

## Update in sepsis guidelines: what is really new?

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**SUMMARY**

Sepsis remains a highly lethal entity resulting in more than 200 000 deaths in the USA each year. The in-hospital mortality approaches 30% despite advances in critical care during the last several decades. The direct health care costs in the USA exceed \$24 billion dollars annually and continue to escalate each year especially as the population ages. The Surviving Sepsis Campaign published their initial clinical practice guidelines for the management of severe sepsis and septic shock in 2004. Updated versions were published in 2008, 2012 and most recently in 2016 following the convening of the Third International Consensus Definitions Task Force. This task force was convened by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine to address prior criticisms of the multiple definitions used clinically for sepsis-related illnesses. In the 2016 guidelines, sepsis is redefined by the taskforce as a life-threatening organ dysfunction caused by a dysregulated host response to infection. In addition to using the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score to more rapidly identify patients with sepsis, the task force also proposed a novel scoring system to rapidly screen for patients outside the ICU who are at risk of developing sepsis: the 'quickSOFA' (qSOFA) score. To date, the largest reductions in mortality have been associated with early identification of sepsis, initiation of a 3-hour care bundle and rapid administration of broad-spectrum antibiotics. The lack of progress in mortality reduction in sepsis treatment despite extraordinary investment of research resources underscores the variability in patients with sepsis. No single solution is likely to be universally beneficial, and sepsis continues to be an entity that should receive high priority for the development of precision health approaches for treatment.

**INTRODUCTION**

The exact number of patients suffering from sepsis is difficult to capture, but it is estimated to affect at least 1–1.5 million persons each year in the USA,<sup>1–4</sup> and 19 million patients worldwide.<sup>5,6</sup> Sepsis remains a highly lethal entity resulting in more than 200 000 USA deaths per year<sup>7</sup> and an in-hospital mortality upward of 30% despite advances in critical care.<sup>2,4</sup> During the last several decades, the mortality rates have decreased, but the incidence is rising.<sup>4,8</sup> The condition affects all ages, however, among those with sepsis, 49% are between the ages of 65–84 years old.<sup>7</sup> It also commonly affects those with compromised immune systems, chronic disease, infants and those suffering traumatic injury. The direct healthcare costs in the USA exceed \$24 billion dollars per year<sup>4</sup> and rises on average more than 11% per year in cost. Sepsis remains in the top 10

leading causes of death despite plentiful investigative attention toward new therapies and adjuncts to mitigate poor outcome.

The newest developments in our understanding of sepsis reflect revisions to the definitions of the terms sepsis, septic shock and severe sepsis. Since 1991 there have been three consensus conferences convened (in 1991, 2001 and 2014) to adjudicate the definition of sepsis. In 2016, the Third International Consensus Definitions Task Force published the 'The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).'<sup>9</sup> This task force was convened by the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine to address prior criticisms of the multiple definitions used clinically for sepsis-related illnesses. These new definitions were followed shortly by the 'Assessment of Clinical Criteria for Sepsis For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).'<sup>3</sup> The aim of this publication was to evaluate and recommend clinical criteria that could help identify patients at risk of developing sepsis.<sup>3</sup>

The clinical recommendations for managing sepsis have also recently been updated. The Surviving Sepsis Campaign (SSC) published their initial clinical practice guidelines (CPG) for the management of severe sepsis and septic shock in 2004. Updated versions were published in 2008,<sup>10</sup> 2012<sup>11</sup> and most recently in 2016.<sup>9</sup> The 2016 CPG is largely similar to the 2012 version, but there are differences in recommendations in a number of categories, including initial resuscitation parameters, vasopressor selection, antibiotic selection and ventilation. After the release of the Sepsis-3 definition revisions, the SCCM SSC released a practice guideline update to provide clinical context to the guidelines and help providers expeditiously screen, identify and treat patients with sepsis. In this update, they reiterate adherence to the campaign recommendations from 2012. Providers should 'continue to use signs and symptoms of infection to promote early identification' and those with suspected infection should begin immediate management to include 'obtaining blood and other cultures... administering tailored antibiotics as appropriate, and simultaneously obtain laboratory results'.<sup>12</sup>

