show a statistically significant difference (RR 1.02;95% CI 0.84–1.24). Similarly, Laupland et al. [331] founda significant reduction in mortality with the use of IVIg treatment (OR 0.66; 95% CI 0.53–0.83; $p < 0.005$). Whenonly high-quality studies were pooled, the results were nolonger statistically significant (OR 0.96); OR for mortality was 0.96 (95% CI 0.71–1.3; $p = 0.78$). Two meta-analyses that used less strict criteria to identify sources of bias or did not state their criteria for the assessment of study quality found significant improvement in patient mortality with IVIg treatment [333–335]. Finally, there are nocutoffs for plasma IgG levels in septic patients, for which substitution with IVIgG improves outcome data [334].

Most IVIg studies are small, and some have a high risk of bias; the only large study (n = 624) showed no effect [328]. Subgroup effects between IgM-enriched and non-enriched formulations reveal significant heterogeneity. Indirectness and publication bias were considered, but not invoked ingrading this recommendation. The low certainty of evidenceled to the grading as a weak recommendation. The statistical information that comes from the high-qualitytrials does not support a beneficial effect of polyclonal IVIg. We encourage conduct of large multicenter studies to further evaluate the effectiveness of other IV polyclonal immunoglobulin preparations in patients with sepsis.

K. BLOOD PURIFICATION

1. We make no recommendation regarding the use of blood purification techniques.

Rationale Blood purification includes various techniques,such as high-volume hemofiltration and hemoadsorption(or hemoperfusion), where sorbents, removing either endotoxin or cytokines, are placed in contact with blood; plasma exchange or plasma filtration, throughwhich plasma is separated from whole blood, removed,and replaced with normal saline, albumin, or fresh frozenplasma; and the hybrid system: coupled plasma filtration adsorption (CPFA), which combines plasma filtration and adsorption by a resin cartridge that removes cytokines.

When these modalities of blood purification are considered versus conventional treatment, the available trials are, overall, small, unblinded, and with high risk of bias. Patient selection was unclear and differed with the varioustechniques. Hemoadsorption is the technique most largely investigated, in particular with polymyxin B-immobilized polystyrene-derived fibers to remove endotoxin from theblood. A recent meta-analysis demonstrated a favourable effect on overall mortality with this technique [336]. The composite effect, however, depends on a series of studies performed in a single country (Japan), predominantly by one group of investigators. A recent large RCT performedon patients with peritonitis related to organ perforation within 12 h after emergency surgery found no benefitof polymyxin B hemoperfusion on mortality and organfailure, as compared to standard treatment [337]. Illness severity of the study patients, however, was low overall, which makes these findings questionable. A multicentre blinded RCT is ongoing, which should provide stronger evidence regarding this technique [338].

Few RCTs evaluated plasma filtration, alone or combinedwith adsorption for cytokine removal (CPFA). Arecent RCT comparing CPFA with standard treatment was stopped for futility [339]. About half of the patients randomized to CPFA were undertreated, primarily because of clotting of the circuit, which raises doubts about CPFA feasibility. In consideration of all these limitations, our confidencein the evidence is very low either in favor of oragainst blood purification techniques; therefore, we do not provide a recommendation. Further research is needed to clarify the clinical benefit of blood purification techniques.

L. ANTICOAGULANTS

1. We recommend against the use of antithrombin for the treatment of sepsis and septic shock (strong recommendation, moderate quality of evidence).

Rationale Antithrombin is the most abundant anticoagulant circulating in plasma. The decrease of its plasma activity at onset of sepsis correlates with disseminated intravascular coagulation (DIC) and lethal outcome. However, a phase III clinical trial of high-dose antithrombin for adults with sepsis and septic shock as well as systematic reviews of antithrombin for critically ill patients did not demonstrate any beneficial effect on overall mortality. Antithrombin was associated with an increased risk of bleeding [340, 341]. Although post hoc subgroup analyses of patients with sepsis associated with DIC showed better survival in patients receiving antithrombin, this agent cannot be recommended until further clinical trials are performed.

2. We make no recommendation regarding the use of thrombomodulin or heparin for the treatment of sepsis or septic shock.

Rationale Most RCTs of recombinant soluble thrombomodulin have been targeted for sepsis associatedwith DIC, and a systematic review suggested a beneficialeffect on survival without an increase of bleeding risk [342, 343]. A phase III RCT is ongoing for sepsis associatedwith DIC. The guideline panel has elected to make no recommendation pending these new results. Two systematic reviews showed a potential survival benefitof heparin in patients

with sepsis without an increase in major bleeding [344]. However, overall impact remains uncertain, and heparin cannot be recommended until further RCTs are performed.

Recombinant activated protein C, which was originally recommended in the 2004 and 2008 SSC guidelines, was not shown to be effective for adult patients with septic shock by the PROWESS-SHOCK trial, and was withdrawn from the market [345].

M. MECHANICAL VENTILATION

1. We recommend using a target tidal volume of 6 mL/kg predicted body weight (PBW) compared with 12 mL/kg in adult patients with sepsis-induced ARDS (strong recommendation, high quality of evidence).
2. We recommend using an upper limit goal for plateau pressures of 30 cmH_2O over higher plateau pressures in adult patients with sepsis-induced severe ARDS (strong recommendation, moderate quality of evidence).

Rationale This recommendation is unchanged from 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 [346]. For the current document, we used the 2012 Berlin definition and the terms mild, moderate, and severe ARDS (Pao_2 /Fio_2 ≤ 300, ≤ 200, and ≤ 100 mm Hg, respectively) [347]. Several multicenter randomized trials have beenperformed in patients with established ARDS to evaluatethe effects of limiting inspiratory pressure through moderation of tidal volume [348 –351]. These studies showed differing results, which may have been caused by differencesin airway pressures in the treatment and control groups [347, 351, 353]. 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/kgcompared with 12 mL/kg PBW, and aiming for plateau pressure ≤30 cmH_2O [350]. 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 cmH_2O [355, 356]. The validity of this ceiling value will depend on the patient's effort, because those who are actively breathing generate higher transpulmonary pressures for a given plateau pressure than patients who are passively inflated. Conversely, patients with very stiff chest/abdominal walls and high pleural pressures may tolerate plateau pressures >30 cmH_2O because transpulmonary pressures will be lower. A retrospectivestudy suggested that tidal volumes should be lowered even with plateau pressures ≤ 30 cmH_2O [357] because lower plateau pressures were associated with reduced hospital mortality [358]. 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 cmH_2O may be advantageous in

patients without spontaneous breathing efforts [359]. Prospective validation of tidal volume titration by driving pressure is needed before this approach can be recommended.

High tidal volumes coupled with high plateau pressures should be avoided in ARDS. Clinicians should use as a startingpoint 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 cmH_2O. If plateau pressure remains >30 cmH_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. 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.

3. We suggest using higher PEEP over lower PEEP in adult patients with sepsis-induced moderate to severe ARDS (weak recommendation, moderate quality of evidence).

Rationale Raising PEEP in ARDS may open lung unitsto participate in gas exchange. This may increase Pao_2 when PEEP is applied through either an endotracheal tube or a face mask [360–362]. In animal experiments, avoidance of end-expiratory alveolar collapse helps minimize ventilator-induced lung injury when relatively high plateau pressures are in use. Three large multicenter trials and a pilot trial using higher versus lower levels ofPEEP in conjunction with low tidal volumes did not show benefit or harm [363–366]. A patient-level metaanalysis showed no benefit in all patients with ARDS; however, patients with moderate or severe ARDS (Pao_2 /Fio_2 ≤200 mm Hg) had decreased mortality with the use of higher PEEP, whereas those with mild ARDS did not [367]. A patient-level analysis of two of the randomized PEEP trials suggested a survival benefit if Pao_2 /Fio_2 increased with higher PEEP and harm if Pao_2 /Fio_2 fell [368]. A small randomized trial suggested that adjusting PEEP to obtain a positive transpulmonary pressure as estimated by esophageal manometry improved outcomes; a confirmatory trial is underway [369]. An analysis of nearly all the randomized trials of lung-protective ventilation suggested a benefit of higher PEEP if driving pressure fell with increased PEEP, presumably indicating increased lung compliance from opening of lung units [359].

While moderate-quality evidence suggests that higherPEEP improves outcomes in moderate to severe ARDS, the optimal method for selecting a higher PEEP level isunclear. One option is to titrate PEEP according to bedsidemeasurements of thoracopulmonary compliance with the objective of obtaining the best compliance or lowest driving pressure, reflecting a favorable balance of lung recruitment and overdistension [370]. The second option is to titrate PEEP upward on a tidal volumeof 6 mL/kg PBW until the plateau airway pressure is 28 cmH_2O [365]. 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 [350, 363–365, 368]. A PEEP >5 cmH_2O is usually required to avoid lung collapse [371].

4. We suggest using recruitment maneuvers in adultpatients with sepsis-induced, severe ARDS (weakrecommendation, moderate quality of evidence).

Rationale Many strategies exist for treating refractory hypoxemia in patients with severe ARDS [372]. Temporarily raising transpulmonary pressure may facilitate opening atelectatic alveoli to permit gas exchange [371], but could also overdistend aerated lung units, leading to ventilator-induced lung injury and transient hypotension.The application of sustained continuous positive airway pressure (CPAP) appears to improve survival (RR 0.84; 95% CI 0.74–0.95) and reduce the occurrence of severe hypoxia requiring rescue therapy (RR 0.76; 95% CI 0.41–1.40) in patients with ARDS. Although the effects of recruitment maneuvers improve oxygenation initially, the effects can be transient [373]. Selected patients with severe hypoxemia may benefit from recruitment but little evidence supports the routine use in all ARDS patients [373]. Any patient receiving this therapy should be monitored closely and recruitment maneuvers discontinued if deterioration in clinical variables is observed.

