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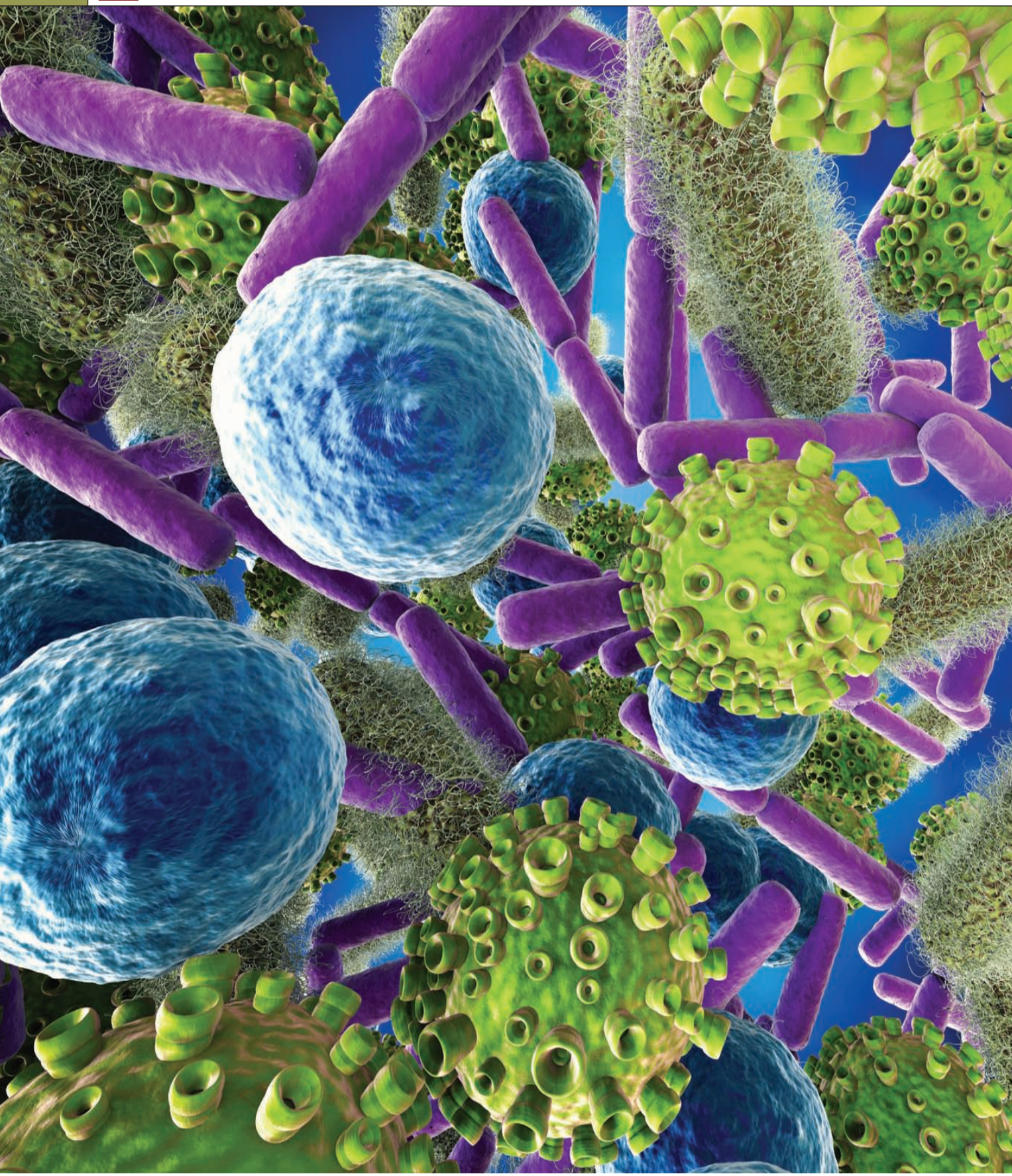

