The incidence of sepsis and mortality rates have remained consistent over the years despite advances in therapy, with mortality rates reported to be as high as 23.6% for patients diagnosed with septic shock.1,2 However, since 2014, how we identify sepsis and how we treat affected patients has changed substantially.3,4 In addition, although the topic is beyond the scope of this article, controversy remains about which criteria should be used when screening for and diagnosing sepsis.5 The purpose of this article is to provide an overview of some of the updates to the Surviving Sepsis Campaign (SSC) guidelines, adjustments in traditional approaches to the management of sepsis, and novel therapies that have yet to be described extensively in the literature, such as the use of ascorbic acid, thiamine, and angiotensin II.

Surviving Sepsis Campaign Updates

The main update in the 2016 SSC guideline recommendations was that the use of early goal-directed therapy (EGDT) did not confer a mortality benefit compared with standard of care.6 In the important studies on which the 2016 SSC recommendations were based, the framework of EGDT was still used in the standard-of-care groups (early antibiotic administration and fluids for patients with hypotension); however, dynamic variables to assess fluid responsiveness were promoted over the use of static variables.4

In 2018 the SSC released another update to their guidelines, recommending that fluid resuscitation and antibiotics should not be lumped into 3- and 6-hour bundles, but should be started within 1 hour of recognition of possible sepsis or septic shock.7 However, whether this strategy should be considered a best practice remains controversial. In May 2018, the Infectious Diseases Society of America (IDSA) responded by not endorsing the SSC guidelines, especially as they pertained to a strict 1-hour bundle, because of concerns that a significant percentage of patients might receive antibiotics who are not actually infected.8 By September 2018, additional concerns had been raised related to the release of the 1-hour bundle; the Society of Critical Care Medicine and the American College of Emergency Physicians released a joint statement advising that hospitals in the United States should not implement the 1-hour bundle.
as routine care. The 2 groups announced they would be organizing a meeting to provide guidance on treatment strategies for patients with potential sepsis. Delaying antibiotics is known to increase mortality up to 8% for every hour of delay in administration to patients with septic shock. However, according to the IDSA, 40% of patients in the intensive care unit (ICU) who receive antibiotics to manage potential sepsis may not be infected. For now, initiating early antibiotics for patients believed to have sepsis is a reasonable strategy, but it remains to be seen how and whether the bundled care initially promoted by the SSC will be endorsed as a best practice.

### Traditional Management Strategies

#### Fluid Stewardship

Fluids remain a central part of the treatment of patients with sepsis, though overuse of fluids can lead to harmful effects in some critically ill patients. Fluid stewardship may be considered a coordinated effort to ensure selection of appropriate fluids and volumes based on individual clinical needs. Similar to antibiotic stewardship—in which antibiotic selection, dose, and duration are assessed frequently—fluids should be reassessed continually for patients with sepsis.

Fluids used in the resuscitation of patients with sepsis may be categorized as crystalloids, such as normal saline (NS), and colloids, such as albumin. Most data suggest that colloids confer no mortality benefit compared with crystalloid therapy. Also, colloids are associated with a higher cost than crystalloids, higher rates of renal replacement therapy, and increased use of blood products. With the higher cost, increased adverse effects, and lack of mortality benefit associated with colloid use, the SSC recommends the use of crystalloids for initial resuscitation in sepsis.

Advantages of crystalloid use for resuscitation include the ability to expand extracellular volume, especially in hypovolemic or distributive shock; disadvantages include increased rates of edema with large volume resuscitation and increased incidence of acute kidney injury (AKI), especially when associated with use of chloride-rich solutions such as NS.