5. We recommend using prone over supine positionin adult patients with sepsis-induced ARDS and a Pao_2 /Fio_2 ratio <150 (strong recommendation, moderate quality of evidence).

Rationale In patients with ARDS and a Pao_2 /Fio_2 ratio<150, the use of prone compared with supine position within the first 36 h of intubation, when performed for>16 h a day, showed improved survival [374]. Meta-analysis including this study demonstrated reduced mortality in patients treated with prone compared with supine position (RR 0.85; 95% CI 0.71–1.01) as well as improved oxygenation as measured by change in Pao_2 /Fio_2 ratio (median 24.03 higher, 95% CI 13.3–34.7 higher) [375]. Most patients respond to the prone position withimproved oxygenation and may also have improved lung compliance [374, 376-379]. 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 1.37; 95% CI 1.05–1.79) [375], and some patients have contraindications to the prone position [374].

In patients with refractory hypoxia, alternative strategies, including airway pressure release ventilation and extracorporeal membrane oxygenation, may be considered as rescue therapies in experienced centers [372, 380–383].

6. We recommend against using high-frequency oscillatory ventilation (HFOV) in adult patients with sepsis-induced ARDS (strong recommendation, moderate quality of evidence).

Rationale HFOV has theoretical advantages that make it an attractive ventilator mode for patients with ARDS. Two large RCTs evaluating routine HFOV in moderate-severe ARDS have been recently published [384, 385]. One trial was stopped early because the mortality was higher in patients randomized to HFOV [384]. Including these recent studies, a total of five RCTs (1580 patients) have examined the role of HFOV in ARDS. Pooled analysis demonstrates no effect on mortality (RR 1.04; 95%CI 0.83–1.31) and an increased duration of mechanical ventilation (MD, 1.1 days higher; 95% CI 0.03–2.16) in patients randomized to

HFOV. An increase in barotrauma was seen in patients receiving HFOV (RR 1.19;95% CI 0.83–1.72); however, this was based on very low quality evidence.

The role of HFOV as a rescue technique for refractory ARDS remains unclear; however, we recommend against its early use in moderate-severe ARDS given the lack of demonstrated benefit and a potential signal for harm.

7. We make no recommendation regarding the use of noninvasive ventilation (NIV) for patients with sepsis-induced ARDS.

Rationale NIV may have theoretical benefits inpatients with sepsis-induced respiratory failure, such as better communication abilities, reduced need for sedation, and avoidance of intubation. However, NIV may preclude the use of low tidal volume ventilation or achieving adequate levels of PEEP, two ventilation strategies that have shown benefit even in mild-moderate ARDS [365 , 386]. Also, in contrast to indications such as cardiogenic pulmonary edema or chronic obstructivepulmonary disease exacerbation where NIV use is brief,ARDS often takes days or weeks to improve, and prolongedNIV use may lead to complications such as facialskin breakdown, inadequate nutritional intake, and failureto rest respiratory muscles.

A few small RCTs have shown benefit with NIV for early or mild ARDS or *de novo* hypoxic respiratory failure; however, these were in highly selected patient populations [387, 388]. More recently, a larger RCT in patients with hypoxemic respiratory failure compared NIV to traditional oxygen therapy or high-flow nasal cannula [389]. This study demonstrated improved 90-day survivalwith high-flow oxygen compared with standard therapy or NIV; however, the NIV technique was not standardized and the experience of the centers varied. Although high-flow oxygen has not been addressed here, it is possible that this technique may play a more prominent role in the treatment of hypoxic respiratory failure and ARDS moving forward.

Given the uncertainty regarding whether clinicians can identify ARDS patients in whom NIV might be beneficial, we have not made a recommendation for or against this intervention. If NIV is used for patients with ARDS, we suggest close monitoring of tidal volumes.

8. We suggest using neuromuscular blocking agents (NMBAs) for ≤48 h in adult patients with sepsis-induced ARDS and a Pao_2/Fio_2 ratio <150 mm Hg (weak recommendation, moderate quality of evidence)

Rationale The most common indication for NMBA use in the ICU is to facilitate mechanical ventilation [390]. When appropriately used, these agents may improve chest wall compliance, prevent respiratory dyssynchrony, and reduce peak airway pressures [391]. Muscle paralysis may also reduce oxygen consumption by decreasing the work of breathing and respiratory muscle blood flow [392]. However, a placebo-controlled RCT in patients with severe sepsis demonstrated that oxygen delivery, oxygen consumption, and gastric intramucosal pH were not improved during deep neuromuscular blockade [393].

An RCT of continuous infusions of cisatracurium in patients with early ARDS and a Pao_2 /Fio_2 <150 mmHg showed improved adjusted survival rates and more organ failure-free days without an increased risk in ICU-acquired weakness compared with placebo-treated patients [394]. The investigators used a high fixed dose ofcisatracurium without train-of-four monitoring; half of the patients in the placebo group received at least a single NMBA dose. Of note, groups in both the interventionand control groups were ventilated with volume-cycled and pressure-limited mechanical ventilation. Although many of the patients in this trial appeared to meet sepsis criteria, it is not clear whether similar results would occur in sepsis patients or in patients ventilated with alternate modes. Pooled analysis including three trials that examined the role of NMBAs in ARDS, including the one above, showed improved survival (RR 0.72; 95% CI 0.58–0.91) and a decreased frequency of barotrauma (RR0.43; 95% CI 0.20–0.90) in those receiving NMBAs [395].

An association between NMBA use and myopathies and neuropathies has been suggested by case studies and prospective observational studies in the critical care population [391, 396–399], but the mechanisms by which NMBAs produce or contribute to myopathies and neuropathies in these patients are unknown. Pooled analysis of the RCT data did not show an increase in neuromuscular weakness in those who received NMBAs (RR 1.08; 95% CI 0.83–1.41); however, this was based on very low quality of evidence [395]. Given the uncertainty that still exists pertaining to these important outcomes and the balance between benefits and potential harms, the panel decided that a weak recommendation was most suitable. If NMBAs are used, clinicians must ensure adequatepatient sedation and analgesia [400, 401]; recently updated clinical practice guidelines are available for specific guidance [402].

9. We recommend a conservative fluid strategy for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion (strong recommendation, moderate quality of evidence).

Rationale Mechanisms for the development of pulmonary edema in patients with ARDS include increased capillary permeability, increased hydrostatic pressure, and decreased oncotic pressure [403]. Small prospective studies in patients with critical illness and ARDS have suggested that low weight gain is associated with improved oxygenation [404] and fewer days of mechanical ventilation [405, 406]. A fluid-conservative strategy to minimize fluid infusion and weight gain in patients with ARDS, based on either a CVP or a pulmonary artery (PA) catheter (PA wedge pressure) measurement, along with clinical variables to guide treatment, led to fewer days of mechanical ventilation and reduced ICU LOS without altering the incidence of renal failureor mortality rates [407]. This strategy was only used inpatients with established ARDS, some of whom had shock during their ICU stay, and active attempts to reduce fluid volume were conducted only outside periods of shock.

10. We recommend against the use of β-2 agonists for the treatment of patients with sepsis-induced ARDS without bronchospasm (strong recommendation, moderate quality of evidence).

Rationale Patients with sepsis-induced ARDS often develop increased vascular permeability; preclinical data suggest that β-adrenergic agonists may hasten resorption of alveolar edema [408]. Three RCTs (646 patients) evaluated β-agonists in patients with ARDS [408–410]. In

two of these trials, salbutamol (15 μg/kg of ideal body weight) delivered intravenously [408, 409] was compared with placebo, while the third trial compared inhaled albuterol versus placebo [410]. Group allocation was blinded in all three trials, and two trials were stopped early for futility or harm [409–411]. More than half of the patients enrolled in all three trials had pulmonary or non-pulmonary sepsis as the cause of ARDS.

Pooled analysis suggests β-agonists may reduce survival to hospital discharge in ARDS patients (RR 1.22; 95% CI0.95–1.56) while significantly decreasing the number of ventilator-free days (MD, −2.19; 95% CI −3.68 to −0.71)[412]. β-Agonist use also led to more arrhythmias (RR1.97; 95% CI 0.70–5.54) and more tachycardia (RR 3.95; 95% CI 1.41–11.06).

β-2 agonists may have specific indications in the critically ill, such as the treatment of bronchospasm andhyperkalemia. In the absence of these conditions, werecommend against the use of β-agonists, either in IV or aerosolized form, for the treatment of patients with sepsis-induced ARDS.

11. We recommend against the routine use of the PA catheter for patients with sepsis-induced ARDS (strong recommendation, high quality of evidence).

Rationale This recommendation is unchanged from the previous guidelines. Although insertion of a PA catheter may provide useful information regarding volume status and cardiac function, these benefits may be confounded by differences in interpretation of the results [413, 414], poor correlation of PA occlusion pressures with clinical response [415], and lack of a PA catheter-based strategy demonstrated to improve patientoutcomes [416]. Pooled analysis of two multicenter randomizedtrials, one with 676 patients with shock or ARDS [417] and another with 1000 patients with ARDS [418], failed to show any benefit associated with PA catheter use on mortality (RR 1.02; 95% CI 0.96–1.09) or ICU LOS (mean difference 0.15 days longer; 95% CI 0.74 days fewer—1.03 days longer) [407, 419 –421] This lack of demonstrated benefit must be considered in the context of the increased resources required. Notwithstanding, selected sepsis patients may be candidates for PA catheter insertion if management decisions depend on information solely obtainable from PA catheter measurements.

12. We suggest using lower tidal volumes over higher tidal volumes in adult patients with sepsis-inducedrespiratory failure without ARDS (weak recommendation, low quality of evidence).