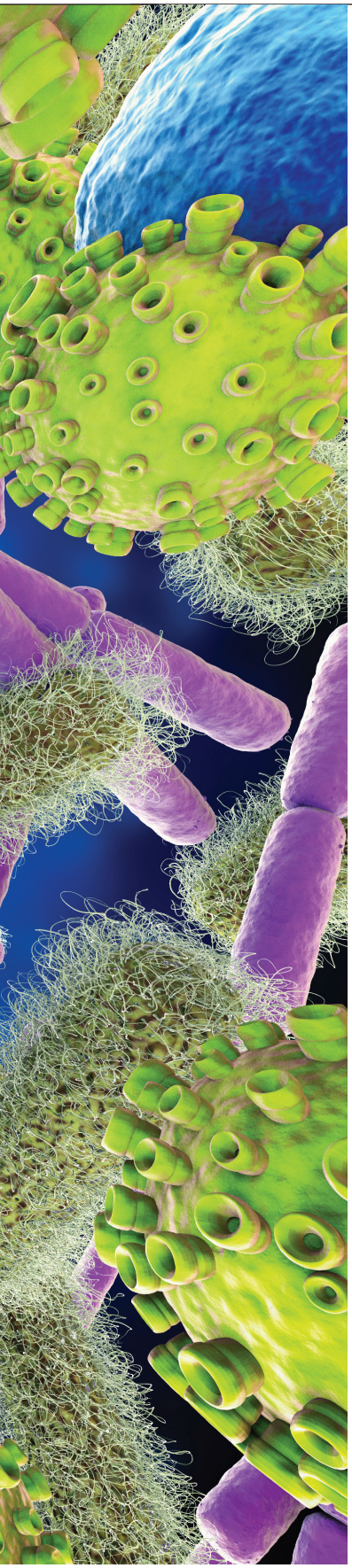

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Evidence-based updates to the 2021 Surviving Sepsis Campaign guidelines

Part 1: Background, pathophysiology, and emerging treatments

Abstract: *Sepsis identification and treatment has changed significantly over the last few decades. Despite this, sepsis is still associated with significant morbidity and mortality. This first of a two-part series reviews the history of modern sepsis and presents new research in pathophysiology, treatment, and postsepsis care.*

By Karen D. Lehman, DNP, APRN-BC

Sepsis and septic shock represent substantial sources of mortality and healthcare costs. In 2017, there were 48.9 million sepsis cases and 11 million sepsis-related deaths worldwide; sepsis was responsible for nearly 20% of all deaths.[1] In the US, sepsis is the cause of an estimated 1.7 million adult hospitalizations and 270,000 deaths per year.[2] Sepsis accounts for 3.6%-6% of hospital admissions, yet is responsible for a disproportionate 13% of total US hospital costs, with the mean cost of index hospitalization exceeding $16,000 for sepsis and over $38,000 for septic shock.[2,3] Sepsis is also the most frequent cause of 30-day hospital readmission; patients with diabetes or chronic kidney disease and those discharged to a facility are at higher risk of readmission.[4] Among hospitalized patients, sepsis is the most common cause of death; mortality among those with septic shock ranges from 34% to 39% and up to 60% for Medicare beneficiaries.[3,5,6] Despite overall reductions in sepsis mortality, the treatment of sepsis continues to be a major focal point in healthcare.[1,2] The newest Surviving Sepsis Campaign (SSC) guidelines, published in 2021, provide best-practice statements in an effort to reduce sepsis mortality.[7] This first article in a two-part series provides a history of the sepsis guidelines and reviews new understandings in pathophysiology and sepsis risk factors, sepsis diagnosis, and sepsis treatment and recovery, with occasional comparisons to current SSC guidelines. Part two will take an extensive dive into the SSC 2021 guidelines and discuss implications for NPs.

Keywords: biomarkers, pathophysiology, postsepsis syndrome, sepsis, Surviving Sepsis Campaign

History

The concept of sepsis was identified in written language about 2,700 years ago, when the word described "decay."[8] A modern definition, however, did not present until the early 20th century, at which time sepsis was attributed to a blood stream infection.[8] In 1991, sepsis was defined as systemic inflammatory response syndrome (SIRS) combined with various degrees of organ dysfunction.[9] In 2004, the SSC published the first set of guidelines for managing sepsis and septic shock. Since then, the SSC has presented new updates about every 4 years, based on contemporary evidence. The latest set of guidelines were published in 2021 and will be reviewed in part two of this article. The cornerstones of treatment have consistently been fluid resuscitation and hemodynamic stability, early antibiotics, and source control. While new research has delineated optimal crystalloid fluid, vasopressor, and antibiotic selections, these three topics have remained consistent over the last 2 decades. Updates in crystalloid, vasopressor, and antibiotic selection will also be reviewed in part two of this article given their importance in the SSC guidelines.