**NEW DEFINITIONS FROM SSEPSIS-3  
Sepsis, severe sepsis and the SOFA score**

The 2012 sepsis guidelines defined sepsis as 'the presence (probable or documented) of infection together with systemic manifestations of infection'.<sup>11</sup> In the 2016 guidelines, sepsis is redefined by the taskforce as 'a life-threatening organ dysfunction caused by a dysregulated host response to infection'.<sup>9</sup> This new definition highlights the three

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critical components of sepsis, namely the presence of infection, the abnormal regulation of the host response to infection and the resulting organ system dysfunction as a result of the host response.<sup>9</sup>

One of the most significant changes in the new definitions was the elimination of a defined condition of systemic inflammatory response syndrome (SIRS). The SIRS criteria have included temperature  $>38^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$ , heart rate more than 90 beats per minute, respiratory rate of more than 20 breaths per minute and white blood cell count  $>12\,000/\mu\text{L}$  or  $<4000/\mu\text{L}$  or  $>10\%$  immature (band) forms. Traditionally, more than two SIRS criteria were felt to represent patients at risk of or suffering from sepsis. The taskforce determined that the inclusion of two SIRS criteria did not provide appropriate discrimination between those suffering sepsis and an appropriate physiological response to insult (infection or otherwise). Likewise, many patients with two or more SIRS criteria never go on to develop an infection or sepsis.<sup>3,9</sup> Thus, the presence of SIRS criteria has been removed from the definition of sepsis. In addition, the term 'severe sepsis' (previously defined as sepsis accompanied by sepsis-induced organ dysfunction) was removed from the guidelines, as this term is redundant to the 2016 definition of sepsis. This change highlights the taskforce's focus on organ dysfunction as a critical component in the diagnosis of sepsis. The taskforce identified 'life-threatening organ dysfunction' by 'an increase [from baseline] in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more'.<sup>9</sup>

For the purposes of assessing sepsis at presentation, they recommend that the baseline SOFA score is zero unless a patient has known pre-existing organ dysfunction before the onset of current infection.<sup>9</sup> They used the SOFA score as an indicator of organ dysfunction because it is familiar to most clinicians and because a change in SOFA score is more predictive of in-hospital mortality from sepsis than the presence of SIRS criteria. Patients with an increase of 2 or more in the SOFA score have an estimated in hospital mortality of 10% due to sepsis and a 2-fold to 25-fold increased risk of death compared with patients with a SOFA score of  $<2$ .<sup>3</sup> As a result, the task force recommended that patients with sepsis meeting this definition be observed in a location with a 'greater level of monitoring' than a routine inpatient floor environment.

### Septic shock

Septic shock has been defined in a variety of ways depending on the clinical variables chosen to characterize its associated organ dysfunction and hypotension. The 2012 taskforce definition of septic shock is 'sepsis-induced hypotension' that persists despite adequate fluid resuscitation. Sepsis-induced tissue hypoperfusion is defined as hypotension (systolic blood pressure (SBP)  $<90$  mm Hg, mean arterial pressure (MAP)  $<70$  mm Hg, or SBP decrease  $>40$  mm Hg or less than 2 SD below normal for age in the absence of other causes), elevated lactate ( $>1$  mmol/L) or oliguria (urine output  $<0.5$  mL/kg/hour for 2 hours despite fluid resuscitation) secondary to infection.<sup>11</sup> In developing the 2016 guidelines, the taskforce emphasized cellular and metabolic dysfunction as critical factors that differentiate septic shock from sepsis. They explored a number of thresholds and criteria through an iterative Delphi process and came to the following definition of septic shock: 'sepsis with persistent hypotension requiring vasopressors to maintain MAP  $\geq 65$  mm Hg and having a serum lactate  $>2$  mmol/L (18 mg/dL) despite adequate volume resuscitation'.<sup>9</sup> Both hypotension and elevated lactate were included because the presence of both

### Box 1 The 'quickSOFA' (qSOFA) score

Patients outside the ICU are at risk of sepsis development if two or more of the following are abnormal:

- ▶ Elevated respiratory rate  $\geq 22$  breaths per minute
- ▶ Altered mental status (Glasgow Coma Scale score  $<15$ )
- ▶ Systolic blood pressure of 100 mm Hg or less

variables results in higher risk-adjusted mortality than with either variable alone.

