

## REVIEW

## Sepsis: An Update in Management

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Hospitalists are a critical link in providing evidence-based care for patients with sepsis across the disease spectrum, from early recognition to recovery. The past decade of sepsis research has led to significant findings that will change clinical practice for hospital medicine practitioners. Although the incidence of severe sepsis in the United States has continued to rise, in-hospital mortality has declined. Management of the spectrum of sepsis disorders is no longer restricted to the intensive care unit (ICU). This review article will provide

an update in the management of sepsis for hospitalists based on recently published pivotal studies. The expanding evidence base in sepsis includes early goal-directed therapy/clinical endpoints/sepsis bundles, antibiotics and source control, volume resuscitation, ICU considerations (including the use of insulin and corticosteroids), mortality/complications, and the newly recognized condition of “sepsis survivorship”. *Journal of Hospital Medicine* 2015;10:746–752. © 2015 Society of Hospital Medicine

Sepsis is “one of the oldest and most elusive syndromes in medicine,” and remains a significant contributor to morbidity, mortality, and healthcare expenditure.<sup>1</sup> A 1992 American College of Chest Physicians and Society of Critical Care Medicine consensus conference statement introduced the systemic inflammatory response syndrome (SIRS) into the medical lexicon, along with definitions of sepsis, severe sepsis, and septic shock.<sup>2</sup> A 2003 consensus panel expanded the list of signs and symptoms associated with sepsis, and warned that the findings of SIRS do not differentiate sepsis from other noninfectious conditions.<sup>3</sup> The terminology is important, as these definitions resulted in a shift of the label of the syndrome of infection complicated by end-organ dysfunction from “sepsis” to “severe sepsis” or “septic shock.” Overlap of these terms has implications for categorizing such infections for the purpose of investigation, estimating epidemiology and outcome, and coding, billing, and reimbursement.<sup>1</sup>

Traditional definitions of the spectrum of sepsis disorders are outlined in Table 1,<sup>2,3</sup> and it is important to note that an update to these definitions is anticipated in the near future. A recent publication has called into question the sensitivity and categorical requirement of at least 2 SIRS criteria to define severe sepsis.<sup>4</sup> This study of more than 1 million patients from 172 intensive care units (ICUs) in Australia and New Zealand from 2000 to 2013 found that the

cutoff of 2 SIRS criteria to define severe sepsis excluded 1 in 8 patients with infection and end-organ hypoperfusion. SIRS-negative severe sepsis patients experienced the same mortality as SIRS-positive patients. In addition, adjusted analysis determined a stepwise increase in mortality risk associated with each additional SIRS criterion without a transition point in risk noted at 2.<sup>4</sup>

From 1979 through 2000, there were over 10 million reported cases of sepsis, which accounted for 1.3% of all hospitalizations in the United States.<sup>5</sup> Normalized to the population distribution of the 2000 US Census, there was an annualized increase in sepsis cases of 8.7%. A 2011 report revealed rates of hospitalization for patients with septicemia or sepsis in the United States more than doubled from 2000 through 2008.<sup>6</sup> Patients with sepsis experienced longer length of stay than other inpatients and were 8 times more likely to die during hospitalization.<sup>6</sup> Estimates of severe sepsis incidence are complicated by how acute organ dysfunction is defined and whether it is related to infection. As of 2001, the number of severe sepsis cases in the United States was believed to exceed 750,000 and comprise approximately 10% of ICU admissions.<sup>1</sup> The incidence of severe sepsis cases in the United States continues to rise.<sup>7–9</sup> However, a more than doubling of the use of sepsis International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes from 2004 through 2009 has also been noted.<sup>8</sup> Based on ICD-9-CM codes indicating the presence of sepsis and organ system failure, the number of severe sepsis hospitalizations per 100,000 persons in the United States increased from 143 in 2000 to 343 in 2007.<sup>7</sup> Total hospital costs for patients with severe sepsis were estimated to increase 57%, from \$15.4 billion in 2003 to \$24.3 billion in 2007.<sup>9</sup> The Agency for Healthcare Research and Quality considered septicemia the most expensive medical condition in the United States in a 2011 data