Although the SSC guidelines recommend crystalloids as the initial fluid of choice for patients with sepsis, they do not recommend which crystalloid should be administered. The Table compares concentrations of components in 2 of the most widely used crystalloid solutions in critically ill patients: NS and lactated Ringer’s (LR) solution. LR is one of several “balanced” crystalloid fluids that closely resembles physiologic chloride concentrations. Hyperchloremic metabolic acidosis can be caused by chloride-rich solutions such as NS and has been shown to reduce overall renal blood flow via a feedback mechanism that regulates filtration. When decreased chloride is being filtered through the kidneys, serum chloride concentration decreases, which decreases serum pH. Overall, the decrease in renal blood flow can result in AKI and associated adverse outcomes in patients with sepsis.

Large-volume resuscitation with chloride-rich fluids, such as NS, generally has been thought to result in higher rates of AKI compared with balanced crystalloids. Raghunathan et al compared outcomes-based data for balanced crystalloids and NS in critically ill patients with sepsis who were not undergoing surgical procedures. Patients in the balanced crystalloid group had a lower risk of in-hospital mortality than did the NS group (19.6% vs 22.8%; relative risk 0.86; 95% confidence interval [CI], 0.78-0.94). No significant differences were found in the incidence of AKI between the treatment groups. The median crystalloid volumes used for the NS and balanced crystalloids groups were 5 and 7 L, respectively. The researchers concluded that balanced crystalloids were associated with lower in-hospital mortality but

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**Table: Concentration of Components in Normal Saline Versus Lactated Ringer’s Solution**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal Saline</th>
<th>Lactated Ringer’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium, mEq/L</td>
<td>154</td>
<td>130</td>
</tr>
<tr>
<td>Potassium, mEq/L</td>
<td></td>
<td>4.5</td>
</tr>
<tr>
<td>Chloride, mEq/L</td>
<td>154</td>
<td>109</td>
</tr>
<tr>
<td>Calcium, mEq/L</td>
<td></td>
<td>2.7</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>Osmolarity, osmol/L</td>
<td>308</td>
<td>273</td>
</tr>
<tr>
<td>pH</td>
<td>5.5</td>
<td>6.5</td>
</tr>
</tbody>
</table>
recommended further validation with a larger randomized controlled trial. Some limitations of the study included its retrospective nature and identification of sepsis based on claims data/coding. However, this trial remains one of the largest data sets (>50,000 patients) comparing fluid choice for resuscitation in patients with sepsis. Despite several limitations evident in the study, use of balanced crystalloids is a more reasonable option compared with NS for large-volume resuscitation of patients with sepsis.

The SMART (Isotonic Solutions and Major Adverse Renal Events Trial) study evaluated balanced crystalloids versus saline in critically ill adults in the largest randomized controlled trial to date comparing both therapies. More than 15,000 patients admitted to the ICU were randomized to receive either NS or balanced crystalloids (LR or another type). The primary outcome was the composite incidence of death, initiation of renal replacement therapy, or renal dysfunction. The study population was composed entirely of critically ill patients; however, a subgroup analysis was performed in patients with sepsis, even though this subgroup accounted for only 5% of the study population. Patients in the sepsis subgroup analysis who received balanced crystalloids versus NS had a lower incidence of the primary composite outcome (odds ratio, 0.8; 95% CI, 0.67-0.94; P = .02). The median volume of fluid received was about 1 L for each group.

These findings must be interpreted with caution, because the study was not powered to detect a difference in the subgroup analysis and patients were identified as having sepsis from coding data. The fact that patients with sepsis received only 1 L of fluid for total resuscitation could suggest that these patients were less acutely ill than were patients in the rest of the study population; however, overall, more than one-third of patients required mechanical ventilation and 25% of the study population received vasopressor support. Lastly, whereas the study design allowed for crossover between each group, treating clinicians were unblinded, making provider bias a possibility. Although the sepsis subgroup was small, findings from that subanalysis were consistent with previously reported data. Therefore, LR could be considered a viable option for resuscitation and may confer some mortality benefit.

