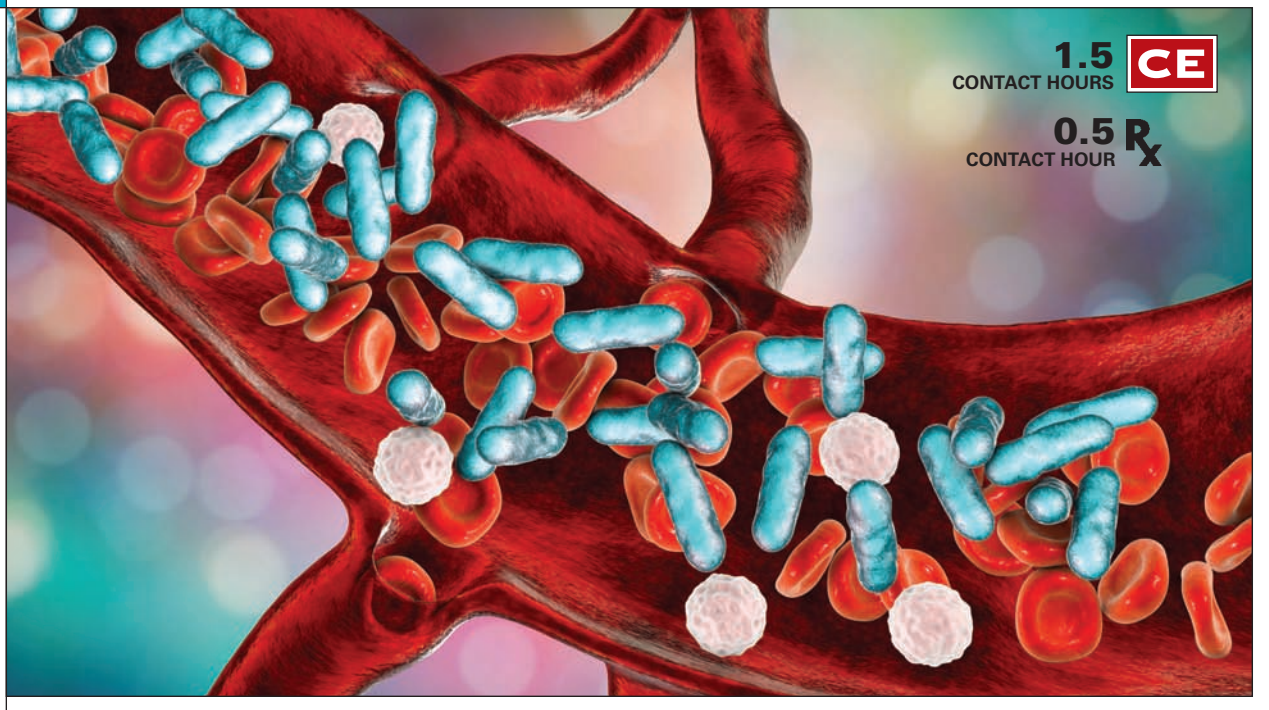


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# Evidence-based updates to the 2016 Surviving Sepsis Guidelines and clinical implications

***Abstract: Despite numerous advances in understanding the pathophysiology of sepsis and its treatment, sepsis morbidity and mortality remain high. The 2016 Surviving Sepsis Campaign guidelines incorporated the latest research to formulate new sepsis diagnoses and updated treatment recommendations. This article reviews how to manage patients with sepsis and provides insight into the 2016 guidelines, updates, and suggestions.***

**By Karen D. Lehman, DNP, APRN, FNP-C**

Although the treatment of sepsis has been a top international priority for several years, associated mortality and treatment costs remain high. Each year, more than 19 million patients require hospitalization because of sepsis, and approximately 15% of patients with severe sepsis and 30% of patients with septic shock will not survive.[1-4] At $23.6 million, sepsis was the most expensive condition treated in US hospitals in 2013.[5] Sepsis prevalence and cost are expected to rise as the older adult population increases.[6,7] The Surviving Sepsis Campaign (SSC) recognized this daunting international burden and set a goal to reduce sepsis mortality by 25% by promoting sepsis awareness and healthcare provider education.[8] The SSC released its first set of guidelines in 2004, with updates every 4 years thereafter. The SSC 2016 guidelines offered several modifications and have been met with both support and controversy.