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**TABLE 1.** Traditional Definitions of Sepsis Spectrum Disorders<sup>2,3</sup>

	Definition
SIRS	The systemic inflammatory response to a variety of severe insults. Requires 2 of the following: Temperature >38°C or <36°C Heart rate >90 beats/minute Respiratory rate >20 breaths/minute or partial pressure of carbon dioxide (PaCO <sub>2</sub> ) <32 mm Hg White blood cell count >12,000 or <4,000 cells/μL or 10% immature ("band") forms
Sepsis	The systemic response to infection, with SIRS criteria met in the setting of documented or strongly suspected infection
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion (including but not limited to lactic acidosis, oliguria, or acute alteration in mental status), or hypotension (systolic blood pressure <90 mm Hg or >40 mm Hg below baseline).
Septic shock	Sepsis-induced hypotension despite adequate volume resuscitation (20–30 mL/kg) with perfusion abnormalities including but not limited to lactic acidosis, oliguria, or acute alteration in mental status

NOTE: Abbreviations: SIRS, systemic inflammatory response syndrome.

brief, with annual aggregate hospital costs exceeding \$20 billion.<sup>10</sup>

Although many hospitalists care for patients in the ICU and other higher acuity or step-down units, a significant proportion of patients with severe sepsis receive care on a general medical floor.<sup>11–13</sup> Sepsis is also clearly not an issue restricted to patients on internal medicine services. Of over 360,000 general surgery patients from 2005 to 2007, the incidences of sepsis (2.3%) and septic shock (1.6%) greatly exceeded those of pulmonary embolism (0.3%) and myocardial infarction (0.2%). In this cohort, the need for emergency surgery and the presence of any comorbidity increased the number of sepsis cases.<sup>14</sup>

Despite difficulties obtaining exact estimates of case numbers, the following appears true: the spectrum of sepsis disorders (including severe sepsis and septic shock) remains a common, costly, and increasing clinical entity that is encountered by hospital medicine physicians in a variety of inpatient settings. This review will provide an update for hospitalists based on many important studies that have been published since the last review of this topic in this journal.<sup>15</sup> The expanding evidence base in sepsis includes early goal-directed therapy (EGDT), clinical endpoints, and bundles of care for sepsis; antibiotics (choice and timing); volume resuscitation; ICU considerations, including the use of insulin and corticosteroids; and mortality, complications, and the advent of the condition of "sepsis survivorship."

## EARLY GOAL-DIRECTED THERAPY

A 2001 prospective, randomized trial of EGDT initiated in the emergency department (ED) for patients with severe sepsis and septic shock resulted in an impressive 16% reduction of in-hospital mortality

compared to standard therapy.<sup>16</sup> The intervention protocol included central venous catheter placement and a 500-mL bolus of crystalloid every 30 minutes to establish a central venous pressure (CVP) of 8 to 12 mm Hg. Vasopressors were used to maintain a mean arterial pressure (MAP) greater than 65 mm Hg, and patients with a MAP greater than 90 mm Hg were given vasodilators. Patients with a central venous oxygen saturation (ScvO<sub>2</sub>) of less than 70% received red blood cell transfusion with a goal hematocrit of 30%. If central venous oxygen saturation remained less than 70% despite these interventions, dobutamine was used for inotropic effect until this goal was achieved or was limited by tachycardia or hypotension.<sup>16</sup>

