Emergency Medicine and the Surviving Sepsis Campaign: An International Approach to Managing Severe Sepsis and Septic Shock

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THE SIZE OF THE PROBLEM AND THE BEGINNING OF THE SOLUTION

Sepsis syndrome is a significant health care challenge with documented fatalities ranging from 23% and 46% depending on the phase of disease process evaluated.[1-3] The 750,000 cases of severe sepsis per year estimated in the United States are greater than congestive heart failure or breast cancer, colon cancer, and AIDS combined. With 500 deaths each day, the mortality parallels that of out-of-hospital acute myocardial infarction. Annual US costs are an estimated $16.7 billion.[3] Global estimates in Europe and Australia range from 51 to 206 cases per 100,000.[4,5] These figures underscore that severe sepsis is a common global disease entity that demands attention.

Emergency medicine plays a key role in the chain of survival for acute and highly prevalent diseases such as cardiac arrest, trauma, acute myocardial infarction, and stroke. Advancements in emergency medicine have led to improvements in morbidity and mortality, and sepsis is no exception. An estimated 387,616 patients with severe sepsis and septic shock initially present to the emergency department (ED) each year.[3,6] Additionally, the current national rate is expected to increase during the next several years, with a projected incidence of more than 1 million cases annually by 2020.[3]

The devastating consequences of severe sepsis and septic shock on mortality and utilization of health care resources have been prevalent for years but without the worldwide attention it has received recently. An international collaboration, the Surviving Sepsis Campaign (SSC), was formed under the administration of the Society of Critical Care Medicine, the European Society of Intensive Care Medicine, and the International Sepsis Forum.

The purpose of the SSC is to achieve a mortality reduction of 25% in 5 years and secure funding for research and improvements in patient care. Eight additional international multidisciplinary organizations subsequently joined the effort, with the first major goal being the creation of evidence-based guidelines for the management of severe sepsis and septic shock. The SSC and the American College of Emergency Physicians (ACEP) recognized the current and future impact of severe sepsis and septic shock on ED patients and resources while also realizing the importance of the ED in this chain of survival. Therefore, ACEP joined our international colleagues and represents the interests of emergency physicians across the United States in this global effort to improve patient care worldwide (phase I). After creation of the guidelines (phase II),[7] ACEP has taken a major leadership role in phase III of the campaign, converting guidelines to clinical practice change and improvement in outcome. This editorial updates the ACEP membership about ACEP's efforts on their behalf in this process.

The SSC incorporates a 3-phase focused effort.

Phase I: The Barcelona Declaration: Completed

The objectives of this phase were to determine a baseline of physician and public awareness of severe sepsis and septic shock. Additionally, this phase created a system of global accountability as the goal of mortality reduction was announced during the European Society of Intensive Care meeting in Barcelona, Spain, October 2002.

As part of this effort, the SSC sought to determine physician awareness of severe sepsis and septic shock and define areas of potential improvement. To this end, an international survey of 1,058 physicians from 6 countries was conducted.[8] The respondents were categorized as either "intensivist" (>50% clinical time in an adult ICU) or "other" (<10% clinical time in an adult ICU), of whom emergency physicians composed 23% (n=119). Sixty-eight percent of respondents were concerned about the lack of a common definition of sepsis. Of respondents concerned about a common definition, 83% stated that it may result in missed diagnosis. Less than 17% of physicians agreed on a common definition of sepsis despite the publication of definitions in the 1992 American College of Chest Physicians and Society of Critical Care Medicine sepsis definitions consensus statement[9] published before the survey was conducted in 2000. The results of this survey support the need for adoption of standardized nomenclature. Additionally, previous literature suggests that multiple definitions have led to considerable confusion.[8-10]

The survey highlighted the need for updated, objective, and functional definitions of sepsis phases, dissemination of the

Table 1. Definition of sepsis: documented or presumed infection and 2 or more of the following clinical variables.*

Categories	Variables	Definitions
Documented or presumed infection	Confirmed or clinically suspected pathologic process induced by microorganisms	Pathologic or radiographic confirmation not required to begin therapy if bedside clinical suspicion is high
General inflammatory variables		
	Hypo-/hyperthermia	Core Temperature >38.3°C or <36°C (>100.9°F or <96.8°F)
	Tachycardia	>90 Beats/min or >2 SD above normal for age
	Tachypnea	>20 Breaths/min
	Altered mental status	
	Hyperglycemia†	>120 mg/dL Or 7.7 mmol/L in the absence of diabetes
	Leukocytosis/ leukopenia	WBC >12 μL^{-1} or <4 μL^{-1} or normal WBC count with >10% immature forms
	or >10% Bands	
Tissue-perfusion variables		
	Hyperlactemia	Lactate >2 mmol/L‡
	Decreased capillary refill/mottling	>2 seconds
Mild organ dysfunction	Support clinical suspicion of sepsis	

*This table includes only parameters pertinent to US-based emergency physicians. European emergency physicians may also include C-reactive protein levels >2 SD above normal and procalcitonin levels >2 SD above normal. Table adopted from 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference; see reference[11]. Clinical variables should not be easily explained by another etiology.
†In the immunocompromised population (ie, transplant patients), hypoglycemia in the absence of diabetes should increase the suspicion of infection.
‡Definition lists as lactate >1; however, most US-based laboratories consider lactate increased when levels are >2 mmol/L.