Definitions. The 2021 SSC Guidelines use the Third International Consensus definitions, also known as Sepsis-3. With Sepsis-3, sepsis is defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection."[10] Organ dysfunction is evidenced by an increased score of 2 or more in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA), and septic shock is considered as "a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone."[10] To diagnose septic shock, a euvolemic patient must require vasopressor support to achieve a mean arterial pressure of at least 65 mm Hg and have a lactate level above 2 mmol/L.[10]

Before Sepsis-3, the Sepsis-2 definition utilized SIRS as a screening tool to diagnose sepsis.[11] Both Sepsis-2 and Sepsis-3 have been critiqued. Requiring at least two SIRS criteria for the definition of severe sepsis excluded 12.5% of otherwise similar patients, and has been criticized as being common but not necessarily specific for infection.[12,13] Nonetheless, SIRS is associated with mortality and organ dysfunction and can be a helpful tool in identifying sepsis, particularly in patients in the ED.[14,15] The Sepsis-3 definition is common among patients in the ICU, yet may fail to identify sepsis.[16] Sepsis-3 has been criticized for delaying identification and intervention for early sepsis, and according to one study, Sepsis-3 criteria missed 57% of patients who still had substantial organ failure and mortality.[16-18] Ultimately, using both SIRS criteria and SOFA criteria may improve sepsis identification.[15]

Regardless of definition used, identifying sepsis early and providing prompt, appropriate treatment improves outcomes.[7] In 2015, the Centers for Medicare and Medicaid Services introduced the SEP-1 core measure, which provides reimbursement for hospitals who comply with the measure (see *SEP-1*).[19] SEP-1 compliance is associated with improved sepsis outcomes, including shorter length of stay and reduced mortality.[20] The conundrum with SEP-1 is that it utilizes the Sepsis-2 definitions, in contrast to the Sepsis-3 definition adopted by the SSC.[21] It is this author's recommendation to follow institutional recommendations regarding preferred sepsis definition.

Review of current findings

The definition of sepsis has changed over the last few decades as new studies emerged. Sepsis is now understood to be an extremely intricate process that encompasses numerous pathophysiologic pathways and depends upon several pathogen and host factors. Hypoperfusion, increased vascular permeability causing significant relative hypovolemia, and uncontrolled proinflammatory mediators are the crux of sepsis.

Organ dysfunction. In sepsis, all organ systems are affected. Sepsis causes myocardial dysfunction due to reductions in vascular tone, an increase in nitric oxide, downregulation of adrenergic receptors, and mitochondrial dysfunction.[22,23] Sepsis-induced respiratory distress syndrome may result from uncontrolled interactions between cellular mediators and inflammatory cytokines, subsequently causing destruction of the alveolocapillary system and pulmonary edema and/or hemorrhage.[24] Sepsis-induced acute renal failure is not completely understood, though hypoperfusion may result in tubular necrosis. Renal injury has also been seen in cases with hemodynamic stability or even increased perfusion.[25] Sepsis affects microcirculation, and with erratic blood flow, clotting pathways are activated, further complicating organ function.[26] In addition, mitochondrial dysfunction compromises adenosine triphosphate (ATP) production and causes an excess of reactive oxygen species, disrupting the electron transport chain and triggering oxidative

damage to DNA, lipids, and proteins.[27] Typically, cell death would be an expected consequence of mitochondrial dysfunction. Instead, the cell adapts and relegates usual metabolic function in order to preserve ATP, which is postulated to be an adaptive mechanism in times of profound stress.[28] Sepsis also induces a number of hormonal shifts in cortisol, insulin resistance, and sex hormones.[29,30] Finally, after the proinflammatory state, there is an attempt at correction toward an anti-inflammatory condition, causing immunosuppression and setting the stage for secondary infection immediately after sepsis and for months following.[31]

Sepsis risk factors. Sepsis-induced immunosuppression is a primary cause for a large portion of hospital readmissions after sepsis, along with chronic diseases and environmental aspects. Adult sepsis survivors were found to have higher readmission rates compared with patients with nonsepsis diagnoses.[32] Among those readmitted, infection was the most common diagnosis.[32] Those who had more comorbid conditions, were admitted for a nonelective diagnosis, and had higher illness severity were at higher risk for rehospitalization.[32] Studies have also shown that patients who are male, identify as Native American or Black, have lower income, urban residence, comorbid chronic conditions, or lower educational level, or who are uninsured not only experience increased rehospitalization rates after sepsis but also increased risk of repeat sepsis.[32,33]

Diagnosis and novel treatment approaches. Best practices of many aspects of sepsis care remain ambiguous, such as the choice of biomarkers and alternative treatment strategies, despite the many advancements that have been made toward identifying risk factors, pathophysiology, and postsepsis care.