These results prompted inclusion of the specific hemodynamic targets (CVP, MAP, and ScvO<sub>2</sub>) into the original 2004 Surviving Sepsis Campaign guidelines and spurred a decade of interest worldwide.<sup>17</sup> The incremental importance of these individual components in managing severe sepsis and septic shock has since come under scrutiny. A recent randomized trial suggested that EGDT guided by venous lactate clearance of >10% was noninferior to the goal ScvO<sub>2</sub> of >70%. However, only 10% of the study population required transfusion or dobutamine.<sup>18,19</sup> Prospective ICU data on lactate-guided therapy<sup>20</sup> supported the revised 2012 Surviving Sepsis Campaign (SSC) guidelines to recommend lactate normalization as part of initial resuscitation efforts, particularly when ScvO<sub>2</sub> is not available.<sup>21</sup> Lactate measurement may assist in recognition of cases of severe sepsis or septic shock and provide valuable triage information, as serum lactate has been shown to predict mortality from severe sepsis independent of shock or organ failure.<sup>22</sup> In a retrospective study of patients presenting to the ED with sepsis, a lactate >4 mmol/L was associated with progression to septic shock within 4 to 48 hours.<sup>23</sup>

Our understanding of the specific benefits of EGDT is far from complete, as 3 recent large prospective, multicenter, randomized trials ProCESS (Protocolized Care for Early Septic Shock), ARISE (Australasian Resuscitation In Sepsis Evaluation), and ProMISe (Protocolised Management in Sepsis) did not show EGDT protocols to be superior to usual care.<sup>24–26</sup> Interpreted collectively, the benefit of EGDT may not be from targeting specific physiologic parameters, but rather from the early recognition of sepsis and the appropriate use of well-supported interventions like aggressive fluid resuscitation and early/efficacious antibiotics.<sup>27</sup>

Although the precise benefit of EGDT as a package versus its individual components remains in question, we have a decade of experience in delivering this care as an integral component of the bundles put forth in the SSC guidelines.<sup>28</sup> Observational and retrospective studies have shown increased compliance with guidelines and improved mortality after implementing these protocols, although early bundles for severe sepsis

included therapies that have subsequently been called into question on an individual basis like drotrecogin alfa (activated) and glucocorticoid therapy.<sup>29–31</sup> The mortality benefit from sepsis bundles deserves further explanation, although education and early recognition are likely contributory.<sup>32</sup>

Several studies evaluated individual components of EGDT. The TRISS (Transfusion Requirements in Septic Shock) trial randomized ICU patients with septic shock to 2 different red blood cell transfusion strategies, and found no mortality benefit or reduction in ischemic events for patients transfused at a hemoglobin of 9 g/dL compared to the 7 g/dL threshold.<sup>33</sup> The SEPSISPAM (Assessment of Two Levels of Arterial Pressure on Survival in Patients With Septic Shock) trial compared the MAP goal of 65 to 70 mm Hg to 80 to 85 mm Hg for patients with septic shock in a randomized, multicenter trial.<sup>34</sup> Although there was no difference in 28-day mortality, more atrial fibrillation was diagnosed in the higher target group. For patients with chronic hypertension, targeting the higher MAP led to less renal injury and reduced the need for renal-replacement therapy.<sup>34,35</sup> Identifying specific subsets of patients with sepsis who benefit most from particular therapies should help clinicians set patient-specific goals and targets.

Although we can expect additional studies to provide further guidance, it is reasonable at present to adhere to protocols designed to improve timely sepsis detection and management with aggressive volume resuscitation, early/efficacious antibiotic administration, and effective infection source control.

## ANTIBIOTICS AND SOURCE CONTROL

Administration of broad-spectrum antibiotics has long been the cornerstone of sepsis management. Timely antibiotic infusion is an integral part of the 2004 and 2012 SSC guidelines,<sup>17,21</sup> with the caveat that blood cultures should be obtained prior to antibiotic therapy provided that no significant delay (>45 minutes) occurs.<sup>21</sup> Recent studies have begun to address fundamental clinical questions, including the timing of antibiotic administration and the efficacy of empiric antibiotic choice. A landmark retrospective cohort study of ICU patients with septic shock demonstrated survival to hospital discharge was highest in patients who received antibiotics within the first hour of hypotension.<sup>36</sup> Survival decreased on average by 7.6% with each hour that antibiotics were delayed. Only 50% of patients with septic shock in this study received effective antibiotic therapy within 6 hours of documented hypotension.<sup>36</sup> A subsequent retrospective, single-center cohort study of ED patients with severe sepsis or septic shock undergoing EGDT showed a mortality benefit when antibiotics were administered within the first hour. However, it did not demonstrate a statistically significant decline in survival on an hourly basis thereafter.<sup>37</sup>