Rationale Low tidal volume ventilation (4–6 mL/kg) has been shown to be beneficial in patients with established ARDS [422] by limiting ventilator-induced lung injury. However, the effect of volume- and pressure-limitedventilation is less clear in patients with sepsis who do not have ARDS. Meta-analysis demonstrates the benefits of low tidal volume ventilation in patients without ARDS, including a decrease in the duration of mechanical ventilation (MD, 0.64 days fewer; 95% CI 0.49–0.79) and the decreased development of ARDS (RR 0.30; 95%CI 0.16–0.57) with no impact on mortality (RR 0.95; 95%CI 0.64–1.41). Importantly, the certainty in this data is limited by indirectness because the included studies varied significantly in terms of populations enrolled, mostly examining perioperative patients and very few focusing on ICU patients. The use of low tidal volumes in patients who undergo

abdominal surgery, which may include sepsispatients, has been shown to decrease the incidence of respiratory failure, shorten LOS, and result in fewer postoperative episodes of sepsis [423]. Subgroup analysis of only the studies that enrolled critically ill patients [424] suggests similar benefits of low tidal volume ventilationon duration of mechanical ventilation and development of ARDS, but is further limited by imprecision given the small number of studies included. Despite these methodologic concerns, the benefits of low tidal volume ventilation in patients without ARDS are thought to outweigh any potential harm. Planned RCTs may inform future practice.

13. We recommend that mechanically ventilated sepsis patients be maintained with the head of the bed elevated between 30° and 45° to limit aspiration risk and to prevent the development of VAP (strong recommendation, low quality of evidence).

Rationale The semi-recumbent position has beendemonstrated to decrease the incidence of VAP [425]. Enteral feeding increased the risk of developing VAP; 50% of the patients who were fed enterally in the supine position developed VAP, compared with 9% of those fed in the semi-recumbent position [425]. However, the bed position was monitored only once a day, and patients who did not achieve the desired bed elevation were not included in the analysis [425]. One study did not show a difference in incidence of VAP between patients maintained in supine and semi-recumbent positions [426]; patients assigned to the semi-recumbent group did not consistently achieve the desired head-of-bed elevation, and the head-of-bed elevation in the supine group approached that of the semi-recumbent group by day 7 [426]. When necessary, patients may be laid flat when indicated for procedures, hemodynamic measurements, and during episodes of hypotension. Patients should not be fed enterally while supine. There were no new published studies since the last guidelines that would inform a change in the strength of the recommendation for the current iteration. The evidence profile for this recommendation demonstrated low quality of evidence. The lack of new evidence, along with the low harms of head of-bed and high feasibility of implementation given the frequency of the practice resulted in the strong recommendation. There is a small subgroup of patients, such as trauma patients with a spine injury, for whom this recommendation would not apply.

14. We recommend using spontaneous breathing trials in mechanically ventilated patients with sepsis who are ready for weaning (strong recommendation, high quality of evidence).

Rationale Spontaneous breathing trial options includea low level of pressure support, CPAP (≈5 cmH_2O), or use of a T-piece. A recently published clinical practice guideline suggests the use of inspiratory pressure augmentation rather than T-piece or CPAP for an initial spontaneous breathing trial for acutely hospitalized adults on mechanical ventilation for more than 24 h [427]. Daily spontaneous breathing trials in appropriately selected patients reduce the duration of mechanical ventilation and weaning duration both in individual trials as well as withpooled analysis of the individual trials [428–430]. These breathing trials should be conducted in conjunction with a spontaneous awakening trial [431]. Successful completion of spontaneous breathing trials leads to a high likelihood of successful early discontinuation of mechanical ventilation with minimal demonstrated harm.

15. We recommend using a weaning protocol in mechanically ventilated patients with sepsis-induced respiratory failure who can tolerate weaning (strong recommendation, moderate quality of evidence).

Rationale Protocols allow for standardization of clinical pathways to facilitate desired treatment [432]. These protocols may include both spontaneous breathing trials, gradual reduction of support, and computer-generated weaning. Pooled analysis demonstrates that patients treated with protocolized weaning compared with usual care experienced shorter weaning duration (–39 h; 95%CI −67 h to −11 h), and shorter ICU LOS (–9 h; 95% CI−15 to −2). There was no difference between groups in ICU mortality (OR 0.93; 95% CI 0.58–1.48) or need for reintubation (OR 0.74; 95% CI 0.44–1.23) [428].

N. SEDATION AND ANALGESIA

1. We recommend that continuous or intermittent sedation be minimized in mechanically ventilated sepsis patients, targeting specific titration end points (BPS).

Rationale Limiting the use of sedation in critically ill ventilated patients reduces the duration of mechanical ventilation and ICU and hospital LOS, and allows earlier mobilization [433, 434]. While these data arise from studies performed in a wide range of critically ill patients, there is little reason to believe that septic patients will not derive the same benefits from sedation minimization.

Several strategies have been shown to reduce sedative use and the duration of mechanical ventilation. Nurse-directed protocols that incorporate a sedation scale likely result in improved outcomes; however, the benefit depends on the existing local culture and practice [435,436]. Another option for systematically limiting the use of sedation is the administration of intermittent rather than continuous sedation [437, 438]. Daily sedation interruption (DSI) was associated with improved outcomes in a single-center randomized trial compared with usual care [430]; however, in a multicenter RCT there was no advantage to DSI when patients were managed with a sedation protocol, and nurses perceived a higher workload [439]. A recent Cochrane meta-analysis did not find strong evidence that DSI alters the duration of mechanical ventilation, mortality, ICU or hospital LOS, adverse event rates, or drug consumption for critically ill adults receiving mechanical ventilation compared to sedation strategies that do not include DSI; however, interpretation of the results is limited by imprecision and clinical heterogeneity [440]. Another strategy is the primary use of opioids alone and avoidance of sedatives, which was shown to be feasible in the majority of ventilated patients in a single-center trial, and was associated with more rapid liberation from mechanical ventilation [441]. Finally, the use of short-acting drugs such as propofol and dexmedetomidine may result in better outcomes than the use of benzodiazepines [442–444]. Recent pain, agitation, and delirium guidelines provide additional detail on implementation of sedation management, including nonpharmacologic approaches for the management of pain, agitation, and delirium [445].

Regardless of approach, a large body of indirect evidence is available demonstrating the benefit of limiting sedation in those requiring mechanical ventilation and without

contraindication. As such, this should be best practice for any critically ill patient, including those with sepsis.

O. GLUCOSE CONTROL

1. We recommend a protocolized approach to blood glucose management in ICU patients with sepsis, commencing insulin dosing when two consecutive blood glucose levels are >180 mg/dL. This approach should target an upper blood glucoselevel ≤180 mg/dL rather than an upper target blood glucose level ≤110 mg/dL (strong recommendation, high quality of evidence).
2. We recommend that blood glucose values be monitored every 1–2 h until glucose values and insulin infusion rates are stable, then every 4 h thereafter in patients receiving insulin infusions (BPS).
3. We recommend that glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution because such measurements may not accurately estimate arterial blood or plasma glucose values (BPS).
4. We suggest the use of arterial blood rather than capillary blood for point-of-care testing using glucose meters if patients have arterial catheters (weak recommendation, low quality of evidence).

Rationale A large single-center RCT in 2001 demonstrated a reduction in ICU mortality with intensive IV insulin (Leuven protocol) targeting blood glucose to80–110 mg/dL [446]. A second randomized trial of intensive insulin therapy using the Leuven protocol enrolled medical ICU patients with an anticipated ICU LOS of more than three days in three medical ICUs; overall mortality was not reduced [447].

Since these studies [446, 447] appeared, several RCTs [448–455] and meta-analyses [456–462] of intensive insulin therapy have been performed. The RCTs studied mixed populations of surgical and medical ICU patients and found that intensive insulin therapy did not significantly decrease mortality, whereas the NICE-SUGAR trial demonstrated an increased mortality [451]. All studies reported a much higher incidence of severe hypoglycaemia (glucose ≤40 mg/dL) (6–29%) with intensive insulin therapy. Several meta-analyses confirmed that intensive insulin therapy was not associated with a mortality benefit in surgical, medical, or mixed ICU patients. The meta-analysis by Song et al. [462] evaluated only septic patients and found that intensive insulin therapy did not change 28- or 90-day mortality, but was associated with a higher incidence of hypoglycemia. The trigger to start an insulin protocol for blood glucose levels >180 mg/dL with an upper target blood glucose level <180 mg/dL derives from the NICE-SUGAR trial, which used these values for initiating and stopping therapy. The NICE-SUGAR trial is the largest, most compelling study to date on glucose control in ICU patients given its inclusion of multiple ICUs and hospitals and a general patient population. Several medical organizations, including the American Association of Clinical Endocrinologists, American Diabetes Association, American Heart Association, American College of Physicians, and Society of Critical Care Medicine, have published consensus statements for glycemic control of hospitalized patients [463, 465]. These statements usually targeted glucose levels between 140 and 180 mg/dL. Because there is no evidence that targets between 140 and 180 mg/dL are different from targets of 110–140 mg/dL, the present recommendations use an upper target blood glucose ≤180

mg/dL without a lower target other than hypoglycemia. Stricter ranges, such as 110–140 mg/dL, may be appropriate for selected patients if this can be achieved without significant hypoglycemia [463, 465]. Treatment should avoid hyperglycemia (>180 mg/dL), hypoglycemia, and wide swings in glucose levels that have been associated with higher mortality [466–471]. The continuationof insulin infusions, especially with the cessation of nutrition, has been identified as a risk factor for hypoglycaemia [454]. Balanced nutrition may be associated with a reduced risk of hypoglycemia [472]. Hyperglycemia and glucose variability seem to be unassociated with increased mortality rates in diabetic patients compared to nondiabetic patients [473–475]. Patients with diabetes and chronic hyperglycemia, end-stage renal failure, or medical versus surgical ICU patients may require higher blood glucose ranges [476, 477].