### The quickSOFA score

In addition to using the SOFA score to identify patients with sepsis, the task force also proposed a novel scoring system to rapidly screen for patients outside the ICU who are at risk of developing sepsis: the 'quickSOFA' (qSOFA) score (box 1).

The quickSOFA score was designed for use both in the inpatient and outpatient setting. On statistical review, it had predictive validity that was similar to that of the SOFA score for patients outside the ICU. It is not intended to substitute for good clinical judgment or as the sole criteria for ruling sepsis in or out, rather it is an adjunct to aid in early recognition of patients at high risk for sepsis. The SCCM SSC emphasizes that the qSOFA 'does not define sepsis,<sup>12</sup>' but is an indicator of increased risk for clinical deterioration. These patients should be assessed for the presence of infection and organ dysfunction, treatment of infection and organ dysfunction should be initiated early, and consideration should be given to transferring these patients to a higher level of care for closer monitoring.<sup>9</sup> The key benefits of the qSOFA score are that it is simple to measure and does not require laboratory testing; thus it can be performed rapidly and repeatedly.

After the release of the Sepsis-3 definition revisions, the SCCM SSC released a practice guideline update to provide clinical context to the guidelines and help providers expeditiously screen, identify and treat patients with sepsis. In this update, they reiterate adherence to the campaign recommendations. Providers should 'continue to use signs and symptoms of infection to promote early identification' and those with suspected infection should begin immediate management to include 'obtaining blood and other cultures...administering tailored antibiotics as appropriate, and simultaneously obtain laboratory results'.<sup>12</sup> For patients identified with organ dysfunction, the group emphasizes adherence to the 3-hour and 6-hour bundles.

### UPDATE ON EARLY GOAL DIRECTED THERAPY AND THE SURVIVING SEPSIS CAMPAIGN

Early goal-directed therapy (EGDT) became the mainstay of the approach to the patient with sepsis when in 2001 Rivers *et al* reported a survival benefit to those treated on a protocol versus standard therapy (46.5% vs 30.5%).<sup>13</sup> Following the report, the Society of Critical Care Medicine embraced this as part of the SSC. However, three subsequent randomized controlled trials and a meta-analysis of those trials have failed to replicate the same benefits reported by Rivers *et al*.<sup>14</sup> In 2016, a meta-analysis was reported examining the effects of EGDT (fluid resuscitation to goal central venous pressure (CVP), MAP, urine output and mixed venous oxygen saturation) on mortality in patients suffering from severe sepsis or septic shock. The study included more than 4000 patients from five randomized control trials. The study, although it had several limitations, also failed to find a statistically significant mortality benefit for EGDT.<sup>15</sup> There

**Box 2 Three-hour and 6-hour sepsis bundles**

Within 3 hours of presentation:

- ▶ Measure lactate
- ▶ Obtain blood cultures
- ▶ Bolus 30 mL/kg crystalloid for hypotension of lactate  $\geq 4$  mmol/L

Within 6 hours of presentation:

- ▶ If persistent hypotension (mean arterial pressure  $\leq 65$  mm Hg) despite adequate volume resuscitation, consider addition of vasopressors
- ▶ Frequently re-assess volume status and tissue perfusion for those with persistent hypotension and/or initial lactate  $\geq 4$  mmol/L
- ▶ Normalization of lactate

were modest decreases in mortality rates but they did not reach statistical significance.<sup>15</sup> A subsequent meta-analysis of 3723 patients comparing 90-day mortality between EGDT and usual care in a sicker cohort than prior studies also failed to find a benefit.<sup>14</sup> In addition, although EGDT was not harmful, it was associated with higher costs.<sup>14</sup>

With the increasing literature demonstrating a more modest to no effect of EGDT,<sup>14</sup> the SSC has continued to evolve in the components encompassed in the endorsed sepsis treatment bundles. The SSC also addresses a number of additional therapies beyond the original components of the Rivers *et al* trial which are felt to provide benefit for those suffering from sepsis and septic shock.<sup>11</sup> The Surviving Sepsis Guidelines of the SCCM were revised in 2012, updated in 2015 with the publication of the SCCM 'Updated Bundles in Response to New Evidence' and updated again with the publication of the 2016 International Guidelines for the Management of Sepsis and Septic Shock. A number of the 2012 and 2015 recommendations have changed in the newest iteration of the guidelines.