A prospective, multicenter ED trial that included patients with severe sepsis in addition to septic shock<sup>38</sup> did not show a mortality benefit to administration of antibiotics within the first hour. In-hospital mortality risk for patients undergoing EGDT was similar across patients in whom time to antibiotics was delayed up to 6 hours after triage.<sup>36,38</sup> However, patients with severe sepsis in whom antibiotics were delayed until shock was recognized faced a statistically significant increased risk of death (odds ratio = 2.35; 95% confidence interval = 1.12–4.53).<sup>38,39</sup> A retrospective study of 28,150 patients from the SSC database demonstrated a statistically significant increase in mortality for each hour that empiric antibiotics were delayed.<sup>40</sup> Importantly, this trend was preserved regardless of location of sepsis diagnosis (ED, ICU, and hospital ward) and across illness severity. Though there remains debate about the critical importance of the “golden hour” for antibiotic administration, overall current evidence supports early empiric antibiotics in severe sepsis and septic shock.

Choosing an empiric antibiotic regimen, based on infection source and host factors, also plays a key role in sepsis outcomes. A retrospective study of patients with septic shock from 1996 to 2005 showed that inappropriate initial antibiotics (based on eventual *in vitro* culture sensitivities or evaluation of clinical syndrome) were used 20% of the time and resulted in a 5-fold reduction in survival.<sup>41</sup> A retrospective cohort study of patients with gram-negative bacteremia and severe sepsis or septic shock found prior antibiotic exposure within 90 days to be an independent risk factor for drug resistance and in-hospital mortality.<sup>42</sup> However, careful consideration of side effects should also influence choice of initial antibiotic therapy. A Cochrane review citing 69 trials and containing 7863 subjects with sepsis compared empiric  $\beta$ -lactam therapy to  $\beta$ -lactam–aminoglycoside combination therapy.<sup>43</sup> All-cause mortality and clinical failure was similar in both groups, as was the rate of resistance. Importantly, nephrotoxicity was significantly less in the  $\beta$ -lactam monotherapy group.<sup>43</sup>

Infection source control is an essential component of sepsis management that should occur simultaneously with antibiotic administration. The 2012 SSC guidelines promote infection source control within 12 hours of diagnosis, with consideration of the risks and benefits therein and preference for interventions with the lowest associated physiologic insult.<sup>21</sup> Intravascular access devices should be recognized as a common source of infection, and should be removed after alternative access has been established.<sup>21</sup>

## FLUID RESUSCITATION

Volume resuscitation is an essential component of sepsis management, regardless of algorithm or endpoint. Three main types of non-blood product fluid resuscitation have been used: crystalloid (saline and Ringer’s



solutions), colloid (typically an albumin-containing solution), and synthetic volume expanders (hydroxethyl starch [HES] and similar compounds).

Multiple large studies confirmed the lack of a favorable risk-benefit ratio with synthetic volume expanders. Among nearly 800 patients with severe sepsis who were randomized to receive either Ringer's acetate or HES 130/0.4, a significantly higher number of patients receiving HES died (51% vs 43%, relative risk [RR] = 1.17), and required renal-replacement therapy (22% vs 16%, RR = 1.35). One patient in each group was dialysis dependent at 90 days.<sup>44</sup> An additional multicenter, prospective study of HES versus 0.9% (normal) saline for fluid resuscitation in the ICU found no significant difference in mortality (18% vs 17%,  $P = 0.26$ ), but did note a higher need for renal-replacement therapy in the HES group (7.0% vs 5.8%, RR = 1.21).<sup>45</sup> A systematic review incorporating 9 trials that randomized approximately 3400 patients with sepsis receiving either HES, crystalloid, or colloid showed no difference in mortality, although there was an excess risk for renal-replacement therapy (RR = 1.36), serious adverse events (RR = 1.30), and red blood cell transfusion (RR = 1.29) in patients receiving HES.<sup>46</sup> A second, larger systematic review concluded that HES was associated with an increased mortality compared with crystalloids, albumin, or gelatin (RR = 1.09). Additionally, an increase in renal failure (RR = 1.27) and renal-replacement therapy (RR = 1.32) was also noted.<sup>47</sup>