This article will examine the SSC 2016 guidelines, review sepsis risks and sequelae, discuss the major

**Keywords: sepsis, Sepsis-3, septic shock, Sequential (sepsis-related) Organ Failure Assessment, Severe Sepsis/Septic Shock Early Management Bundle, Surviving Sepsis Campaign 2016 Guidelines, systemic inflammatory response syndrome variables**

changes from the SSC and bundle updates, and debate controversial points through a clinical scenario that encompasses treatment recommendations from the 2012 guidelines, 2016 guidelines, and updates since the 2016 guidelines were published. For the NP, this article will explain the best practice guidelines and designate which components can be applied to the clinic, emergency, and hospital settings.

## Background

In 2014, sepsis was responsible for 1.7 million adult hospitalizations and 270,000 deaths in the US.[3] Among inpatients, sepsis caused 35% to 56% of deaths, and most deaths occurred in a cohort of patients who were normotensive and had lactate levels of less than 4 mmol/L.[9] Higher illness severity is correlated with higher mortality and hospital costs.[2,10,11] The financial burden, however, continues because of readmission penalties. Thirty-day sepsis readmission rates are similar to or higher than rates for pneumonia, heart failure (HF), chronic obstructive pulmonary disease, and acute myocardial infarction.[12,13] One-fourth of severe sepsis survivors are readmitted within 1 month, and 75% within 6 months.[14,15] Those with underlying chronic diseases have an even higher readmission risk.[16]

Over 30% of the patients who had sepsis and were discharged were readmitted for ambulatory care-sensitive conditions within 90 days, signifying the importance of astute outpatient monitoring.[16] Close outpatient follow-up could also minimize additional postdischarge complications. Following discharge, sepsis survivors are at greater risk for recurrent infection and persistent functional impairments.[16,17] These functional limitations include cognitive deficits, anxiety, depression, and posttraumatic stress disorder.[18-20] In addition, mortality risk remains elevated for 5 years after hospitalization for sepsis.[21]

## Methodology for best practice recommendations

The 2016 SSC Guidelines provide best practice recommendations for managing patients with sepsis and septic shock.[22] Several pertinent reports, studies, and articles were reviewed as support for the guidelines and integration into APRN practice. The author conducted a literature search using PubMed and CINAHL through October 4, 2018. The key search words were "sepsis," "sepsis syndrome," "septic shock," "Sepsis-3," "guidelines," and "evidence-based medicine."[22] The bibliographies of retrieved studies were searched for relevant published research corresponding with the search terms used. The years were predominantly limited to 2010 through 2018.

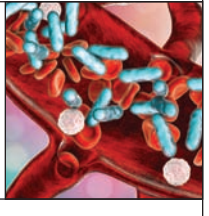
To reach guideline consensus, 55 international experts used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool to devise strong or weak recommendations. In the 2016 guidelines, 32 were strong recommendations, 39 were weak, and 18 were deemed best practice statements (BPSs).[22] The authors of the guidelines conveyed that the 2016 guidelines were intended to represent best practice, not to reflect standard of care.[22]

## Guideline updates and practice changes

Sepsis is a medical emergency, and prompt identification and treatment are paramount in reducing morbidity, mortality, and associated financial burden. The SSC 2016 guidelines were formulated for adults with sepsis and septic shock.[22]

**New definitions.** The 2016 revised definition of sepsis, termed *Sepsis-3*, is "a life-threatening organ dysfunction caused by a dysregulated host response to infection."[22] Clinically, sepsis is represented by organ dysfunction. *Septic shock* is defined as "a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality."[22] Clinically, a patient with septic shock is identified as needing vasopressors to maintain a mean arterial pressure (MAP) of at least 65 mm Hg, and also having a lactate level over 2 mmol/L after fluid resuscitation.[23]

*Following discharge, sepsis survivors are at greater risk for recurrent infection and persistent functional impairments.*

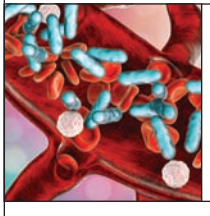


For comparison, the 2012 definition divided sepsis into three categories: sepsis, severe sepsis, and septic shock.[24] Severe sepsis was defined as two or more systemic inflammatory response syndrome variables (SIRS) plus organ dysfunction, and septic shock was defined as hypoperfusion despite volume resuscitation.[24]

The SSC 2016 guidelines enforce prompt treatment (BPS). An I.V. crystalloid fluid bolus of at least

30 mL/kg should be given within the first 3 hours of presentation (strong recommendation, low quality of evidence). Hemodynamic reassessment should guide the decision for additional fluids (BPS). Frequent clinical examinations (BPS) and serial lactate levels (weak recommendation, low quality of evidence) may guide treatment and resuscitation. Dynamic variables should be used to assess fluid responsiveness (weak recommendation, low quality of evidence). Two recommended dynamic variables include the passive leg raise and, in ventilated patients, an assessment of stroke volume variations.