The SSC guidelines recommend 30 mL/kg of crystalloid for initial resuscitation in patients who are hypotensive or have a lactate concentration of more than 4 mmol/L. The SSC gives this recommendation a strong rating; however, it is based on low-quality evidence. Patients with shock secondary to sepsis typically have intravascular depletion and require fluid for adequate resuscitation. Although large-volume administration of crystalloids has been shown to increase the incidence of AKI, pulmonary edema, and congestive heart failure, these risks should not delay fluid resuscitation for patients with shock secondary to sepsis. What remains in doubt is whether the 30-mL/kg bolus of crystalloid recommended by the SSC is appropriate for all patients.

Andrews et al evaluated the effects of an early resuscitation protocol, which included the comparison of large-volume versus conservative fluid management in 212 adult patients with sepsis. Patients in the large-volume management group received 2 L of NS within 1 hour of resuscitation followed by 2 L over 4 hours, whereas the conservative fluid management group received 2 L total over 6 hours. The primary outcome of in-hospital mortality occurred in 48.1% of the large-volume resuscitation group compared with only 33% of the conservative fluid management group (relative risk 1.46; 95% CI, 1.04-2.05). The researchers concluded that large-volume resuscitation was associated with worsening hypoxemia and tachypnea, which may have resulted in higher in-hospital mortality.

As a randomized controlled trial assessing 2 resuscitation strategies for patients with sepsis, this study was well designed. One limitation, however, was exclusive use of NS for resuscitation in light of a known mortality risk associated with NS use. Also, the findings are not generalizable to all institutions because the trial was conducted in a resource-limited setting—a factor that may have influenced the high mortality rates seen in both treatment groups. Overall, the study highlights the importance of adequate fluid resuscitation but suggests that large-volume resuscitation could be associated with increased mortality in patients with sepsis.

A prospective cohort study evaluated fluid intake and output for 7 days for more than
170 consecutive adult patients treated for sepsis to determine whether a positive fluid balance over a hospital course was an independent prognostic factor for outcomes.\textsuperscript{19} Daily fluid intake was higher in the nonsurvivor group than in the survivor group (mean [SD], 59 [24] vs 48 [23] mL/kg; \( P = .03 \)). The daily fluid balance was 2 times larger in the nonsurvivor group than in the survivor group (29 [22] vs 13 [19] mL/kg; \( P < .001 \)), which, adjusted for multiple variables, was shown to be an independent risk factor for higher in-hospital mortality (adjusted hazard ratio 1.01 [1.007-1.022] per mL/kg increase; \( P < .001 \)). Although this study was limited by its small sample size and possible observer bias due to nonblinding, it nevertheless highlights the detrimental effects of overresuscitation in patients with sepsis. Fluids can be harmful at supratherapeutic volumes; the study underscores the importance of fluid stewardship and continual assessment of the need for fluids throughout a patient’s course of treatment.

**Fluid Volume Assessment**

Fluid boluses are initially administered to replace intravascular depletion in patients with sepsis; however, they result in an increase in venous return to the heart that increases left ventricular filling pressures (LVFP).\textsuperscript{20} This increase in LVFP leads to a subsequent increase in stroke volume (SV) and cardiac output (CO). However, once LVFP has reached its maximum, fluid administration is counterproductive and could hinder CO. Knowing whether a patient will be fluid responsive is critical for avoiding volume overload. Passive leg raising (PLR), ultrasound-guided echocardiography, and noninvasive dynamic tests, which measure SV in some capacity, all have been evaluated as strategies to assess fluid responsiveness.\textsuperscript{20} No specific strategy is currently recommended over another, but recent data suggest that dynamic variables (eg, PLR, ultrasound-guided echocardiography) may be more sensitive and specific for identifying patients who are fluid responsive compared with static variables (eg, vital signs, capillary refill).\textsuperscript{20}

A meta-analysis published in 2017 evaluated the incorporation of dynamic tests into EGDT (ie, a 30-mL/kg bolus) to monitor fluid responsiveness.\textsuperscript{20} The authors found that ICUs that used fluid responsiveness measures had decreased overall mortality, ICU length of stay, and duration of mechanical ventilation compared with the standard of care. Limitations of the study included the trial selection, which had high risk for bias; use of differing dynamic tests; and the inability to generalize to medical patients because most patients included had undergone surgery.