The debate between crystalloid and colloid (namely albumin) for fluid resuscitation is ongoing, with recent important additions to the literature. The SAFE (Saline Versus Albumin Fluid Evaluation) study investigators in 2004 randomized nearly 7000 patients to receive either 4% albumin solution or normal saline. At 28 days, no significant differences were found in mortality, new organ failure, ICU and hospital length of stay, days of mechanical ventilation, or days of renal-replacement therapy.<sup>48</sup> In 2014, another multicenter prospective study of 1800 patients with severe sepsis or septic shock in 100 ICUs in Italy compared 20% albumin and crystalloid solution to crystalloid solution alone. Mortality, end-organ dysfunction, and ICU length of stay did not differ between groups.<sup>49</sup> Two 2014 systematic reviews and meta-analyses on fluid resuscitation produced somewhat differing conclusions. Patel et al. evaluated data from 16 randomized trials including more than 4000 patients receiving albumin for volume resuscitation in adults with sepsis. Albumin provided no significant survival advantage in total or in any subgroup, regardless of severity of illness or baseline albumin level, thus arguing against its routine use.<sup>50</sup> Rochwerf et al. evaluated 14 studies with approximately 19,000 patients using Bayesian network meta-analysis technique. This study concluded that albumin is associated with reduced mortality compared with other fluids, and also that

balanced crystalloids (eg, Ringer's lactate and similar) may have lower mortality than normal saline.<sup>51</sup> A chloride-restrictive resuscitation approach has also been associated with a lower incidence of acute kidney injury in critically ill adults.<sup>52</sup>

The SSC confirmed its recommendations of a minimum of 30 mL/kg of crystalloids as the initial fluid of choice in sepsis in 2012, but added a suggestion for the addition of albumin in patients requiring substantial amounts of crystalloid.<sup>21</sup> The currently available data suggest crystalloid fluids to be the best-supported initial fluid in the management of sepsis, and that synthetic colloids should be avoided. Prospective data are still required to answer questions regarding the potential advantages of albumin or balanced and/or chloride-restricted crystalloids.

## ICU CONSIDERATIONS

Appropriate management of patients with the syndrome of sepsis, severe sepsis, and septic shock on the hospital ward requires a working knowledge of recent research conducted in the ICU setting. Although conclusions based on data from patients with septic shock might not be generalizable to less severe cases of sepsis, recent trials on glucose control and corticosteroids deserve consideration.

Intensive insulin treatment in the medical ICU is no longer standard practice. In the NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) trial, a large, multicenter randomized controlled trial of ICU patients, close to 20% of patients had severe sepsis at the time of randomization.<sup>53</sup> This subgroup did not benefit from intensive glucose control (a target of 81–108 mg/dL) in terms of 90-day mortality.<sup>53</sup> In contrast to prior studies of glycemic control in the critically ill, the intensive treatment group overall suffered increased mortality.<sup>54</sup> The COITSS (Combination of Corticotherapy and Intensive Insulin Therapy for Septic Shock) trial looked at intensive insulin therapy in patients with septic shock being treated with corticosteroids, a group particularly at risk for hyperglycemia. In this study, intensive insulin therapy did not improve in-hospital mortality.<sup>55</sup> Based on these and other ICU data, the current SSC recommendation is to target a blood glucose of  $\leq 180$  mg/dL for patients with severe sepsis.<sup>21,56</sup>