Several factors may affect the accuracy and reproducibility of point-of-care testing of blood capillary blood glucose, including the type and model of the device used, user expertise, and patient factors, including haematocrit (false elevation with anemia), Pao_2, and drugs [478]. Plasma glucose values by capillary point-of-care testing have been found to be potentially inaccurate, with frequent false elevations [479–481] over the range of glucose levels, but especially in the hypoglycemic and hyperglycemic ranges [482] and in shock patients (receiving vasopressors) [478, 480]. A review of studies found the accuracy of glucose measurements by arterial blood gas analyzers and glucose meters by using arterial blood significantly higher than measurements with glucose meters using capillary blood [480].

The U.S. Food and Drug Administration has stated that “critically ill patients should not be tested with a glucosemeter because results may be inaccurate,” and Centers for Medicare and Medicaid Services have plans to enforce the prohibition of off-label use of point-of-care capillary blood glucose monitor testing in critically ill patients [483]. Several medical experts have stated the need for a moratorium on this plan [484]. Despite the attempt to protect patients from harm because of inaccurate capillary blood testing, a prohibition might cause more harm because a central laboratory test may take significantly longer to provide results than point-of-care glucometer testing.

A review of 12 published insulin infusion protocols for critically ill patients showed wide variability in doserecommendations and variable glucose control [485]. This lack of consensus about optimal dosing of IV insulin may reflect variability in patient factors (severity of illness, surgical versus medical settings), or practice patterns (e.g., approaches to feeding, IV dextrose) in the environments in which these protocols were developed and tested. Alternatively, some protocols may be more effective than others, a conclusion supported by the wide variability in hypoglycemia rates reported with protocols. Thus, the use of established insulin protocols is important not only for clinical care, but also for the conduct of clinical trials to avoid hypoglycemia, adverse events, and premature termination of trials before the efficacy signal, if any, can be determined. Several studies have suggested that computer-based algorithms result in tighter glycemic control with a reduced risk of hypoglycaemia [486, 487]. Computerized decision support systems and fully automated closed-loop systems for glucose control are feasible, but not yet standard care. Further study of validated, safe, and effective protocols and closed-loop systems for controlling blood glucose concentrations and variability in the sepsis population is needed.

P. RENAL REPLACEMENT THERAPY

1. We suggest that either continuous RRT (CRRT) or intermittent RRT be used in patients with sepsis and acute kidney injury (weak recommendation, moderate quality of evidence).
2. We suggest using CRRT to facilitate management of fluid balance in hemodynamically unstable septic patients (weak recommendation, very low quality of evidence).
3. We suggest against the use of RRT in patients with sepsis and acute kidney injury for increase in creatinine or oliguria without other definitive indications for dialysis (weak recommendation, low quality of evidence).

Rationale Although numerous non-randomized studies have reported a nonsignificant trend toward improved survival using continuous methods [488-494], two meta-analyses [495, 496] reported the absence of significant differences in hospital mortality between patients who receive CRRT and intermittent RRT. This absence of apparent benefit of one modality over the other persists even when the analysis is restricted to RCTs [496]. To date, five prospective RCTs have been published [497–501]; four found no significant difference in mortality [497, 498, 500, 501], whereas one found significantly higher mortality in the continuous treatment group [499]; but imbalanced randomization had led to a higher baseline severity of illness in this group. Whena multivariable model was used to adjust for severity of illness, no difference in mortality was apparent between the groups. Most studies comparing modes of RRT in the critically ill have included a small number of outcomes and had a high risk of bias (e.g., randomization failure, modifications of therapeutic protocol during the study period, combination of different types of CRRT, small number of heterogeneous groups of enrollees). The most recent and largest RCT [501] enrolled 360 patients and found no significant difference in survival between the continuous and intermittent groups. We judged the overall certainty of the evidence to be moderate and not in support of continuous therapies in sepsis independent of renal replacement needs.

For this revision of the guidelines, no additional RCTs evaluating the hemodynamic tolerance of continuous versus intermittent RRT were identified. Accordingly, the limited and inconsistent evidence persists. Two prospective trials [497, 502] have reported a better hemodynamic tolerance with continuous treatment, with no improvement in regional perfusion [502] and no survival benefit [497]. Four other studies did not find any significant difference in MAP or drop in systolic pressure between the two methods [498, 500, 501, 503]. Two studies reported a significant improvement in goal achievement with continuous methods [497, 499] regarding fluid balance management. Two additional RCTs reporting the effect of dose of CRRT on outcomes in patients with acute renal failure were identified in the current literature review [504, 505]. Both studies enrolled patients with sepsis and acutekidney injury and did not demonstrate any difference in mortality associated with a higher dose of RRT. Two large, multicenter, randomized trials comparing the dose of renal replacement (Acute Renal Failure Trial Network in the United States and RENAL Study in Australia and New Zealand) also failed to show benefit of more aggressive renal replacement dosing [506, 507]. A meta-analysis of the sepsis patients included in all relevant RCTs (n = 1505) did not demonstrate any significant relationshipbetween dose and mortality; the point estimate, however, favors CRRT doses >30 mL/kg/h. Because of risk of

bias, inconsistency, and imprecision, confidence inthe estimate is very low; further research is indicated. A typical dose for CRRT would be 20–25 mL/kg/h of effluent generation.

One small trial from 2002 [504] evaluated early versus “late” or “delayed” initiation of RRT; it included only four patients with sepsis and did not show any benefitof early CRRT. Since then, two relevant RCTs [508, 509] were published in 2016. Results suggest the possibility of either benefit [509] or harm [508] for mortality, increased use of dialysis, and increased central lineinfections with early RRT. Enrollment criteria and timingof initiation of RRT differed in the two trials. Results were judged to be of low certainty based on indirectness (many nonseptic patients) and imprecision for mortality. The possibility of harm (e.g., central line infections) pushes the balance of risk and benefit against early initiation of RRT. Meanwhile, the undesirable effects and costs appear to outweigh the desirable consequences; therefore, we suggest not using RRT in patients with sepsis and acute kidney injury for increase in creatinine or oliguria without other definitive indications for dialysis.

Q. BICARBONATE THERAPY

1. We suggest against the use of sodium bicarbonate therapy to improve hemodynamics or to reduce vasopressor requirements in patients with hypoperfusion-induced lactic acidemia withpH ≥7.15 (weak recommendation, moderate quality of evidence).

Rationale Although sodium bicarbonate therapy may be useful in limiting tidal volume in ARDS in some situationsof permissive hypercapnia, no evidence supportsthe use of sodium bicarbonate therapy in the treatmentof hypoperfusion-induced lactic acidemia associated with sepsis. Two blinded, crossover RCTs that compared equimolar saline and sodium bicarbonate in patients with lactic acidosis failed to reveal any difference in hemodynamic variables or vasopressor requirements [510, 511]. The number of patients with <7.15 pH in these studies was small, and we downgraded the certainty of evidence for serious imprecision; further, patients did not have exclusively septic shock, but also had other diseases, such as mesenteric ischemia. Bicarbonate administrationhas been associated with sodium and fluid overload, an increase in lactate and $Paco_2$, and a decrease in serum ionized calcium, but the directness of these variables to outcome is uncertain. The effect of sodium bicarbonateadministration on hemodynamics and vasopressor requirements at lower pH, as well as the effect on clinical outcomes at any pH level, is unknown. No studies have examined the effect of bicarbonate administration on outcomes. This recommendation is unchanged from the 2012 guidelines.

R. VENOUS THROMBOEMBOLISMPROPHYLAXIS

1. We recommend pharmacologic prophylaxis [unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH)] against venous thromboembolism (VTE) in the absence of contraindications to the use of these agents (strong recommendation, moderate quality of evidence).
2. We recommend LMWH rather than UFH for VTE prophylaxis in the absence of contraindications to the use of LMWH (strong recommendation, moderate quality of evidence).

3. We suggest combination pharmacologic VTE prophylaxis and mechanical prophylaxis, whenever possible (weak recommendation, low quality of evidence).
4. We suggest mechanical VTE prophylaxis when pharmacologic VTE is contraindicated (weak recommendation, low quality of evidence).

Rationale ICU 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% [512]; the incidence of acquired PE may be 2–4% [513, 514]. Patients with sepsis and septic shock are likely at increased risk for this complication. Vasopressor use, which is frequent in these patients, has been found to be an independent risk factor for ICU-acquired DVT.

A meta-analysis of pharmacologic prophylaxis with UFH or LMWH in critically ill patients showed significant reductions in both DVT and PE, with no significant increase in bleeding complications. Mortality was lower in the patients receiving prophylaxis, although this did not reach statistical significance [514]. All studies included in the meta-analysis were cited in the 2012 guideline, which recommended pharmacologic prophylaxis. No additional prospective randomized controlled trials related to this topic have been identified since the meta-analysis and the previous guideline were published (ESM 12). Data in support of pharmacologic prophylaxis are considered somewhat indirect. Except for a large prospective randomized controlled trial comparing VTE in septic patients treated with drotrecogin alfa who were randomized to receive placebo versus UFH versus LWMH [515], all studies have been in an undifferentiated population of critically ill patients. Overall, we made a strong recommendation in favor of pharmacologic prophylaxis against VTE in critically ill patients based on the overall efficacy of this intervention, although the evidence was downgraded to moderate because of indirectness of the populations studied.