### Initial resuscitation

The 2012 guidelines recommended a 'protocolized, quantitative resuscitation... of patients with sepsis induced hypoperfusion as defined as hypotension persistent after initial fluid challenge or lactate  $\geq 4$  mmol/L'.<sup>11</sup> Care bundles were developed to reflect this goal and were revised in 2015 to specify goals to be met within the first 3 hours of care and those to be achieved by 6 hours. The goals of the first bundle should be achieved within the first 3 hours of 'presentation', defined as either arrival in the emergency department or the time of the first chart documentation consistent with the patient meeting criteria for sepsis or septic shock<sup>16</sup> (box 2). Time to completion of the 3-hour bundle has been shown to strongly correlate with mortality with an increased OR of 1.04 for each hour of delay.<sup>17</sup>

The 2016 guideline update continues to emphasize initial resuscitation with a 30 mL/kg crystalloid bolus within the first 3 hours of presentation.<sup>16</sup> After this initial bolus, resuscitation should be guided by either a 'repeat focused exam after initial fluid resuscitation including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings'<sup>16</sup> or two of the following: CVP, superior vena cava oxygenation saturation (ScvO<sub>2</sub>), bedside ultrasound or dynamic assessment of fluid responsiveness. The focused examination includes reassessment of physiological parameters such as heart rate, blood pressure, arterial oxygen saturation and urine output.<sup>1</sup> The dynamic assessment

includes response to straight leg raise, stroke volume variation and pulse pressure variation.<sup>1</sup>

These new guidelines do not include prescribed resuscitative targets such as CVP or ScvO<sub>2</sub> to guide resuscitation.<sup>18</sup> This is in contrast to the prior guidelines that advocated for achieving a CVP of 8–12 mm Hg, and an ScvO<sub>2</sub> of 70% or SvO<sub>2</sub> (mixed venous oxygen saturation) of 65%.<sup>11</sup> The movement away from a prescribed static variables such as CVP and ScvO<sub>2</sub> as a goal reflects the results of three recent clinical trials (PROMISE,<sup>19</sup> ARISE,<sup>20</sup> PROCESS<sup>21</sup>) that called in to question the utility and benefit of EGDT including the need for a mandatory central line.<sup>1,22</sup>

The guidelines also recommend obtaining a lactate in the first 3 hours with a goal of normalization by hour 6. Their lactate should also be re-measured if it was elevated initially. If a patient remains in shock at 6 hours or has an elevated lactate  $\geq 4$  mmol/L, the SSC recommends achieving a MAP  $\geq 65$  mm Hg for the typical patient with sepsis.<sup>11,23</sup> Clinicians should be cautious that although a MAP  $> 65$  mm Hg is appropriate for the average patient, this recommendation should be viewed as general guideline tailored to the specific patient comorbidities and physiological baseline.<sup>23</sup> By 6 hours after presentation, patients should receive vasopressors if they continue to be hypotensive with MAP  $\leq 65$  mm Hg despite initial resuscitation.

### Intravenous fluid therapy

Overall, the 2016 guidelines are similar to the 2012 guidelines in terms of fluid therapy recommendations. Crystalloids remain the recommended initial fluid strategy, but the 2016 guidelines suggest that either balanced crystalloids or normal saline is acceptable given that the available data demonstrate potential benefits to either solution. If high volume crystalloid is required, albumin should be considered in addition to crystalloids. Use of hydroxyethyl starches is still discouraged.<sup>18</sup> Further fluid resuscitation should be discontinued when there is no longer a physiological response.<sup>1</sup> Judicious fluid management is important to avoid the complications of pulmonary edema and volume overload.<sup>17</sup>

### Vasopressors

The following recommendations for vasoactive medications are similar to the 2012 guidelines. Norepinephrine continues to be the first-line agent for blood pressure support. Vasopressin at a dose of 0.03 units/minute should be considered to decrease the dose of norepinephrine or augment the MAP with goal MAP  $\geq 65$  mm Hg. Epinephrine is considered the second-line agent. Dopamine should be considered instead of norepinephrine only in patients with relative or absolute bradycardia who have a low risk of tachyarrhythmias. Dobutamine is still recommended for patients with persistent hypoperfusion despite adequate intravascular volume and vasopressor administration. However, the initial dobutamine dose is no longer specified in the 2016 guidelines.<sup>18</sup> In the 2016 update, phenylephrine is no longer recommended for treatment of septic shock outside of research protocols.