Biomarkers. Lactate measurement is currently the dominant biomarker in sepsis, even though it is not a direct marker of tissue perfusion.[34] The lactate rise in sepsis was originally thought to be the result of cellular hypoxia and anaerobic metabolism, as seen in various hypermetabolic conditions, but this viewpoint is challenged.[34] There are numerous other factors that cause lactate elevation, such as mitochondrial dysfunction, liver dysfunction, and skeletal sodium-potassium-ATPase pumps which allow lactate as a source of energy.[35,36] Lactic acidosis is also present in conditions that do not have an effect on tissue perfusion, such as diabetes and metformin use, malignancy, severe alcohol consumption, HIV infection and antiretroviral therapies, the use of beta-adrenergic agonists such as albuterol and epinephrine, acquired or congenital mitochondrial dysfunction, drug-induced mitochondrial dysfunction as seen with propofol and linezolid, or in cases of intestinal malabsorption.[37] NPs should recognize that elevated lactate does not consistently represent sepsis, and understand the differential diagnoses associated with a high lactate level.

SEP-1[56]

Within 3 hours

Check lactate level

Obtain blood cultures before antibiotics

Start antibiotics

Initiate 30 mL/kg crystalloid fluid bolus if hypotensive

Within 6 hours

Start vasopressors if hypotensive after fluid resuscitation

Reassess tissue perfusion and volume status if hypotension persists or initial lactate was ≥4 mmol/L

Recheck lactate if initial level was elevated

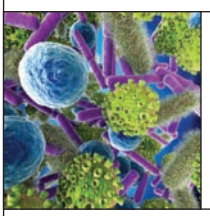
Over 250 biomarkers of sepsis have been identified, but only a handful have been rigorously studied and few demonstrate clinical significance.[38] Biomarkers should be reproducible and accurate in identifying patients for an appropriate degree of intervention.[39] Biomarkers represent several different pathophysiologic roles. Biomarkers manifest as a result of systemic infection, along with a myriad of bodily responses to infection that include hormonal triggers, acute-phase and inflammatory markers, and specific cellular indicators.

Beyond lactate, procalcitonin (PCT) and C-reactive protein (CRP) have been the most studied biomarkers.[40] PCT is a hormonal biomarker produced by the thyroid, and CRP is a common acute-phase protein.[39] PCT is considered superior to CRP. PCT rises rapidly during proinflammatory states, particularly in bacterial infections.[40] Combining both PCT and CRP may prove helpful in ruling out bacterial sepsis.[41]

During inflammation, the cytokines interleukin (IL)-6 and IL-1 beta activate the rise in CRP.[39] Cytokines such as tumor necrosis factor-alpha (TNF-alpha), interferons, monocyte chemoattractant protein-1 (MCP-1), IL-1 beta, IL-6, and IL-8 also rise during proinflammatory states and show promise in sepsis diagnosis and mortality prediction.[39] Subsequently, damage-associated molecular patterns increase as a

response to infection.[39] Calprotectin, a protein that is released following cellular damage, is higher in sepsis nonsurvivors.[39] High-mobility group box 1, a nuclear protein that promotes inflammation, was also associated with a poorer prognosis.[39]

Cellular constituents, for example membrane receptors and metabolites, may be beneficial for diagnosis and outcome prediction.[39] The cluster of differentiation (CD) helps with immunophenotyping cells, and CD13, CD14, CD25, and CD64 along with human leukocyte antigen (HLA-DR) have been studied in sepsis mortality prediction.[39] Presepsin (P-SEP) is released with activation of the immune response, and declines with appropriate antimicrobial therapy.[39] P-SEP has been studied more than other emerging biomarkers and is comparable to PCT in diagnosis and prognostication, with the added benefit of being detected earlier in the course of sepsis compared with PCT.[42]



Since NPs may encounter sepsis at any point in the care continuum, the ability to apply new findings and evidence-based recommendations to practice is unquestionably essential.