The 2016 guidelines recommend obtaining cultures before starting antimicrobials, as long as there is no delay in care (BPS). Antimicrobials should be initiated within 1 hour of recognition (strong recommendation, moderate quality of evidence). Broad-spectrum therapy should include consideration for bacterial, viral, or fungal causes (strong recommendation, moderate quality of evidence), and at least two classes of antimicrobials should be prescribed for patients in septic shock (weak recommendation, low quality of evidence). Combination therapy is not recommended for patients with neutropenic sepsis (strong recommendation, moderate quality of evidence). In addition, providers should consider pharmacokinetic and pharmacodynamic principles when ordering patient-specific doses (BPS).



***The most common adverse reactions reported in more than 10% of patients treated with angiotensin II were thromboembolic events.***

Source control interventions should be implemented as soon as practically possible (BPS). Antimicrobials should be de-escalated upon pathogen identification or clinical improvement, ideally within a few days (BPS). Typically, 7 to 10 days is an adequate treatment course (weak recommendation, low quality of evidence). Procalcitonin (ProCT) levels may be used to shorten the duration of antimicrobial therapy (weak recommendation, low quality of evidence). Crystalloids are the fluid of choice (strong recommendation, moderate quality of evidence), and albumin should be added if substantial crystalloids are administered (weak recommendation, low quality of evidence). Beyond the initial bolus, a fluid challenge may be used to determine the need for additional fluids (BPS). In hypotensive, euvolemic patients, norepinephrine remains the preferred vasoactive medication (strong recommendation, moderate quality of evidence).

The 2016 guidelines provided recommendations on corticosteroid administration, blood transfusion and blood products, mechanical ventilation, blood glucose control, renal replacement therapy, venous thromboembolism and stress ulcer prophylaxis, nutrition, and goals of care discussion. These guidelines were not significantly changed from the 2012 guidelines. For a full review, please refer to the 2016 guidelines, which can be found on the Surviving Sepsis website at http://survivingsepsis.org/Guidelines/Pages/default.aspx.

**Prompt treatment.** Treatment was guided by early goal-directed therapy (EGDT) and the 3- and 6-hour bundles.[23,25] Since the 2012 guidelines, several studies found that protocol-based care and EGDT had no effect on mortality.[26-30] Although EGDT fell out of favor with the 2016 guidelines, the importance of initiating rapid treatment, ideally within the first hour, should not be overlooked.[31-33] In 2018, the SSC released the Hour-1 bundle, which combined components of the 3-hour and 6-hour bundles.[34,35] The Society of Critical Care Medicine (SCCM) and the American College of Emergency Physicians (ACEP), however, criticized the Hour-1 bundle for appropriateness of implementation in the US.[35] The SCCM and ACEP agree with the importance of prompt diagnosis and treatment, but advise against hospitals implementing the Hour-1 bundle at this time until further review is conducted.[35]

**Vasopressor therapy.** Angiotensin II is a naturally occurring peptide hormone of the renin-angiotensin-aldosterone system that has strong vasopressor properties causing vasoconstriction and an increase in BP.[36] In December 2017, the FDA approved a new drug, angiotensin II (Giapreza), an aqueous solution of synthetic human angiotensin II that is approved for use in adults with septic or other distributive shock to increase the BP.[36] Angiotensin II is administered by an I.V. infusion using an infusion pump through a central line. Angiotensin II is available in 2.5 mg/mL and 5 mg/2 mL vials.[36] The drug must be diluted in 0.9% sodium chloride prior to use to achieve a final concentration of 5,000 nanograms (ng)/mL or 10,000 ng/mL.[36] Caution must be used when calculating the dose because angiotensin II is dosed in nanograms/kilogram/minute