### Screening and diagnosis of septic source

The 2016 guidelines recommend that hospital systems have some type of performance improvement program that includes screening for patients at high risk of developing sepsis. The authors state that although the specifics of these programs may vary between hospitals, the commonality between them is 'a drive toward improvement in compliance with sepsis bundles



and practice guidelines such as SSC'.<sup>18</sup> With respect to diagnosis, the committee continues to recommend obtaining cultures (including aerobic and anaerobic blood) prior to initiating antibiotics, provided that this can be done in a timely fashion and will not delay starting antimicrobial therapy. These antimicrobials are ideally to be initiated within 1 hour of diagnosis of sepsis; however, this can be a challenging benchmark to reach.<sup>23</sup> A recent study demonstrated that the most significant impact on sepsis-related mortality was rapid administration of antibiotics<sup>17</sup> and emphasis should be placed on early initiation. Unlike the prior iteration, the 2016 guidelines do not recommend using 1,3- $\beta$ -D-glucan or anti-mannan antibody assays if invasive candidiasis is a potential diagnosis because the negative predictive value of these tests is too low to justify using them to guide therapy decisions.<sup>18</sup>

### Antimicrobials

The 2016 guidelines recommend administering empiric broad-spectrum antimicrobials that cover all likely pathogens, including bacteria and potentially viruses/fungi (depending on the risk factors of the patient). The initial empiric antibiotic regimen for patients in septic shock should include at least two antibiotics from different classes (combination therapy) directed toward the most likely pathogens. Treatment should be narrowed once the pathogen and its antimicrobial sensitivities are ascertained or when the patient demonstrates clinical improvement. However, patients with bacteremia, neutropenic sepsis or sepsis without shock do not require combination antibiotic therapy. This is a notable difference from the 2012 recommendation that neutropenic sepsis be treated with empiric combination antimicrobials. The authors note, however, that these recommendations do not preclude the use of multiple antibiotics if the goal is to expand the spectrum of pathogens covered.<sup>18</sup>

With respect to antibiotic duration, combination therapy (either empiric or targets) in patients with septic shock should be de-escalated to monotherapy within a few days if clinical improvement or with evidence of infection resolution.<sup>18</sup> This is slightly different than the 2012 guidelines, which recommend that no more than 3–5 days of empiric combination therapy and de-escalation as soon as the responsible organism and susceptibilities are known.<sup>11</sup> Total treatment duration should be 7–10 days for infections with sepsis or septic shock; however, some patients may warrant a prolonged course if they respond slowly to treatment, do not have source control, have bacteremia with *Staphylococcus aureus* or have immunological deficiencies or fungal/viral infections.

One new recommendation in 2016 is that shorter antibiotic courses are indicated in patients whose sepsis resolves rapidly after source previously, the 2016 authors recommend daily assessments for potential de-escalation of antimicrobials. Failure to normalize procalcitonin levels has recently been shown in a prospective multicenter study to be a significant predictor of mortality.<sup>24</sup> For those who initially appear septic, but do not subsequently have clinical evidence of infection, it can also be used to shorten or discontinue antimicrobial therapy.<sup>24</sup> It is important to note that blood cultures can be negative in up to one-third of all patients suffering from sepsis.<sup>5</sup> Lastly, the campaign does not recommend prophylactic antibiotics for non-infectious inflammatory states such as burns or severe pancreatitis.<sup>18</sup>

### Source control

Prompt identification of an infectious source is critical and, when source control is possible, intervention should occur as soon as

is practical from a medical and logistical standpoint. Intravascular access catheters that are a possible septic source should be removed as soon as alternative access is established. Neither of these recommendations is new from 2012, but the committee removed prior recommendations regarding the timing of intervention for peripancreatic necrosis and the suggestion that the least invasive technique be employed to achieve source control. Nevertheless, these principles are still included in the text of the 2016 guidelines and are likely sound despite there not being sufficient evidence for the committee to include them as recommendations.<sup>18</sup>

