JAMA Clinical Guidelines Synopsis

Management of Sepsis and Septic Shock

Michael D. Howell, MD, MPH; Andrew M. Davis, MD, MPH

GUIDELINE TITLE Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

DEVELOPERS Surviving Sepsis Campaign (SSC), Society of Critical Care Medicine (SCCM), and European Society of Intensive Care Medicine (ESICM)

RELEASE DATE January 18, 2017

PRIOR VERSIONS 2012, 2008, 2004

TARGET POPULATION Adults with sepsis or septic shock

SELECTED MAJOR RECOMMENDATIONS

Managing infection:

- Antibiotics: Administer broad-spectrum intravenous antimicrobials for all likely pathogens within 1 hour after sepsis recognition (strong recommendation; moderate quality of evidence [QOE]).
- Source control: Obtain anatomic source control as rapidly as is practical (best practice statement [BPS]).
- Antibiotic stewardship: Assess patients daily for deescalation of antimicrobials; narrow therapy based on cultures and/or clinical improvement (BPS).

Managing resuscitation:

- Fluids: For patients with sepsis-induced hypoperfusion, provide 30 mL/kg of intravenous crystalloid within 3 hours (strong recommendation; low QOE) with additional fluid based on frequent reassessment (BPS), preferentially using dynamic variables to assess fluid responsiveness (weak recommendation; low QOE).
- Resuscitation targets: For patients with septic shock requiring vasopressors, target a mean arterial pressure (MAP) of 65 mm Hg (strong recommendation; moderate QOE).
- Vasopressors: Use norepinephrine as a first-choice vasopressor (strong recommendation; moderate QOE).

Mechanical ventilation in patients with sepsis-related ARDS:

- Target a tidal volume of 6 mL/kg of predicted body weight (strong recommendation; high QOE) and a plateau pressure of $\leq$30 cm H_2O (strong recommendation; moderate QOE).

Formal improvement programs:

- Hospitals and health systems should implement programs to improve sepsis care that include sepsis screening (BPS).

Summary of the Clinical Problem

Sepsis results when the body's response to infection causes life-threatening organ dysfunction. Septic shock is sepsis that results in tissue hypoperfusion, with vasopressor-requiring hypotension and elevated lactate levels.[1] Sepsis is a leading cause of death, morbidity, and expense, contributing to one-third to half of deaths of hospitalized patients,[2] depending on definitions.[3] Management of sepsis is a complicated clinical challenge requiring early recognition and management of infection, hemodynamic issues, and other organ dysfunctions.

Viewpoint

Characteristics of the Guideline Source

The guideline was developed by the SSC, with funding and governance from the SCCM and the ESICM (**Table**).[4] More than 30 additional organizations endorsed the guidelines. Guideline committee members were from numerous specialties and included methods experts and a patient representative. A formal conflict of interest management policy was followed.

Evidence Base

The guideline committee used the GRADE method. Population, intervention, control, and outcomes questions were constructed; professional librarians assisted with evidence reviews. Although the 2016 revision of definitions for sepsis were published during the guideline development process,[1] studies used for guideline evidence used earlier definitions of sepsis syndromes.

Benefits and Harms

The 2012 sepsis guidelines strongly recommended protocolized resuscitation with quantitative end points (early goal-directed therapy [EGDT]). Recommendations included specific goals for central venous pressure (CVP), MAP, and central venous oxygen saturation and formed the basis of national quality and performance metrics.[5]

Table. Guideline Rating

Standard	Rating
Establishing transparency	Good
Management of conflict of interest in the guideline development group	Good
Guideline development group composition	Good
Clinical practice guideline-systematic review intersection	Good
Establishing evidence foundations and rating strength for each of the guideline recommendations	Good
Articulation of recommendations	Fair
External review	Fair
Updating	Fair
Implementation issues	Fair

Since the 2012 guideline, substantial evolution has occurred in understanding the value of EGDT. Three key randomized trials enrolled patients presenting to the emergency department who had sepsis with shock or hypoperfusion. In the PROCESS trial (n=1341 patients from 31 US institutions), protocol-based approaches did not reduce 60-day mortality vs usual care (19.5% vs 18.9%; relative risk [RR], 1.04; 95% CI, 0.82-1.31; *P*=.83).[6] The similarly sized UK-based PROMISE[7] and the ARISE trial[8] from Australia and New Zealand both compared EGDT and usual care at 90 days and again found no difference in mortality (29.5% vs. 29.2%; RR, 1.01; 95% CI, 0.85-1.20; *P*=.90 and 18.6% vs 18.8%; RR, 0.98; 95% CI, 0.80-1.21; *P*=.90, respectively). Taken together, these trials suggest that while EGDT is safe, it is not superior to usual, nonprotocolized care. Usual care has also evolved since these trials to include more aggressive fluid resuscitation.[9] In response, the 2016 guideline has removed standard EGDT resuscitation targets, instead recommending that sepsis-induced hypoperfusion be treated with at least 30 mL/kg of intravenous crystalloid given in 3 hours or less. The authors note that sparse controlled data support this volume but its delivery allows resuscitation to begin during evaluation. In the absence of the former static EGDT targets (eg, CVP), the guideline emphasizes frequent clinical reassessment and the use of dynamic measures of fluid responsiveness (eg, arterial pulse pressure variation), given evidence that dynamic measures predict fluid responsiveness better than static measures do.