Many other studies on potential biomarkers are underway. Noncoding RNA and microRNA may have predictive values in sepsis along with sepsis mortality.[39] Gut permeability markers such as zonulin levels and intestinal fatty acid-binding protein increase accordingly with severity of sepsis.[39] Studies on soluble trigger receptor expressed in the myeloid cell-1 offer moderate accuracy in sepsis diagnosis.[39]

Another promising and readily available marker is the monocyte distribution width (MDW), which is available within the complete blood cell (CBC) count with differential. Sepsis induces morphologic alterations in monocytes, which respond quickly to infection.[43] A rising MDW reflects these changes, and may denote the progression of localized infection to sepsis or septic shock.[43,44] MDW may also be elevated in individuals who are immunocompromised.[43] Combining an MDW value of greater than 19-20 U for patients who are immunocompetent or greater than 22 U for patients who are immunocompromised with SIRS criteria or the qSOFA score enhances early identification of sepsis.[43-45]

Despite numerous promising sepsis biomarkers, more studies must be done to determine optimal tests. NPs already have several options at hand, and should not overlook readily available tests such as the CBC, lactate, urine antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila*, polymerase chain reaction testing, and the detection of resistance genes on standard cultures. Ultimately, a panel of biomarkers may be most appropriate to help diagnose sepsis and predict mortality.

Potential treatments. Novel sepsis treatment options represent another area of clinical imprecision. The SSC provides best-practice guidelines, though current studies are investigating innovative therapies. Extracorporeal blood purification via cytokine adsorption techniques allows for the uptake of inflammatory mediators, activated complement, and cytokines, which may be beneficial in early sepsis when there is an excess of pro- and anti-inflammatory responses.[46] Treatment with hydrocortisone, ascorbic acid, and thiamine resulted in quicker resolution of septic shock in some studies, but mortality was unaffected and the combination therapy has not been consistently helpful.[47-49] I.V. immunoglobulins may favorably modify pro- and anti-inflammatory processes.[50] Also, utilizing artificial intelligence (AI) is gaining traction in sepsis care. AI systems combine existing genetic data of patients who have sepsis with genome-wide studies and machine-learning methodology, thus identifying additional sepsis markers.[51] The SSC 2021 guidelines mention many of these potential treatments, but do not recommend them at this time due to lack of supporting studies. While these emerging concepts are often controversial, NPs should be aware of potential novel tests and treatments for sepsis and be prepared for future changes in guidelines.

Postsepsis ramifications. Understanding the physiologic foundation as well as patient factors that increase the risk of sepsis is not only important for prevention and early identification among those at high risk but also for postsepsis care. Among patients who survive a hospitalization for sepsis, in the 2 years after discharge, about half recover, compared with one-third who die and one-sixth who experience persistent impairments.[52] There is increased attention on postsepsis syndrome, which includes multiple long-term problems that reduce quality of life, such as physiologic or neurocognitive changes, functional disability, and progression of existing disease.[53,54] Sepsis survivors

have a significant increase in multiple physiologic conditions, such as cardiovascular disease, kidney injury, musculoskeletal issues, pulmonary dysfunction, and even integumentary and sensory alterations. Activities like reading and performing daily chores were reported to be more difficult. Sepsis survivors also reported sleep disruption; reduced libido; and increased fatigue, depression, and anxiety.[52,55] The severity of the initial sepsis event, timeliness of treatment, and poorer presepsis health may also contribute to postsepsis complications.[52]

Conclusion

Healthcare is an ever-changing field, and the identification and treatment of sepsis has changed greatly over the last 3 decades. NPs must be prepared to implement knowledge gleaned from well-designed studies and reputable sources. Since NPs may encounter sepsis at any point in the care continuum, the ability to apply new findings and evidence-based recommendations to practice is unquestionably essential. Patients with sepsis may present in the ED and hospital setting, clinic, long-term care facilities, or the community, and treatment may range from acute care to long-term sequelae management. Because NPs work across multiple healthcare settings, they can lead by example by providing education to colleagues and patients, along with promoting evidence-based practice. In the subsequent article, the 2021 SSC guidelines will be reviewed and discussed through a clinical vignette.

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