A number of studies have also compared use of LMWH to UFH for prevention of VTE prophylaxis in critically ill patients. Four trials were included in the meta-analysis of Alhazzani et al. [514]. We did not identify any new trials since then. In this meta-analysis, the overall rate of DVT was lower in patients receiving LWMH compared to UFH, and overall mortality was reduced by 7%; however, these differences did not reach statistical significance. In those trials evaluating PE, the rates were significantly lower in patients receiving LWMH. As with all studies of pharmacologic VTE prophylaxis, only one trial [515] was restricted to septic patients, and that trial utilized drotrecogin alfa in all patients. An additional meta-analysis found that LWMH was more effective than UFH in reducing the incidence of DVT and PE in critically ill patients [516]. However, the authors of this meta-analysis included studies of critically ill trauma patients.

All studies of LMWH have compared these agents against UFH administered twice daily. No high-quality studies in critically ill patients have directly compared LWMH against UFH administered thrice daily. An indirect comparison meta-analysis published in 2011 failed to identify a significant difference in efficacy between twice-daily and thrice-daily heparin in medical patients [517]. However, another review and meta-analysis (also using indirect comparison) suggested greater efficacy but higher rates of bleeding with thrice-daily UFH [518].

A Cochrane review demonstrated a substantial decrease in the incidence of HIT in postoperative patients receiving LMWH compared to UFH [519], although the studies were not specific to either septic or critically ill patients. Finally, a cost-effectiveness analysis based on one trial of LMWH versus UFH [520] suggested that use of LMWH resulted in an overall decrease in costs of care, despite the higher acquisition cost of the pharmaceutical agent [521]. Overall, the desirable consequences (i.e., reduction in PE, HIT, cost savings, and ease of administration) of using LMWH clearly outweigh the undesirable consequences; therefore, we made a strong recommendation in favor of LMWH instead of UFH, whenever feasible. However, the evidence for this was considered only of moderate quality because of indirectness, both with respect to the populations studied and also because LMWH has only been systematically compared to UFH administered twice daily, and not thrice daily.

Precautions are generally suggested regarding use of LMWH in patients with renal dysfunction. In a preliminary trial, no accumulation of anti-Xa levels was demonstrated with dalteparin in patients with a calculated creatinine clearance <30 mL/min [522]. Thus, these patients were included in the PROTECT study [520]. In the actual trial, 118 patients with renal failure were analyzed,60 of whom were randomized to dalteparin and 58 to UFH. There was no evidence of untoward reactions in patients receiving dalteparin compared to UFH. However, dalteparin was not more efficacious than UFH in this small number of patients. These investigators speculated that other types of LMWH might be safe to use in patients with renal failure, but acknowledged no other high-quality data to support this theory. Thus, use of LMWH in septic patients with renal dysfunction might be an option, but data in support of that remain quite limited.

Combined pharmacologic prophylaxis and mechanical prophylaxis with intermittent pneumatic compression (IPC) and/or graduated compression stockings (GCS) is a potential option in critically ill patients with sepsis and septic shock. No high-quality studies of this approach in septic patients, or even critically ill patients in general, exist; however, further research is ongoing [523]. A Cochrane review [524] of 11 studies in surgical patients suggested that combined prophylaxis was more effective than either modality used alone. However, the quality of evidence was low due to indirectness of population and imprecision of estimates. Therefore, we can make only a weak recommendation for combined modality therapy for VTE prophylaxis in critically ill patients with sepsis or septic shock. Recent American College of Chest Physicians guidelines made no recommendation regarding the use of combined modality in critically ill patients, but do suggest use of combined mechanical and pharmacologic prophylaxis in high-risk surgical patients [525, 526]. A significant number of septic patients may have relative contraindications to the use of pharmacologic prophylaxis. These patients may be candidates for mechanicalprophylaxis using IPC and/or GCS. However, relatively little data exist regarding this approach in critically ill patients. Two meta-analyses have been published comparing use of mechanical prophylaxis with no prophylaxis in combined patient groups, primarily those undergoing orthopedic surgery [527, 528]. The former meta-analysis focused on use of GCS and the latter on use of IPC. In these analyses, both modalities appeared more effective than no mechanical prophylaxis, but variable numbers of patients received pharmacologic prophylaxis in both arms, making this evidence indirect. A cohort study of 798 patients using propensity scores for risk adjustment concluded that IPC was the only effective means for mechanical VTE prophylaxis in critically ill patients; however, there was heavy use of

pharmacologic prophylaxis in all groups [529]. Overall, based on these data, we made a weak recommendation for using mechanical prophylaxis in critically ill septic patients with contraindicationsto use of pharmacologic prophylaxis. Very limited evidence indicates that IPC may be more effectivethan GCS alone in critically ill patients, making it thepreferred modality for mechanical prophylaxis.

S. STRESS ULCER PROPHYLAXIS

1. We recommend that stress ulcer prophylaxis be given to patients with sepsis or septic shock who have risk factors for gastrointestinal (GI) bleeding (strong recommendation, low quality of evidence).
2. We suggest using either proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs) when stress ulcer prophylaxis is indicated (weak recommendation, low quality of evidence).
3. We recommend against stress ulcer prophylaxis in patients without risk factors for GI bleeding (BPS).

Rationale Stress ulcers develop in the GI tract of criticallyill patients and can be associated with significant morbidity and mortality [530]. The exact mechanism is not completely understood, but is believed to be related to disruption of protective mechanisms against gastricacid, gastric mucosal hypoperfusion, increased acid production, and oxidative injury to the digestive track [531]. The strongest clinical predictors of GI bleeding risk incritically ill patients are mechanical ventilation for >48 hand coagulopathy [532]. A recent international cohortstudy showed that preexisting liver disease, need for RRT, and higher organ failure scores were independent predictorsof GI bleeding risk [533]. A multicenter prospectivecohort study found the incidence of clinically important GI bleeding to be 2.6% (95% CI 1.6–3.6%) in critically ill patients [533]; however, other observational studies showed lower rates of GI bleeding [534–537].

A recent systematic review and meta-analysis of 20 RCTs examined the efficacy and safety of stress ulcer prophylaxis [538]. Moderate quality of evidence showed that prophylaxiswith either H2RAs or PPIs reduced the risk of GI bleedingcompared to no prophylaxis (RR 0.44; 95% CI 0.28–0.68; low quality of evidence showed a nonsignificant increase in pneumonia risk (RR 1.23; 95% CI 0.86–1.78) [538]. Recently, a large, retrospective cohort study examined the effect of stress ulcer prophylaxis in patients with sepsis and found nosignificant difference in the risk of C difficile infection compared to no prophylaxis [539] (ESM 13). The choice of prophylactic agent should depend on patients' characteristics, patients' values and preferences, and the local incidence of C. difficile infections and pneumonia.

Although published RCTs did not exclusively includeseptic patients, risk factors for GI bleeding are frequentlypresent in patients with sepsis and septic shock [532]; therefore, using the results to inform our recommendationsis acceptable. Based on the available evidence, the desirable consequences of stress ulcer prophylaxis outweigh the undesirable consequences; therefore, we madea strong recommendation in favor of using stress ulcerprophylaxis in patients with risk factors. Patients without risk factors are unlikely to develop clinically important GI bleeding during their ICU stay [532]; therefore, stress ulcer

prophylaxis should only be used when risk factors are present, and patients should be periodically evaluated for the continued need for prophylaxis.

While there is variation in practice worldwide, several surveys showed that PPIs are the most frequently used agents in North America, Australia, and Europe, followed by H2RAs [540–544]. A recent meta-analysis including 19 RCTs (n = 2177) showed that PPIs were more effective than H2RAs in preventing clinically important GIbleeding (RR 0.39; 95% CI 0.21–0.71; p = 0.002; moderate quality), but led to a nonsignificant increase in pneumonia risk (RR 1.17; 95% CI 0.88–1.56; p=0.28; lowquality) [544] prior meta-analyses reached a similar conclusion [545, 546]. None of the RCTs reported the risk of C. difficile infection; nonetheless, a large retrospective cohort study demonstrated a small increase in the risk of C. difficile infection with PPIs compared to H2RAs (2.2v s. 3.8%; p < 0.001; very low-quality evidence). Studies reporting patients' values and preferences concerning the efficacy and safety of these agents are essentially lacking. Furthermore, cost-effectiveness analyses reached different conclusions [547, 548].

Consequently, the benefit of preventing GI bleeding (moderate-quality evidence) must be weighed against the potential increase in infectious complications (very low to low-quality evidence). The choice of prophylactic agent will largely depend on individual patients' characteristics; patients' values; and the local prevalence of GI bleeding, pneumonia, and C. difficile infection. Because of theuncertainties, we did not recommend one agent over the other. Ongoing trials aim to investigate the benefit and harm of withholding stress ulcer prophylaxis (clinicaltrials.gov registration NCT02290327, NCT02467621). The results of these trials will inform future recommendations.

T. NUTRITION

1. We recommend against the administration ofearly parenteral nutrition alone or parenteral nutrition in combination with enteral feedings (but rather initiate early enteral nutrition) in critically ill patients with sepsis or septic shock who can be fed enterally (strong recommendation, moderate quality of evidence).

Rationale Parenteral nutrition delivery can secure the intended amount of calories. This may represent an advantage over enteral nutrition, especially when patients may be underfed due to GI intolerance, which may be pertinent over the first days of care in the ICU. However, parenteral delivery is more invasive and has been associated with complications, including an increased risk of infections. Further, purported physiologic benefits areassociated with enteral feeding, which make this strategy the mainstay of care [549]. To address the question of the superiority of parenteral nutrition for patients with sepsis and septic shock, we evaluated the evidence for patients who could be fed enterally early versus those for whom early enteral feeding was not feasible.