Because infection causes sepsis, managing infection is perhaps the most critical component of sepsis therapy. Mortality increases even with very short delays of antimicrobials. To optimize the risk-benefit profile, the strategy of initial broad-spectrum therapy requires meticulous attention to antimicrobial stewardship, including early appropriate cultures and daily review to reduce or stop antimicrobials. Additionally, anatomic source control (eg, identifying infected central lines, pyelonephritis with ureteral obstruction, intestinal perforation) should occur as soon as is practical.

Discussion

The PROCESS,[6] PROMISE,[7] and ARISE[8] trials have created substantial uncertainty in how to guide clinicians managing patients with sepsis and septic shock.[9] When usual care is equivalent to EGDT, what is a clinician to do? The most significant update to the guideline reflects this shift in evidence: removing most specific EGDT end points and emphasizing frequent reevaluation and patient-specific tailoring of hemodynamic therapy. Even with a change in consensus definitions for sepsis,[1] the guideline provides strong recommendations for a number of elements of standardized care, such as antimicrobial therapy, initial fluid volume, blood pressure goals, and vasopressor choice. Reflecting substantial consensus among experts, voting was by 75% of panel members with at least 80% agreement.

The guideline also provides a BPS for hospitals and health systems to develop formal sepsis performance improvement programs, given a suggestion of a mortality benefit. The recent NICE guidelines include tips on patient populations at higher risk of sepsis, clinical presentations, and initial laboratories for diagnosis and risk stratification. Tools such as order sets, checklists, posters, reminder cards, and electronic medical record decision support may assist clinicians in early recognition and appropriate treatment of sepsis.[10]

Pediatric sepsis guidelines will be published separately, with a specific guideline for ventilation in ARDS expected in 2017.

Areas in Need of Future Study or Ongoing Research

The best approach for hemodynamic therapy for sepsis has become more uncertain as evidence has accumulated. This extends even to the degree to which clinicians should use intravenous fluids as a foundation for resuscitation in some patient groups. The guideline correctly identifies this as a key area for further research.

The best way to improve public health related to sepsis also remains unsettled. For example, most US hospitals are required to report sepsis process measures. Collection of these data may be resource intense and may distract from other improvement efforts,[5] inadvertently promote overtreatment or unnecessary testing, or delay nonsepsis diagnoses.[3] At present, the international consensus definition of sepsis,[1] the new guidelines,[4] and CMS's core measure requirements are unsynchronized. Thoughtful alignment is in order to ensure meaningful reporting and improve patient outcomes.

Related Guidelines and Other Resources

UK National Institute for Health and Care Excellence (NICE)

Surgical Infection Society and Infectious Diseases Society of America (abdominal infections)

Infectious Diseases Society of America and American Thoracic Society (ventilator-associated pneumonia)

Surviving Sepsis Campaign

ARTICLE INFORMATION

Author Affiliations: Center for Healthcare Delivery Science and Innovation, University of Chicago, Chicago, Illinois (Howell); Pulmonary and Critical Care, University of Chicago, Chicago, Illinois (Howell); General Internal Medicine, University of Chicago, Chicago, Illinois (Davis).

Corresponding Author: Michael D. Howell, MD, MPH, University of Chicago, 850 E 58th St, Chicago, IL 60615 (mdh@uchicago.edu).

Published Online: January 19, 2017. doi:10.1001/jama.2017.0131

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Howell reports royalties from UpToDate and anticipated royalties from McGraw-Hill. No other disclosures were reported.

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801-810.
2. Liu V, Escobar GJ, Greene JD, et al. Hospital deaths in patients with sepsis from 2 independent cohorts. *JAMA*. 2014;312(1):90-92.
3. Rhee C, Gohil S, Klompas M. Regulatory mandates for sepsis care—reasons for caution. *N Engl J Med*. 2014;370(18):1673-1676.
4. Rhodes A, Evans L, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock. *Crit Care Med*. doi:10.1097/CCM.0000000000002255
5. Wall MJ, Howell MD. Variation and cost-effectiveness of quality measurement programs. *Ann Am Thorac Soc*. 2015;12(11):1597-1599.
6. Yealy DM, Kellum JA, Huang DT, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med*. 2014;370(18):1683-1693.
7. Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med*. 2015;372(14):1301-1311.
8. Peake SL, Delaney A, Bailey M, et al. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med*. 2014;371(16):1496-1506.
9. Levy MM. Early goal-directed therapy: what do we do now? *Crit Care*. 2014;18(6):705.
10. Damiani E, Donati A, Serafini G, et al. Effect of performance improvement programs on compliance with sepsis bundles and mortality. *PLoS One*. 2015;10(5):e0125827.