Despite these limitations, data in the study supported the use of monitoring fluid responsiveness in critically ill patients.\textsuperscript{20} Measuring fluid responsiveness ensures that patients are monitored for an optimal volume that is patient specific and not a “one-size-fits-all” model. Monitoring fluid responsiveness and exercising fluid stewardship when appropriate can improve the treatment of patients with sepsis.

Bedside nurses play a critical role with respect to fluid stewardship for patients with sepsis. If SV measurement is available, a bedside nurse could consider a patient fluid responsive if he or she has a 10% to 15% increase in SV after a fluid challenge; considering additional fluid resuscitation thereafter would be feasible.\textsuperscript{20,21} If the patient has less than a 10% increase in SV after a fluid challenge, then considering alternatives for resuscitation would be reasonable. If SV or CO data are not available, assessing PLR would be a reasonable alternative. If the patient has a 10% increase in pulse pressure (measured from an arterial catheter if possible) following PLR, he or she would be considered fluid responsive and additional fluids should be considered. Static variables such as heart rate and blood pressure should not be used routinely for identifying patients who are fluid responsive. Because of its relatively low interobserver reliability, capillary refill also should not be used routinely to assess for fluid responsiveness.

**Adjunctive Therapies**

**Ascorbic Acid and Thiamine**

Ascorbic acid (vitamin C) and thiamine have been evaluated for their use in combination therapy or as monotherapy in patients with severe sepsis and septic shock. Vitamin C functions as an antioxidant and cofactor in many biochemical reactions.\textsuperscript{22} Thiamine also is vital in many biochemical reactions of cellular metabolism; like vitamin C, it is associated with deficiencies in critically ill patients. A retrospective trial compared the combination of intravenous vitamin C, thiamine, and hydrocortisone (CTH) with standard of care.
for patients with septic shock. The study included 47 patients stratified into each group; the CTH treatment group had a lower mortality rate than did the control group (8.5% vs 40.4%; \( P = .001 \)). The researchers concluded that early use of the combination of CTH had a positive organ-protective effect, with an overall decrease in mortality in patients with sepsis. Although the use of thiamine and vitamin C is not new for septic or critically ill patients, this study provides some of the first meaningful outcomes data associated with their use. Although this therapy has garnered attention on social media, the study had numerous limitations that call for a cautious interpretation of the findings. For example, the trial included fewer than 100 patients, lacked blinding or randomization, and had no concurrent control group for comparison; the 2 groups were studied during different time frames. The trial nevertheless has sparked interest in this combination therapy, and larger randomized controlled trials are being conducted to ascertain its efficacy and safety in patients with sepsis. At this point, insufficient evidence exists to support routine use of this “sepsis cocktail.”

Vasopressin

Norepinephrine remains the initial guideline-recommended vasopressor for patients in whom hypotension persists after adequate fluid resuscitation. If norepinephrine alone does not maintain adequate blood pressure and tissue perfusion, adding a secondary agent is a reasonable next step. No consensus has been reached on a threshold for adding additional vasopressor support, but vasopressin remains a commonly used secondary agent for patients with shock secondary to sepsis. Vasopressin offers a different mechanism of vasoconstriction by acting on vasopressin-1 receptors in the vascular smooth muscle and may have a benefit over catecholamine vasopressors in the presence of acidosis. Patients in septic shock have lower levels of endogenous vasopressin, which may contribute to hypotension.