Our first systematic review examined the impact of an early parenteral feeding strategy alone or in combination with enteral feeding versus enteral feeding alone on mortality in patients who could be fed enterally. We identified a total of 10 trials with 2888 patients that were conductedin heterogeneous critically ill and surgical patients, trauma and traumatic brain injury, and those with severe acute pancreatitis [550–559]. No evidence showed that

early parenteral nutrition reduced mortality (RR 0.97;95% CI 0.87–1.08; n=2745) or infection risk (RR 1.52;95% CI 0.88–2.62; n=2526), but ICU LOS was increased (MD, 0.90; 95% CI 0.38–1.42; n=46). The quality of the evidence was graded as moderate to very low. In the largest randomized trial that addressed this study question (CALORIES, n=2400), there were fewer episodes of hypoglycemia and vomiting in the early parenteral group,but no differences in death between the study groups [553, 560]. Due to the lack of mortality benefit, the addedcost of parenteral nutrition in absence of clinical benefit [550, 551, 555, 560], and the potential physiologic benefits of enteral feeding [549 , 561 , 562], we recommend early enteral nutrition as the preferred route of administration in patients with sepsis or septic shock who can be fed enterally.

2. We recommend against the administration of parenteral nutrition alone or in combination with enteral feeds (but rather to initiate IV glucose and advance enteral feeds as tolerated) over the first 7 days in critically ill patients with sepsis or septic shock for whom early enteral feeding is not feasible (strong recommendation, moderate quality of evidence).

Rationale In some patients with sepsis or septic shock, feeding enterally early may not be feasible because of contraindicationsrelated to surgery or feeding intolerance.These patients represent another subgroup of criticallyill patients for whom the clinician may question whetherto start parenteral nutrition early with or without someenteral feeding to meet nutritional goals, versus trophic/hypocaloric enteral feeding alone, or nothing except theaddition of IV glucose/dextrose for the provision of somecalories. To address this question, we conducted a systematicreview, which included a total of four trials and 6087patients [563 –566]. Two of the included trials accounted for 98.5% of the patients included in the review and, ofthese trials, more than 65% of the patients were surgical critically ill patients [564, 567]. Seven (20%) of the patients from these two trials were considered septic and patients with malnourishment were either excluded or represented a very small fraction (n=46, 3.3%) of the included patients. In three of the included trials, parenteral nutritionwas initiated if enteral feeding was not tolerated after the first 7 days of care [564, 566, 567]. Our review found that early parenteral nutrition with or without supplementation of enteral nutrition was not associated with reduced mortality (RR 0.96; 95% CI 0.79–1.16; n = 6087;moderate-quality evidence), but was associated withincreased risk of infection (RR 1.12; 95% CI 1.02–1.24; 3trials; n=6054; moderate-quality evidence) (ESM 14).Length of ventilation outcomes were reported divergently in the two large trials, with one suggesting an increase [567] and the other a decrease [564] in ventilation time associated with early parenteral nutrition. One trial also reported less muscle wasting and fat loss in the early parenteralnutrition group according to a Subjective Global Assessment Score [564]. In summary, due to the lack of mortality benefit, the increased risk of infection, and the extra cost for parenteral nutrition in the absence of clinical benefit [568], current evidence does not support the initiation of early parenteral nutrition over the first 7 days of care for patients with contraindications or intolerance to enteral nutrition. Specific patient groups may benefit more or incur more harm with early initiation of parenteral nutrition in this context. We encourage future research according to individual patient level meta-analyses to characterize these subgroups and plan for future randomized trials. It is important to note that patients who were malnourished were either excluded or rarely represented in the included trials from our systematic review. Since so few malnourished

patients were enrolled, evidence to guide practice is lacking. Malnourished patients may represent a subgroup of critically ill patients for whom the clinician may consider initiating parenteral nutrition early when enteral feeding is not feasible.

3. We suggest the early initiation of enteral feedingrather than a complete fast or only IV glucose in critically ill patients with sepsis or septic shock who can be fed enterally (weak recommendation, low quality of evidence).
4. We suggest either early trophic/hypocaloric or early full enteral feeding in critically ill patientswith sepsis or septic shock; if trophic/hypocaloric feeding is the initial strategy, then feeds should be advanced according to patient tolerance (weak recommendation, moderate quality of evidence).

Rationale The early administration of enteral nutritionin 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 ofmetabolic responses that may reduce insulin resistance[561 , 562]. To examine evidence for this nutrition strategy, we asked if early full feeding (started within the first 48 h and feeding goals to be met within 72 h of ICU admission or injury) as compared to a delayed strategy (feeds delayed for at least 48 h) improved the outcome of our critically ill patients. In our systematic review, we identified a total of 11 trials in heterogeneous critically ill patient populations (n=412 patients) [569–579]. Only one trial was specifically conducted in patients with sepsis (n=43 patients) [577]. The risk of death was not significantly different between the groups (RR 0.75; 95% CI0.43–1.31; n=188 patients), and infections were not significantly reduced (RR 0.60; 95% CI 0.34–12.07; n=122 patients). Other recent systematic reviews in the critically ill focused specifically on trauma (three trials, 126 patients) or more heterogeneous critically ill populations (6 trials, n=234 patients) and found that early enteral feeding reduced death and pneumonia [580, 581]. However, in contrast to our systematic review, these latter reviews did not include studies in which enteral feeding in the intervention arm was both early and full and where the control arm feeding strategy was delayed for at least the first 48 h. We also examined whether the provision of an early trophic/hypocaloric feeding strategy (defined by enteral feeding started within the first 48 h and up to 70% of target caloric goals for at least 48 h) was superior to a delayed enteral feeding strategy. In the two trials that fit these criteria, there were no statistical differences indeath (RR 0.67; 95% CI 0.35–1.29; n=229; low-quality evidence) or infection (RR 0.92; 95% CI 0.61–1.37; n=229; very low-quality evidence) between the groups [582, 583]. Since the present evidence does not suggest harm with early versus delayed institution of enteralfeeding, and there is possible benefit from physiologic evidence suggesting reduced gut permeability, inflammation,and infection risk, the committee issued a weakrecommendation to start feeding early in patients with sepsis and septic shock.

Some evidence suggests that intentional early underfeeding as compared to early full feeding of critically ill patients may lead to immune hyporesponsiveness and an increase in infectious complications [549]. Further, because critical illness is associated with loss of skeletal mass, it is possible that not administering adequate protein may lead to challenges weaning from the ventilator and more general weakness. However, a biological rationale for a trophic/hypocaloric or hypocaloric feeding strategy exists, at least as the initial approach

to feeding the critically ill as compared to a fully fed strategy. Limiting caloric intake stimulates autophagy, which is considered a defense mechanism against intracellular organisms and therefore raises the possibility that this approach could reduce infection risk [584, 585].

We defined feeds as trophic/hypocaloric if goal feeds were 70% or less of standard caloric targets for at least a 48-hour period before they were titrated toward goal. Our systematic review identified seven randomized trials and 2665 patients studied [584, 586–591]. Patient populations included heterogeneous critically illpatients and those with acute lung injury and/or ARDS. Patients who were malnourished were excluded from four of the trials [588 – 591] and the average body mass index in the remaining three trials ranged from 28 to 30 [584, 586, 587]. Targets for trophic/hypocaloric feeding groups ranged from 10 to 20 kcal/h to up to 70% of target goal. Study intervention periods ranged from 6 to 14 days (or until ICU discharge). In three of the trials, protein (0.8–1.5 g/kg/days) was administered to the trophic/hypocaloric group to meet protein requirements[584, 586, 587]. Overall, there were no differences in mortality (RR 0.95; 95% CI 0.82–1.10; n=2665; high quality evidence), infections (RR 0.96; 95% CI 0.83–1.12; n=2667; moderate-quality evidence), or ICU LOS (MD, –0.27 days; 95% CI –1.40 to 0.86, n=2567; moderate-quality evidence between the study groups)(ESM 15). One trial that instituted hypocaloric feeding (goal 40–60% target feeds for up to 14 days) reported a subgroup of 292 patients with sepsis; there were also no detectable differences in death at 90 days between the study groups (RR 0.95; 95% CI 0.71–1.27; p = 0.82for interaction) [584]. A recently published systematic review of normocaloric versus hypocaloric feeding also found no differences in hospital mortality, infections, ICU LOS, or ventilator-free days between the study groups [585]. Some evidence also suggests a lack ofadverse consequences even with longer-term outcomes. A trophic/hypocaloric feeding trial of 525 patients, which instituted the most significant restrictions in enteral feeding (20% of caloric goal) for up to 6 days,found no differences in muscle strength, muscle mass,and 6-min walk test at 6 months or 1 year, although patients in the trophic/hypocaloric feeding group were more likely to be admitted to a rehabilitation facility during the first 12 months of follow-up [592]. The current evidence base would suggest that a trophic/hypocaloric or early full enteral feeding strategy is appropriate. However, for patients with sepsis or septic shock who are not tolerating enteral feeds, trophic/hypocaloric feeding may be preferred, with feeds titrated over timeaccording to patient tolerance. There is insufficient evidence to confirm that a trophic/hypocaloric feeding strategy is effective and safe in patients who are malnourished (body mass index <18.5) because these patients were either excluded or rarely represented in the clinical trials from our systematic review. Until further clinical evidence is generated for this subpopulation, the clinician may consider titrating enteral feeds more aggressively in accordance with patient tolerance while monitoring for re-feeding syndrome. Current evidence did not specifically address patients with high vasopressor requirements, and the decision about withholding the feeds should be individualized.

5. We recommend against the use of omega-3 fatty acids as an immune supplement in critically ill patients with sepsis or septic shock (strong recommendation, low quality of evidence).