**SOFA score**

| SOFA score | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| **Respiration** | | | | |
| ($PaO_2/FiO_2$, mm Hg) | <400 | <300 | <200 with respiratory support | <100 with respiratory support |
| **Coagulation** | | | | |
| Platelets x$10^3$/$mm^3$ | <150 | <100 | <50 | <20 |
| **Liver** | | | | |
| Bilirubin, mg/dL | 1.2-1.9 | 2.0-5.9 | 6.0-11.9 | >12.0 |
| **Cardiovascular** | | | | |
| Hypotension | MAP <70 mm Hg | Dopamine ≤5 or dobutamine (any dose)* | Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1 | Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 |
| **Central nervous system** | | | | |
| Glasgow Coma Scale | 13-14 | 10-12 | 6-9 | <6 |
| **Renal** | | | | |
| Creatinine, mg/dL or urine output | 1.2-1.9 | 2.0-3.4 | 3.5-4.9 or urine output <500 mL/day | >5.0 or urine output <200 mL/day |

*Adrenergic agents administered for at least one hour (doses given are in mcg/kg/min)

Used with permission from Vincent J-L, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med* 1996;22(7):707-710.

rather than micrograms/kilogram/minute. Angiotensin II is titrated in increments to achieve or maintain the target BP.[36] The BP must be monitored during the titration. The most common adverse reactions reported in more than 10% of patients treated with angiotensin II were thromboembolic events.[36] Consult the full prescribing information for complete dosage recommendations, warnings, and precautions.[36]

**SOFA score.** Advances in pathophysiology, including changes in cellular function, organ response, and biochemistry, immunology, neuroendocrine, and metabolomic factors, support the need for an updated definition.[23] The Sepsis-3 authors contend that the 2012 definitions disproportionately focused on inflammation and that the SIRS criteria were inadequate.[4,23] They proposed that clinical criteria be used to diagnose sepsis and septic shock, and recommended the validated tool called Sequential (sepsis-related) Organ Failure Assessment (SOFA).[23,37,38] (See *SOFA score.*) The SOFA score determines mortality risk via identification of progressive organ dysfunction within six systems. A SOFA score of more than 2 points higher than the previous score signifies sepsis and carries a mortality risk of 10%.[23]

An alternate score was suggested for patients in the medical-surgical units, ED, or outpatient setting.[39] The quickSOFA (qSOFA) is comprised of three variables: altered mentation, respiratory rate of at least 22 per minute, and systolic BP of 100 mm Hg or less.[39] The presence of at least two variables should raise suspicion for sepsis, but qSOFA should not replace SIRS as a tool to investigate for an infection.[40]

**Biomarkers.** Biomarkers may help guide resuscitation. Reducing an elevated lactate to a normal level remains a mainstay of management.[41] The 2016 guidelines also recognize ProCT in identifying bacterial insult and de-escalating antibiotics.[42-44] Numerous biomarkers show promise in sepsis prediction, but currently no standard biomarker exists.[23,42-44] Clinicians should use SIRS, SOFA, and qSOFA to promote timely identification, and implement treatment to reduce morbidity and mortality.[35] The current use of two or more SIRS criteria as a tool to identify possible sepsis may be helpful, but Singer and colleagues felt that using SIRS was unhelpful.[23]

**SEP-1.** The importance of early and aggressive treatment was recognized by the Centers for Medicare and Medicaid Services (CMS). In 2015, CMS started collecting data on the Severe Sepsis/Septic Shock Early Management Bundle (SEP-1), the first national quality measure for sepsis.[45] The 2012 guidelines were referenced again when SEP-1 was updated in 2018, including SIRS and the severe sepsis definition.[46]

Healthcare providers are subsequently placed in a quandary, requiring knowledge of the 2012 guidelines

to fulfill SEP-1 reporting, and the updated recommendations within the 2016 guidelines. In October 2018, UnitedHealthcare adopted the Sepsis-3 definition for hospital claim reviews, effective January 1, 2019.[47] UnitedHealthcare encompasses Medicare Advantage, Medicaid, and commercial plans. Uncertainty remains whether CMS will follow UnitedHealthcare's lead.

## Guideline application: A case review

Mr. G is a 63-year-old male with uncontrolled type 2 diabetes mellitus, hypertension, and stage II chronic kidney disease (CKD). He presented to his NP's clinic for evaluation of nontraumatic right lower leg pain, swelling, and redness. He had a normal temperature. His heart rate was 108 beats/minute, respiratory rate was 22 per minute, BP was 176/94 mm Hg, and he had a normal oxygen saturation. A venous Doppler was negative for deep venous thrombosis, white blood cell (WBC) count was 14.6 x $10^3$ cells/$mm^3$, and creatinine was 2.1 mg/dL. The NP prescribed clindamycin and scheduled a follow-up visit.