The use of corticosteroids to treat the host response in septic shock has been re-evaluated.<sup>57</sup> The 2004 SSC guidelines recommended hydrocortisone therapy for 7 days in patients with septic shock requiring vasopressor support after fluid resuscitation.<sup>17</sup> This recommendation was based on data from a placebo-controlled multicenter trial in France that showed improved shock reversal and reduced mortality in patients with septic shock who were treated with hydrocortisone and fludricortisone.<sup>58</sup> Of note, these patients were enrolled on the basis of hypotension despite

intravenous fluids and the initiation of 1 vasopressor. The benefit of corticosteroids was seen only in patients deemed to have “relative adrenal insufficiency” based on response corticotropin testing.<sup>58</sup> However, the CORTICUS (Corticosteroid Therapy of Septic Shock) study, a subsequent multicenter, placebo-controlled, randomized controlled trial failed to show a benefit to corticotropin testing in identifying patients with septic shock who would benefit from corticosteroids.<sup>59</sup> The corticosteroid treatment arm similarly benefited from faster shock reversal, but at the expense of increased superinfection.<sup>59</sup> Although underpowered, CORTICUS did not show a survival benefit to corticosteroids in septic shock.<sup>59</sup> The most recent SSC guidelines do not recommend corticotropin (adrenocorticotrophic hormone) stimulation testing and do not advise corticosteroids in septic shock if fluid resuscitation and vasopressor therapy restore hemodynamic stability during initial resuscitation.<sup>21</sup> Future studies may clarify subpopulations of patients with sepsis who benefit from corticosteroids.

## OUTCOMES: MORTALITY AND COMPLICATIONS

An understanding of the currently available information regarding the morbidity and mortality associated with severe sepsis is essential for the practicing hospitalist. Whether transferring care of patients to or receiving patients from the ICU, hospitalists must lead discussions with patients and families regarding prognosis, especially as it informs disposition. Hospitalists are often asked to make projections on outcome as well as the timing and venue of disposition. Clarification of patient wishes and goals of care remains an essential first step in the care of septic patients. Recently published studies provide prognostic information, including mortality (both short and long term) as well as complications associated with severe sepsis.

The attributable mortality for severe sepsis has been predominantly reported to date as short-term (usually in-hospital). A meta-analysis of US patients from 1991 to 2009 demonstrated a 3% annual decline in the short-term (28 day) mortality from severe sepsis using 2 previously validated algorithms. Data from 36 trials (and approximately 14,000 patients) revealed a decrease in mortality from 47% in the period from 1991 to 1995 to 29% from 2006 to 2009.<sup>60</sup> Although the methods employed (sepsis definitions and ICD-9-CM codes) can have a significant impact on estimates of mortality, these results corroborate a progressive decline in short-term mortality from severe sepsis in the United States between 2004 and 2009 using 4 validated algorithms.<sup>8</sup> Outside the United States, a recent retrospective analysis of more than 1 million patients with severe sepsis treated in the ICU in Australia and New Zealand from 2000 to 2012 also demonstrated a decrease in adjusted in-hospital mortality.

In this study, short-term mortality declined yearly, with an odds ratio of death of 0.49 in 2012 compared with 2000.<sup>61</sup> Hospital case volume has also been shown to impact rates of inpatient death, with higher-volume centers demonstrating lower mortality attributed to severe sepsis.<sup>62,63</sup>

The sufficiency of short-term mortality as the sole metric for severe sepsis outcome has been more recently questioned.<sup>64,65</sup> The extent to which full recovery and significant morbidity are affected relative to the change in death rate is unknown, and as such, more data on morbidity and longer-term mortality are necessary. A Danish study examined data from several registries of patients with severe sepsis. Compared with community-matched controls, patients with severe sepsis had an increased risk of death at 30 days (hazard ratio [HR] = 90.8), from 30 days to 1 year (HR = 2.7), and 1 to 4 years (HR = 2.3) after discharge.<sup>66</sup> Older survivors of severe sepsis also appear to have higher healthcare utilization in the year following discharge. An analysis of older severe sepsis survivors showed a striking increase in healthcare use relative to their prior resource use, driven primarily by higher number of days in inpatient healthcare facilities. Survivors of severe sepsis also had a significantly higher 90-day and 1-year mortality than matched controls.<sup>67</sup>