Rationale Use of omega-3 fatty acids in the contextof clinical trials in the critically ill has been a subject of interest during the past several years because of the immunomodulatory potential [593]. However, systematic reviews of parenteral or enteral omega-3 supplementation in critically ill and ARDS patients have not confirmed their therapeutic benefit [594, 595]. Further, a recent randomized trial of 272 patients with acute lung injury found excess harm related to mortality as well as fewer ventilator- and ICU-free days in the omega-3 arm as compared to the control arm [596]. A limitation of this trial as well as several other omega-3 trials is that the intervention arm also contained vitamins and trace mineral supplementation, making omega-3 fatty acids alone difficult to isolate as the cause for harm or benefit. For these reasons, we conducted a systematic review of clinical trials in the critically ill that administered omega-3 alone in the intervention arm. In a total of 16 trials (n=1216 patients), there were no significant reductions in death (RR 0.86; 95% CI 0.71–1.03; low quality evidence); however, ICU LOS was significantly reduced in the omega-3 group (MD, –3.84 days; 95% CI –5.57 to–2.12, very low-quality evidence). The overall quality of the evidence was graded as low. Due to the uncertaintyof benefit, the potential for harm, and the excess cost and varied availability of omega-3 fatty acids, we make a strong recommendation against the use of omega-3 fatty acids for patients with sepsis and septic shock outside the conduct of RCTs.

6. We suggest against routinely monitoring gastric residual volumes (GRVs) in critically ill patients with sepsis or septic shock (weak recommendation, low quality of evidence). However, we suggest measurement of gastric residuals in patients with feeding intolerance or who are considered to be at high risk of aspiration (weak recommendation, very low quality of evidence).

Remarks This recommendation refers to nonsurgical critically ill patients with sepsis or septic shock.
Rationale Critically ill patients are at significant risk for GI dysmotility, which may then predispose them to regurgitation or vomiting, aspiration, and the development of aspiration pneumonia. The rationale for measurement of GRVs is to reduce the risk for aspiration pneumonia by either ceasing or modifying the enteral feeding strategy based on the detection of excess gastric residuals. The inherent controversy is that observational and interventional studies have not consistently confirmed a relationship between the measurement of GRVs (with thresholds ranging from 200 mL to no monitoring of GRVs) and outcomes of vomiting, aspiration,or pneumonia [597–603]. In our systematic review, we identified one multicenter non-inferiority trial of 452 critically ill patients who were randomized to not monitoring GRVs versus monitoring GRVs at 6-h intervals [602]. Intolerance to feeds was defined as vomiting in the intervention group versus a GRV of >250 mL, vomiting, or both in the control group. Although vomiting was more frequent (39.6 versus 27%; median difference, 12.6;95% CI 5.4–19.9) in the group in which GRVs were not monitored, a strategy of not monitoring GRVs was found to be non-inferior compared to monitoring at 6-h intervals with regard to the primary outcome of VAP (16.7versus 15.8% respectively; difference, 0.9%; 95% CI −4.8to 6.7%). No detectable differences in death were shown between the study groups at 28 and 90 days. Patients who had surgery up to one month prior to study eligibility were not included in this study, so these results should not be applied to surgical critically ill patients. However, the results of this trial question the need to measure GRVs as a method to reduce aspiration pneumonia in all critically ill

patients. Due to the absence of harm and the potential reduction in nursing resources neededto monitor patients, we suggest against routine monitoring of GRVs in all patients with sepsis unless the patient has demonstrated feeding intolerance (e.g., vomiting, reflux of feeds into the oral cavity) or for patients who are considered to be at high risk for aspiration (e.g., surgery, hemodynamic instability). We recommend the generation of further evidence through the conduct of future randomized controlled trials targeted to higher-risk patient groups such as the surgical population or those in shock to determine the threshold and frequency withwhich GRVs should be monitored.

7. We suggest the use of prokinetic agents in critically ill patients with sepsis or septic shock and feeding intolerance (weak recommendation, low quality of evidence).

Rationale Feeding intolerance is defined as vomiting, aspiration of gastric contents, or high GRVs. For multiplereasons, feeding intolerance commonly develops in critically ill patients. Patients with preexisting gastroparesisor diabetes or those who are receiving sedativesand vasopressors are at risk. Prokinetic agents, including metoclopramide, domperidone, and erythromycin,are frequently used in the ICU. Each of these agents hasdifferent pharmacodynamics and pharmacokinetic properties; however, these agents may be associated with prolongation of QT interval and ventricular arrhythmias. A large case–control study in non-ICU patients showed athreefold increase in risk of sudden cardiac death with domperidone use at doses >30 mg/day [604]. Another retrospective cohort study showed that outpatient use of erythromycin is associated with a twofold increase in the risk of sudden cardiac death, especially if concomitantly used with other CYP3A inhibitors [605]. The impact on ventricular arrhythmias in ICU patients is less clear.

A recent systematic review and meta-analysis included 13 RCTs enrolling 1341 critically ill patients showed that prokinetic agent use was associated with lower risk of feeding intolerance (RR 0.73; 95% CI 0.55–0.97; moderate-quality evidence). This was equivalent to an absolute risk reduction of 17%. The use of prokinetic agents did not significantly increase mortality (RR 0.97; 95%CI 0.81–1.1; low-quality evidence); however, the incidence of fatal or nonfatal cardiac arrhythmias was not consistently reported across studies. There was no significant effect on the risk of pneumonia or vomiting. The majority of trials examined the effect of metoclopramide or erythromycin; subgroup analysis by drug class was underpowered to detect important subgroup differences [606]. We considered the desirable consequences (lower risk of feeding intolerance) and the low quality of evidence showing no difference in mortality or pneumonia, and issued a weak recommendation for using prokineticagents (metoclopramide or erythromycin) to treat feeding intolerance in patients with sepsis. Future large comparative trials are needed to determine the relativeefficacy and safety of different agents.

Monitoring the QT interval with serial electrocardiogramsis required when these agents are used in the ICU, especially if concomitantly used with other agents that could prolong the QT interval [607]. The need for prokinetic agents should be assessed daily, and they should be stopped when clinically not indicated.

8. We suggest placement of post-pyloric feeding tubes in critically ill patients with sepsis or septic shock with feeding intolerance or who are considered to be at high risk of aspiration (weak recommendation, low quality of evidence).

Rationale Feeding intolerance is defined as vomiting, abdominal distention, or high GRVs that result in interruptionof enteral nutrition. Critically ill patients are at risk of gastroparesis and feeding intolerance; evidence of delayed gastric emptying can be found in approximately 50% of critically ill patients [608]. The proportion of patients who will progress to develop clinical symptomsis less clear. Feeding intolerance can result in interruptionof nutritional support, vomiting, aspiration of gastriccontents, or pneumonia [609]. The pathophysiologyis not completely understood and is likely to be multifactorial. Gastroparesis can be caused by pharmacologic agents that are frequently used in the ICU (e.g., sedatives, opioids, or NMBAs), gastric hypoperfusion in the contextof shock, hyperglycemia, or vasopressor use [610 –612].

Post-pyloric tubes have the theoretical advantage ofimproving feeding intolerance in patients with gastroparesis, consequently improving the delivery of nutritioninto the gut. Post-pyloric feeding tubes, although safe, are not always available, and require technical skill forsuccessful insertion. Gastric air insufflation and prokinetic agents are both effective strategies to facilitate theinsertion of post-pyloric tubes in critically ill patients [613]. Endoscopy and an external magnet device can also be used to guide post-pyloric tube insertion, but are not always available, are expensive, and require a higher level of expertise.

We conducted a systematic review and meta-analysis of randomized trials to examine the effect of post-pyloric (compared to gastric) feeding on patient important outcomes. We identified 21 eligible RCTs enrolling 1579 patients. Feeding via post-pyloric tube reduced the risk of pneumonia compared to gastric tube feeding (RR 0.75; 95% CI 0.59–0.94; low-quality evidence). This translates into a 2.5% (95% CI 0.6–4.1%) absolute reduction in pneumonia risk. However, there was no significant effect on the risk of death, aspiration, or vomiting (ESM 16). This is consistent with the results of older meta-analyses [614, 615]. Although the use of post-pyloric tubes reduced risk of pneumonia, the quality of evidence was low, the magnitude of benefit was small, and there was uncertainty about the effect onother patient-important outcomes. Cost-effectivenessstudies that describe the economic consequences ofusing post-pyloric feeding tubes are lacking. Therefore, we decided that the balance between desirableand undesirable consequences was unclear in low-risk patients; however, the use of post-pyloric feeding tubes may be justified in patients at high risk of aspiration (i.e., patients with history of recurrent aspiration, severe gastroparesis, feeding intolerance, or refractory medical treatment).

9. We recommend against the use of IV selenium to treat sepsis and septic shock (strong recommendation, moderate quality of evidence).

Rationale Selenium was administered in the hope that it could correct the known reduction of selenium concentration in sepsis patients and provide a pharmacologic effect through an antioxidant defense. Although some RCTs are available, the evidence for the use of IV selenium is not convincing. Two recent meta-analyses suggest, with weak findings, a

potential benefit of selenium supplementation in sepsis [616, 617]. However, a recent large RCT also examined the effect on mortality rates [618]. Overall pooled odds ratio (0.94; CI 0.77–1.15) suggests no significant impact on mortality with sepsis. Also, no differences in secondary outcomes of development of nosocomial pneumonia or ICU LOS were found. When updating our meta-analysis to include the results of this recent study, there was no difference in mortality between both groups (ESM 17).

10. We suggest against the use of arginine to treat sepsis and septic shock (weak recommendation, low quality of evidence).