Mr. G worsened and presented to the ED the following day. He was confused, febrile (101.2° F [38.4° C]), tachycardic (122 bpm), tachypneic (24 respirations per minute), and had a BP of 124/72 mm Hg (MAP 89 mm Hg). His oxygen saturation was 88% on room air and capillary refill time was more than 4 seconds. The ED NP ordered a lactate level, ProCT level, complete blood cell count, comprehensive metabolic panel, urinalysis, and blood cultures. Abnormal results included the following: lactate level 5.5 mmol/L, ProCT 9.78 ng/dL, WBC 22.3 x $10^3$ cells/$mm^3$ creatinine 3.7 mg/dL, total bilirubin 1.8 mg/dL, and blood glucose 583 mg/dL. There were no signs of diabetic ketoacidosis, which could explain an elevated lactate. The ED NP identified four SIRS criteria and two qSOFA components: tachypnea and altered mental status. Because Mr. G was hypoxemic, the ED NP only ordered 1 L of crystalloid I.V. fluids for fear of contributing to pulmonary edema. Vancomycin and ceftriaxone were prescribed to cover for the most common causes of cellulitis. Mr. G was admitted to the ICU with a diagnosis of sepsis.

The hospitalist NP diagnosed Mr. G with septic shock because he had a lactate level higher than 4.0 mmol/L. The hospitalist NP also calculated his SOFA to be 5, based on abnormal GCS, creatinine, and total bilirubin. For SEP-1 reporting, the 3- and 6-hour bundles were followed. His repeat lactate level improved to 3.3 mmol/L. The hospitalist NP reexamined Mr. G and documented a cardiopulmonary exam, his skin temperature and color, strength of peripheral pulses, and capillary refill time. At that time, Mr. G's MAP decreased to 65 mm Hg. His BP responded to a 500 mL fluid bolus, though the NP was prepared to prescribe norepinephrine.

On Mr. G's second hospital day, mild lab improvements were noted. His SOFA score improved to 3. The hospitalist APRN found increasing induration and tenderness along the medial aspect of the gastrocnemius and ordered an MRI. This revealed severe cellulitis with fasciitis and myositis of the medial gastrocnemius with a 3-cm fluid collection. The orthopedic surgeon was consulted and took Mr. G urgently to the OR for incision and drainage.

By Mr. G's fourth hospital day, *Group C streptococcus* was identified from the intraoperative wound cultures. His blood cultures remained negative. Antibiotics were de-escalated to ceftriaxone. After 5 days, labs had attained stable values. Mr. G was discharged home with a prescription for cephalexin to complete a 10-day course.

## Discussion

The clinic NP knew that early identification and prompt antibiotic therapy could improve recovery, and appropriately prescribed an antibiotic. The clinic NP used the 2016 guidelines, which did not recognize his elevated renal function as severe sepsis. His qSOFA score was zero. When Mr. G arrived in the ED, his systolic (S)BP was more than 50 mm Hg lower than his clinic SBP. His delayed capillary refill score was also an ominous finding; in the prehospital setting, a delayed capillary refill was associated with higher mortality.[48] Both NPs were concerned that Mr. G may have had sepsis at his clinic appointment, but it was difficult to tell whether the SIRS criteria indicated an adaptive response versus impending organ dysfunction.[49] Both NPs quietly wondered if earlier, aggressive management could have halted progression into sepsis or septic shock.

The ED NP used SIRS in conjunction with qSOFA. The presence of SIRS criteria predicts clinical decline about 17 hours before it occurs, whereas a positive qSOFA score predicts deterioration about 5 hours before ICU admission.[50] This was evident in Mr. G's case: he was evaluated in the clinic the day prior to ED presentation, and he had a positive qSOFA in the ED before hypotension was identified 6 hours later in the

ICU. The NPs had to ascertain whether Mr. G's organ dysfunction was caused by sepsis or another etiology.