Increased attention is currently being given to sepsis-related complications, especially functional and cognitive impairments in older patients. “Sepsis survivorship” is a swiftly mounting public health issue for older Americans.<sup>68</sup> An 8-year follow-up of older sepsis survivors demonstrated a significant increase in the odds of both physical and cognitive dysfunction. During this period, moderate-to-severe cognitive dysfunction increased 3-fold (6.1% before sepsis, 16.7% after).<sup>69</sup> The mechanism by which this dysfunction occurs is unknown, as are the relative contributions of infection site/etiology, ICU length of stay, and extent of organ dysfunction. New functional impairment has been demonstrated in patients with severe sepsis initially admitted to a general floor, even with good baseline function,<sup>12</sup> as well as decreased quality of life in sepsis survivors.<sup>65,70</sup> Another study showed more admissions complicated by severe sepsis resulted in discharge to a long-term care facility in 2007 compared to 2000.<sup>7</sup>

Additional organ-specific consequences of severe sepsis have also been recently suggested. A retrospective analysis showed an increase in the incidence of new-onset atrial fibrillation in severe sepsis, with an associated increase in risk of in-hospital stroke and death. New-onset atrial fibrillation was present in 5.9% of patients with severe sepsis, compared with 0.65% in patients without. Severe sepsis patients with new-onset atrial fibrillation had an increased risk of in-hospital stroke (adjusted odds ratio = 2.70) and mortality (adjusted RR = 1.07).<sup>71</sup> These findings

suggest association only, and further investigation is warranted. It remains to be seen whether interventions to restore sinus rhythm or anticoagulation are warranted. Preoperative sepsis (within 48 hours) has also been proposed as a risk for postoperative (30 day) arterial (myocardial infarction, stroke) and venous (deep venous thrombosis, pulmonary embolism) thromboembolism. The authors of this study suggest deferral of elective surgery or specific attention to postoperative thromboprophylaxis in patients in whom procedures must occur.<sup>72</sup> This has particular relevance for those septic patients in whom surgical source control is indicated.

Estimates regarding mortality and specific complications attributable to severe sepsis are ongoing, though clearly with a new focus upon metrics other than short-term mortality. Furthermore, recent data to suggest source of infection as a major driver of mortality in septic shock<sup>73</sup> may contribute to the evolution of the conceptualization of sepsis similar to that of cancer: a heterogeneous collection of disease, among which mortality is determined by specific subtypes. At present, this much appears clear: the previously held notion that survival of a septic insult is unlikely to have future implications is under siege.<sup>74</sup> The extent to which complications and increased longer-term mortality may reflect generally poorer health at the time of infection versus a sequelae of the survived episode itself is not yet known.

## CONCLUSIONS

The past decade of sepsis research has led to significant findings that will change clinical practice for hospital medicine practitioners. Although the incidence of severe sepsis in the United States has continued to rise, in-hospital mortality has declined; in this context, the management of the spectrum of sepsis disorders is no longer restricted to the ICU, and the entity of sepsis survivorship has blossomed. Prompt recognition of sepsis and improvements in supportive care are likely responsible for improved patient outcomes. EGDT has been called into question as a protocol whose benefit lies not in specific targets or endpoints, but rather in the early recognition of sepsis, appropriate fluid resuscitation, and early/effective antibiotics. Synthetic volume expanders, intensive insulin therapy, and routine use of corticosteroids are no longer recommended.

Hospitalists are a critical link in providing timely, evidence-based care for patients with sepsis from initial recognition to post-ICU recovery. Specialized care for the survivors of septic shock is a burgeoning area, and hospitalists are integral in the management of the sequelae of multiorgan failure.

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