Rationale Arginine availability is reduced in sepsis, which can lead to reduced nitric oxide synthesis, loss ofmicrocirculatory regulation, and enhanced productionof superoxide and peroxynitrite. However, arginine supplementation could lead to unwanted vasodilation andhypotension [619, 620]. Human trials of l-arginine supplementation have generally been small and reported variable effects on mortality [621–624]. The only study in septic patients showed improved survival, but had limitations in study design [623]. Other studies suggested no benefit or possible harm in the subgroup of septic patients [621, 624, 625]. Some authors found improvement in secondary outcomes in septic patients, such asreduced infectious complications) and hospital LOS, but the relevance of these findings in the face of potential harm is unclear.

11. We recommend against the use of glutamine to treat sepsis and septic shock (strong recommendation, moderate quality of evidence)

Rationale Glutamine levels are also reduced duringcritical illness. Exogenous supplementation can improve gut mucosal atrophy and permeability, possibly leading to reduced bacterial translocation. Other potential benefits are enhanced immune cell function, decreased proinflammatory cytokine production, and higher levels of glutathione and antioxidative capacity [619, 620]. However, the clinical significance of these findings is not clearly established.

Although a previous meta-analysis showed mortality reduction [626], several other meta-analyses did not [627–630]. Four recent well-designed studies also failed to show a mortality benefit in the primary analyses, although none focused specifically on septic patients [631 –634]. Two small studies on septic patients showed no benefit in mortality rates [635, 636], but showed a significant reduction in infectious complications [636] and a faster recovery of organ dysfunction.

12. We make no recommendation about the use of carnitine for sepsis and septic shock.

Rationale Massive disruption in energy metabolism contributes to sepsis severity and end organ failure. The magnitude of the energy shift, and, possibly more importantly, the host's metabolic adaptiveness to the shift in energy demand, likely influence patient survival. Carnitine, endogenously manufactured from lysine and methionine, is required for the transport of long-chain fatty acids into the mitochondria and the generation of energy. As such, carnitine utilization is essential for enabling the switch from glucose to long-chain fatty acid metabolism during the sepsis energy crisis. This is the basis for the rationale of

employing l-carnitine as a therapeutic in sepsis. One small randomized trial in patients with sepsis reported a 28-day mortality decrease in septic shock patients treated with IV l-carnitine therapy within 24 h of shock onset; however, the trial was underpowered to detect such a difference [637]. Larger, ongoing trials should provide more evidence of the usefulness of carnitine supplementation.

U. SETTING GOALS OF CARE

1. We recommend that goals of care and prognosis be discussed with patients and families (BPS).
2. We recommend that goals of care be incorporated into treatment and end-of-life care planning, utilizing palliative care principles where appropriate (strong recommendation, moderate quality of evidence).
3. We suggest that goals of care be addressed as early as feasible, but no later than within 72 h of ICU admission (weak recommendation, low quality of evidence).

Rationale Patients with sepsis and multiple organ system failure have a high mortality rate; some will not survive or will have a poor quality of life. Although the outcome of intensive care treatment in critically ill patients may be difficult to prognosticate accurately, establishing realistic ICU treatment goals is paramount [638], especially because inaccurate expectations aboutprognosis are common among surrogates [639]. Nonbeneficial ICU advanced life-prolonging treatment is not consistent with setting goals of care [640, 641]. Models for structuring initiatives to enhance care in the ICU highlight the importance of incorporating goals of care, along with prognosis, into treatment plans [642]. The use of proactive family care conferences to identify advance directives and treatment goals within 72 h of ICU admissionhas been demonstrated to promote communicationand understanding between the patient's family and the treating team; improve family satisfaction; decrease stress, anxiety, and depression in surviving relatives; facilitate end-of-life decision-making; and shorten ICU LOS for patients who die in the ICU [643, 644]. Promoting shared-decision-making with patients and families is beneficial in ensuring appropriate care in the ICU and that futile care is avoided [641, 645, 646].

Palliative care is increasingly accepted as an essential component of comprehensive care for critically ill patients regardless of diagnosis or prognosis [642, 647].Use of palliative care in the ICU enhances the ability to recognize pain and distress; establish the patient's wishes, beliefs, and values, and their impact on decision-making; develop flexible communication strategies; conduct family meetings and establish goals of care; provide family support during the dying process; help resolve team conflicts;and establish reasonable goals for life support and resuscitation [648].

A recent systematic review of the effect of palliativecare interventions and advanced care planning on ICU utilization identified that, despite wide variation in study type and quality among nine randomized control trials and 13 nonrandomized controlled trials, patients who received advance care planning or palliative care interventions consistently showed a pattern toward decreased ICU admissions and reduced ICU LOS [649].

However, significant inter-hospital variation in ratings and delivery of palliative care is consistent with prior studies showing variation in intensity of care at the end of life [650]. Despite differences in geographic location,legal system, religion, and culture, there is worldwide professional consensus for key end-of-life practices in the ICU [651].Promoting patient- and family-centered care in the ICU has emerged as a priority and includes implementation of early and repeated care conferencing to reduce family stress and improve consistency in communication;open flexible visitation; family presence during clinical rounds, resuscitation, and invasive procedures; and attention to cultural and spiritual support [652-655].

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Table 1 Determination of the quality of evidence

Underlying methodology

1. High: RCTs
2. Moderate: Downgraded RCTs or upgraded observational studies
3. Low: Well-done observational studies with RCTs
4. Very Low: Downgraded controlled studies or expert opinion or other evidence

Factors that may decrease the strength of evidence

1. Methodologic features of available RCTs suggesting high likelihood of bias
2. Inconsistency of results, including problems with subgroup analyses
3. Indirectness of evidence (differing population, intervention, control, outcomes, comparison)
4. Imprecision of results
5. High likelihood of reporting bias

Main factors that may increase the strength of evidence

1. Large magnitude of effect (direct evidence, relative risk >2 with no plausible confounders)
2. Very large magnitude of effect with relative risk > 5 and no threats to validity (by two levels)
3. Dose-response gradientRCT = randomized clinical trial

Table 2 Factors determining strong vs. weak recommendation

What Should Be Considered	Recommended Process
High or moderate evidence *(Is there high-or moderate quality evidence?)*	The higher the quality of evidence, the more likely a strong recommendation
Certainty about the balance of benefits vs. harms and burdens *(Is there certainty?)*	The larger the difference between the desirable and undesirable consequences and the certainty around that difference, the more likely a strong recommendation. The smaller the net benefit and the lower the certainty for that benefit, the more likely a weak recommendation.
Certainty in, or similar, values *(Is there certainty or similarity?)*	The more certainty or similarity in values and preferences, the more likely a strong recommendation.
Resource implications *(Are resources worth expected benefits?)*	The lower the cost of an intervention compared to the alternative and other costs related to the decision (i.e., fewer resources consumed), the more likely a strong recommendation.

Table 3 Comparison of 2016 grading terminology with previous alphanumeric descriptors

	2016 Descriptor	2012 Descriptor
Strength	Strong	1
	Weak	2
Quality	High	A
	Moderate	B
	Low	C
	Very Low	D
Ungraded strong recommendation	Best Practice Statement	Ungraded

Table 4 Implications of the strength of recommendation

	Strong Recommendation	Weak Recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices are likely to be appropriate for different patients, and therapy should be tailored to the individual patient's circumstances. These circumstances may include the patient's or family's values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations, including for use as performance indicators.	Policy-making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management opinions has taken place.

Table 5 Criteria for Best practice statements

	Criteria for Best Practice Statements
1	Is the statement clear and actionable?
2	Is the message necessary?
3	Is the net benefit (or harm) unequivocal?
4	Is the evidence difficult to collect and summarize?
5	Is the rationale explicit?
6	Is this better to be formally GRADEd?

GRADE = Grading of Recommendations Assessment, Development, and EvaluationModified from Guyatt et al (15).

Table 6 Important terminology for antimicrobial recommendations

Empiric therapy	Initial therapy started in the absence of definitive microbiologic pathogen identification. Empiric therapy may be mono-, combination, or broad-spectrum, and/or multidrug in nature.
Targeted/definitive therapy	Therapy targeted to a specific pathogen (usually after microbiologic identification). Targeted/definitive therapy may be mono- or combination, but is not intended to bebroad-spectrum.
Broad-spectrum therapy	The use of one or more antimicrobial agents with the specific intent of broadening the range of potential pathogens covered, usually during empiric therapy (e.g., piperacillin/tazobactam, vancomycin, and anidulafungin; each is used to cover a different group of pathogens). Broad-spectrum therapy is typically empiric since the usual purpose is to ensure antimicrobial coverage with at least one drug when there is uncertainty about the possible pathogen. On occasion, broad-spectrum therapy may becontinued into the targeted/definitive therapy phase if multiple pathogens are isolated.
Multidrug therapy	Therapy with multiple antimicrobials to deliver broad-spectrum therapy (i.e., to broaden coverage) for empiric therapy (i.e., where pathogen is unknown) or to potentially accelerate pathogen clearance (combination therapy) with respect to a specific pathogen(s) where the pathogen(s) is known or suspected (i.e., for both targeted or empiric therapy). This term therefore includes combination therapy.
Combination therapy	The use of multiple antibiotics (usually of different mechanistic classes) with the specific intent of covering the known or suspected pathogen(s) with more than one antibiotic (e.g., piperacillin/tazobactam and an aminoglycoside or fluoroquinolone for gram-negative pathogens) to accelerate pathogen clearance rather than to broaden antimicrobial coverage. Other proposed applications of combination therapy include inhibition of bacterial toxin production (e.g., clindamycin with ß-lactams for streptococcal toxic shock) or potential immune modulatory effects (macrolides with a ß-lactam for pneumococcal pneumonia).