### Corticosteroids

The SSC recommendations for corticosteroids are simplified significantly in the 2016 guidelines, with many of the prior recommendations being removed due to the lack of sufficient supporting evidence. Corticosteroids should empirically be administered (hydrocortisone 200mg intravenous daily in divided bolus doses) in patients in septic shock only if vasopressor therapy and fluid resuscitation fail to achieve hemodynamic stability.<sup>18</sup> ACTH stimulation and random cortisol tests are also not recommended to determine need for initiation of steroid therapy. Despite a recommendation that steroids should be continued until vasopressors are discontinued,<sup>18</sup> there is still no clear consensus on the optimal initiation timing and total duration of steroid treatment.<sup>25</sup>

The evidence regarding the efficacy of corticosteroids for the attenuation of and prevention of septic shock remains conflicting. Yende *et al* in a recent editorial noted that the variation in results from clinical trials may reflect the 'vast array of biological effects' caused by corticosteroid exposure.<sup>25</sup> They further highlight that 'the relative balance of these effects can be difficult to predict'.<sup>25</sup> This is particularly important when using steroids in sepsis because patients exhibit early in the course of illness both elements of inflammation and immunosuppression. The addition of an immunosuppression agent, like corticosteroids, may have undesired effects on restoration of immune system balance whereas its anti-inflammatory properties may be highly desirable early in sepsis.<sup>5, 25</sup> Multiple ongoing large clinical trials are underway to further delineate the role of steroids in sepsis treatment (ClinicalTrials.gov identifier NCT01284452 for sepsis and acute respiratory distress syndrome; and ClinicalTrials.gov identifier NCT01448109 for septic shock).<sup>25</sup>

### Administration of blood products

There are no significant changes in the 2016 guidelines with respect to use of blood products and continued accumulation of new evidence supporting a more restrictive transfusion goal. Once patients have stabilized from their septic shock, transfusion of red blood cells should occur only if the hemoglobin is  $<7$  g/dL except in situations of persistent severe hypoxemia, myocardial ischemia, acute hemorrhage or active ischemic heart disease.<sup>26</sup> A recent post hoc analysis of the TRISS (Transfusion Requirements in Septic Shock) further investigated the role of the restrictive transfusion goal of 7 g/dL in those with significant comorbidities including chronic lung disease and hematologic malignancies.<sup>27</sup> There was no survival benefit to a more liberal transfusion threshold of 9 g/dL compared with 7 g/dL.<sup>27</sup>

Erythropoietin is not recommended to treat sepsis-related anemia. Fresh-frozen plasma (FFP) should only be given in patients with coagulation abnormalities and active bleeding or planned procedures; FFP is not indicated solely for disordered coagulation identified on laboratory testing. However, platelets

should be transfused when levels drop to  $\leq 10\,000/\text{mm}^3$  in the absence of bleeding or below  $\leq 20\,000/\text{mm}^3$  if there is a high risk of bleeding.<sup>11</sup> For patients with active bleeding or planned surgery/invasive procedures, transfusion is recommended to platelet level of  $50\,000/\text{mm}^3$ .<sup>11</sup>

### Mechanical ventilation

Patients suffering sepsis-induced ARDS should still be managed according to ARDSnet protocols, including ventilation to a tidal volume of 6 mL/kg predicted body weight. The initial plateau pressure target should be  $\leq 30$  cm H<sub>2</sub>O. Positive end-expiratory pressure (PEEP) should be used to prevent alveoli collapse and the resulting barotrauma from repeated inflation/collapse cycles. To this end, higher PEEP levels are suggested for patients with moderate-to-severe ARDS.<sup>11</sup> The recommendations regarding prone positioning in patients with sepsis-induced ARDS have been updated to suggest prone position for patient with PaO<sub>2</sub>/FIO<sub>2</sub> ratio  $\leq 150$  mm Hg, as opposed to the previously recommended PaO<sub>2</sub>/FIO<sub>2</sub> ratio  $\leq 100$  mm Hg.<sup>11,18</sup>