Norepinephrine may lead to higher incidences of AKI than vasopressin because norepinephrine acts on both the afferent and efferent renal arteries, thereby decreasing glomerular filtration rate (GFR); vasopressin acts only on the efferent arteries, increasing GFR. The VANISH (Vasopressin vs Norepinephrine as Initial Therapy in Septic Shock) study was a quasi-factorial, multicenter, randomized trial conducted in the United Kingdom that compared early initiation of vasopressin with norepinephrine for the management of septic shock, with the primary outcome of 28-day survival free from kidney failure. A total of 409 patients were included, most of whom were started on norepinephrine, with vasopressin added approximately 3.5 hours after onset of shock. The results showed no significant difference in the primary outcome, suggesting that early initiation of vasopressin does not reduce rates of kidney failure or mortality. Patients in this study received a median of 1 L of fluid for resuscitation, which was lower than the SSC-recommended 30-mL/kg bolus. Although the rate of dialysis was lower in the vasopressin group compared with the norepinephrine group, the decision to initiate dialysis was at the provider’s discretion, which introduced risk for bias and type I error. Overall, considering vasopressin as a second-line agent is still appropriate as recommended by the SSC guidelines; however, additional studies are needed to determine optimal timing for implementation of vasopressin therapy in patients with sepsis.

Angiotensin II

The newest agent approved by the US Food and Drug Administration (FDA) for sepsis and other vasodilatory shock is synthetic human angiotensin II (ATII), which offers a novel mechanism of action by promoting vasoconstriction and fluid retention through the renin-angiotensin-aldosterone system. The drug was granted FDA approval based on results of the Angiotensin II for the Treatment of High-Output Shock (ATHOS-3) study. A total of 321 patients were enrolled to receive ATII or placebo in addition to vasopressors. The primary outcome was a mean arterial pressure (MAP) of at least 75 mm Hg without an increase in vasopressor requirements or an increase in MAP of 10 mm Hg from baseline. Synthetic human angiotensin II was initiated at 20 ng/kg per minute and then titrated in increments of 15 ng/kg per minute every 5 minutes to a maximum dose of 80 ng/kg per minute in the first 3 hours and 40 ng/kg per minute after the initiation phase for no more than 48 hours. The primary endpoint was met in 69.9% of patients given ATII compared with 23.4% in the placebo group \( (P < .001) \). The study was not adequately powered to detect a difference in
mortality. Significant safety concerns were raised from this study because ATII was noted to have a higher incidence of thromboembolic events (12.9% vs 5.1%), delirium (5.5% vs 0.6%), hypokalemia (8% vs 6.3%), acidosis (5.5% vs 0.6%), and peripheral ischemia (4.3% vs 2.5%) compared with placebo. However, ATII is more costly than current options. Therefore, with an unclear mortality benefit, safety concerns, and higher costs compared with current options, ATII should not be considered for routine use at this time. Further research is needed to define an expanded role for ATII in the management of septic shock.

Conclusion
Whereas knowledge of sepsis pathophysiology has improved, the SSC core recommendations of early antibiotics and fluid resuscitation have remained steadfast. Despite these recommendations, frontline staff must be vigilant to ensure patients are receiving the appropriate fluid and volume. Whether novel therapies such as ATII, vitamin C, or thiamine will be included in a future version of the SSC guidelines is unknown; however, based on current evidence, such novel therapies should not be used for routine sepsis management. Even established therapies, such as vasopressin, require further exploration to ensure benefits are maximized and risks are minimized.

REFERENCES
This article has been designated for CE contact hour(s). The evaluation demonstrates your knowledge of the following objectives:

1. Compare the risks and benefits of administering colloids and crystalloids, including saline and chlorine balanced solutions, for fluid resuscitation in patients with septic shock.
2. Explain techniques that can be performed at the bedside to assess a patient’s volume status as part of fluid stewardship.
3. Describe treatment options for refractory hypotension in patients with septic shock including vasopressin and angiotensin II.

Contact hour: 1.0
Pharmacology contact hour: 0.25
Synergy CERP Category: A

To complete evaluation for CE contact hour(s) for this article #ACC9312, visit www.aacnacconline.org and click the “CE Articles” button. No CE evaluation fee for AACN members. This expires on March 1, 2022.

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