The Infectious Diseases Society of America (IDSA) indicated that the challenge of accurately identifying an infection and the cause for organ dysfunction were shortcomings of the SSC 2016 guidelines.[51] Additionally, if an infectious source remained unidentified, clinicians must weigh the risks versus benefits of rapid, and potentially unnecessary, antimicrobial treatment.[51]

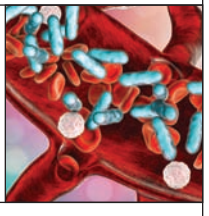
Both NPs acted swiftly and ordered interventions within the first hour, including an initial and repeat lactate level, blood cultures, crystalloid resuscitation, and broad-spectrum antibiotics. Rapid lactate testing ensures timely antibiotic administration and reduces length of stay and in-hospital mortality.[52] Adherence to the 3- and 6-hour bundles has been shown to reduce in-hospital mortality by 40% and 35%, respectively.[53] Pruinelli and colleagues, however, found that even a 3-hour delay may be too long, and recommend that the bundle criteria be completed as quickly as possible.[54] When Mr. G presented, following the Hour-1 bundle was an accepted strategy to enforce prompt identification and treatment.[35] The Hour-1 bundle is no longer recommended for hospital use.[35]

Both NPs failed to order the recommended 30 mL/kg fluid bolus. This fluid volume has been debatable. Some studies found higher mortality among patients with sepsis who have a cumulative fluid balance greater than 2.5 L.[55] Some experts recommend starting with a 500 to 1,000 mL fluid challenge and additional fluids ordered based on patient response.[56] Conversely, another study indicated that the majority of patients, even those with HF and CKD, responded favorably to the full fluid bolus.[57] Mr. G's mild hypoxemia should not have deterred the order for the 30 mL/kg recommended bolus. Frequent reassessment could have provided clues to Mr. G's fluid status.

Within the community hospital, clinicians were encouraged to follow the SEP-1 bundles. However, some experts contend that the SEP-1 approach lacks evidence, places select patients at risk for overresuscitation, and fails to recognize the heterogeneity of patients.[58-60] Both NPs were aware of the differences between the 2012 and 2016 guidelines, and these differences complicated diagnosis and documentation. The ED NP simply diagnosed Mr. G with sepsis, whereas the hospitalist NP ultimately documented both sets of sepsis criterion. At age 63, Mr. G was not yet insured by Medicare. The hospitalist NP had prior experience with private insurance companies denying payment for using the 2012 guidelines, even though CMS reporting measures had not adopted the Sepsis-3 definitions.[61]

Proponents of Sepsis-3 suspect that the updated definition may reduce redundant sepsis definitions. A concrete definition may provide a more accurate measure of incidence and mortality and reduce confusion in the clinical setting.[60,62-64] The SOFA score predicts mortality, but unfortunately does not reduce it.[23,57,61] For this reason, the Sepsis-3 definition is criticized for downplaying early sepsis signs and delaying diagnosis.[61] Sepsis-3 misses patients who previously qualified for septic shock who may benefit from prompt identification and treatment.[63] Both NPs understood the complexities with using each set of guidelines, understanding that the new criteria may have discounted Mr. G's potential sepsis clinic presentation and delayed aggressive care.

***Adherence to the 3- and 6-hour bundles has been shown to reduce in-hospital mortality by 40% and 35%, respectively.***



## Implications for practice

NPs provide high-quality care in multiple sites and are positioned to identify and initiate prompt sepsis treatment. NPs often bridge the gap between several different disciplines and provide expert guidance on implementing institutional protocols, educating peers and the public, and disseminating the latest evidence to influence policy change. In addition, with research emerging about postsepsis ramifications, there may be a heightened push to implement sepsis care across the healthcare continuum. APRNs who understand the context of the guidelines will be more apt to lead colleagues and institutions in delivering the safest and most effective care for the community.

Sepsis remains a devastating and common process with an unacceptably high mortality, and for many more, permanent morbidity. The 2016 SSC guidelines provided an updated definition of sepsis, but early detection and diagnosis remain an emphasis. Additional research is needed to identify which set of guidelines results in

optimal patient outcomes. As trusted and knowledgeable patient advocates, NPs are in pivotal positions to incorporate the 2016 SSC guidelines into practice. Although the guidelines were designed for the critically ill patient, it behooves providers in any setting to understand the clinical criteria that define sepsis and septic shock. Despite the controversy surrounding the 2016 recommendations, the most important qualities remain the same: early identification, source control, and prompt antimicrobial therapy. With the influx of new research on pathophysiology, biomarkers, and best treatment options, clinicians should expect updates and be prepared to incorporate best-care recommendations into practice. NP

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