In the absence of tissue hypoperfusion, the SSC continues to recommend a conservative fluid infusion strategy in patients with sepsis-induced ARDS. They also recommend spontaneous breathing trials and the use of a weaning protocol in mechanically ventilated patients who can tolerate weaning, but the 2016 guidelines does not offer specific criteria to use when determining which patients should be considered for extubation.<sup>11,18</sup> The 2016 guidelines still recommend employing neuromuscular blocking agents for  $\leq 48$  hours in patients with sepsis-induced ARDS and PaO<sub>2</sub>/FIO<sub>2</sub> ratio  $\leq 150$  mm Hg.<sup>18</sup>

### Sedation, glucose control, renal replacement therapy and bicarbonate therapy

The 2016 recommendations for sedation, glucose control, renal replacement therapy (RRT) and bicarbonate therapy remain essentially unchanged from 2012. To summarize, continuous or intermittent sedation in mechanically ventilated should be minimized when possible. One potential therapeutic agent to achieve lighter sedation, dexmedetomidine, was recently investigated in a randomized controlled trial reported in April 2017 in *JAMA*.<sup>28</sup> Dexmedetomidine is a highly selective alpha<sub>2</sub> agonist sedative that has potential anti-inflammatory properties. Although it did not improve mortality or ventilator-free days compared with standard sedation regimens including propofol and midazolam, but it did achieve better control of light sedation<sup>28</sup> and it would be reasonable to consider a sedation strategy favoring dexmedetomidine.

Glucose levels above 180 mg/dL should be treated, with a target glucose of  $< 180$  mg/dL. Glucose levels should be measured every 1–2 hours until a stable insulin regimen is reached and every 4 hours thereafter. Sodium bicarbonate should be reserved to improve hemodynamics or decrease vasopressor needs for patients with a pH  $< 7.15$ . Continuous or intermittent RRT is indicated in patients with sepsis and acute renal failure, with continuous therapies being preferred in hemodynamically unstable patients to minimize further hypotension.<sup>11</sup> New to the 2016 guidelines is a recommendation to avoid using RRT in patients with sepsis and acute kidney solely for an increase in creatine or oliguria in the absence of other indications for hemodialysis.<sup>18</sup>

### Venous thromboembolism and stress ulcer prophylaxis

All patients should receive DVT prophylaxis, preferably with low molecular weight heparin as opposed to unfractionated

heparin in the absence of contraindications. Mechanical prophylaxis should be used in addition to pharmacological prophylaxis and in patients for whom pharmacological prophylaxis is contraindicated.<sup>18</sup> Stress ulcer prophylaxis with H<sub>2</sub> blockers or proton pump inhibitors (PPI) should be used only in patients with sepsis or septic shock and risk factors for upper gastrointestinal bleeding. There is no longer a preference in the guidelines for PPIs over H<sub>2</sub> blockers.<sup>18</sup>

### Nutrition

Early enteral nutrition should be given in patients with sepsis or septic shock who can tolerate enteral feeding. Both trophic (500 kcal/day limit) and full enteral feeds may be appropriate in certain circumstances; there is no longer a recommendation to avoid full enteral feeds during the first week in all patients with sepsis or septic shock.<sup>11,18</sup> If trophic feeds are the initial feeding strategy, the feeding rate should be increased based on patient tolerance. The 2016 guidelines include a new recommendation to avoid routine monitoring of gastric residuals, instead measuring them only in patients who demonstrate feeding intolerance or who are considered to be at high risk of aspiration. Also new to the 2016 guidelines is a suggestion to use prokinetic agents and place feeding tubes in a postpyloric position in patients with feeding intolerance.<sup>18</sup>

### Goals of care

The SSC continues to recommend engaging in early goals of care discussion with patients and family members, using palliative care strategies when appropriate. These discussions should be initiated within 72 hours of ICU admission.<sup>18</sup>

### CONCLUSIONS

The last few decades of sepsis research have helped clinicians better understand the importance of identifying sepsis early and treating aggressively. Nonetheless, there is still much debate about how to identify these patients and which criteria are most predictive for the development of sepsis and septic shock. The recent updates, particularly the recommendations regarding SOFA and qSOFA scores, operationalize the definitions of sepsis into a clinically useful model that can be used by clinicians to identify the patients most at risk of deterioration. The lack of progress in mortality reduction in sepsis treatment despite extraordinary investment of research resources underscores the variability in patients with sepsis. No single solution is likely to be universally beneficial and sepsis continues to be an entity that should receive high priority for the development of precision health approaches for treatment.

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