Table 2. Definition of the phases of sepsis, severe sepsis, and septic shock.[7-9]

Variable	Definition
Inflammatory response	>/=2 Of the following:
	*Temperature >38.3°C or <36°C (>100.9°F or <96.8°F)
	WBC count >12,000 or <4,000 or >10% bands
	Pulse rate >90 beats/min
	Respiratory rate >20 breaths/min
	Hyperglycemia >120 mg/dL†
	Altered mental status
	Lactate >2‡
	Decreased capillary refill/mottling (See Table 1)
Sepsis	Inflammatory response + a presumed or identified source of infection
Severe sepsis	Sepsis + organ dysfunction, hypotension, before fluid challenge, or lactate ≥4 mmol/L§
Septic shock	Severe sepsis + hypotension (despite 20–40 mL/kg fluid challenge)

*Hyper/hypothermia in the pediatric population: core temperature >38.5°C or <35°C.[11]
†Hyperglycemia without history of diabetes. Hypoglycemia without diabetes, in an immunocompromised patient increases suspicion of infection.
‡Definition listed as lactate >1; however, most US-based laboratories consider lactate increased when lactate >2.
§Organ dysfunction can be defined as respiratory failure, acute renal failure, acute liver failure, coagulopathy, or thrombocytopenia. Laboratories that will suggest organ dysfunction include Pao_2 (mm Hg)/Fio_2 <300, creatinine >2.0, or creatinine increase >0.5 mg/dL, INR >1.5, PTT >60 s, platelets <100,000/μL, total bilirubin >4 mg/dL, Glasgow Coma Scale score <13, see references[11,21]. Clinical variables should not be easily explained by another etiology.

updated definitions, and availability of tools to assist in identification and treatment of patients in the various phases of this disease process. Subsequently, updated definitions were completed at the 2001 International Sepsis Definitions Conference,[11] which included updating and expanding the definition of sepsis (Table 1) while maintaining the established definition of severe sepsis and septic shock (Table 2). Although the new definitions assist in the evolution of understanding, sepsis syndrome remains an elusive entity recognized by most and clearly defined by none. Currently there are over 7 different models for the quantification of organ dysfunction and failure. A common observation is that outcome is related to the number of failing organs and the degree of dysfunction within each organ system. Inherent in the ambiguity is the balance between the clinicians' desire to clearly define organ dysfunction as discrete numerical values with the evolving clinical reality of a syndrome which may be defined by graded degrees of organ dysfunction rather than irreversible failure. The new definitions are another essential step directing the framework of terminology which may assist the physician in providing optimal care.[12]

Additionally identified in phase I was the desire of physicians to have one source that highlights management updates of severe sepsis and septic-shock patients with levels of supporting evidence, which became the focus of phase II.

Phase II: Surviving Sepsis Guideline Development for the Management of Severe Sepsis and Septic Shock: Completed

In phase II, 40 representatives from 11 international medical professional organizations from around the world reviewed the literature pertaining to severe sepsis and septic shock management. The goal was to provide guidelines that would be of practical use for the bedside physician. The representatives agreed on a series of recommendations from the acute management to the subacute management of this disease process.[7] The ACEP representative to the SSC and additional ACEP members contributed significantly to the process of guideline development. Seventy-five percent of what the ACEP representatives considered moderately important content and revisions was incorporated. Moreover, 100% of what the ACEP representatives considered major content and revisions was incorporated into the guidelines. ACEP's Clinical Policies Committee provided additional revisions

Table 3. Preliminary 6-hour severe sepsis/septic shock bundle (subject to revision; once severe sepsis or septic shock has been established, accomplishing the following endpoints completes the bundle).*

Bundle Element	Description
1. Measure serum lactate level	If sepsis, severe sepsis, or septic shock suspected
2. Appropriate cultures and broad-spectrum antibiotics	Within 3 hours of presentation
3. In the event of hypotension (SBP <90 mm Hg, MAP <65 mm Hg) or lactate ≥4 mmol/L	Initial fluid resuscitation with 20–40 mL/kg body weight crystalloid or colloid equivalent
4. Vasopressors	For hypotension not responding to initial resuscitation to maintain MAP >65 mm Hg
5. In the event of septic shock (MAP <65 despite 20–40 mL/kg fluid bolus) or lactate >4 mmol/L	CVP and Scv_{O2} measured. Maintain CVP >8 mm Hg Activate MAP >65 mm Hg Measure Scv_{O2}
6. If Scv_{O2} <70% with CVP >8–12 mm Hg, and MAP >65 mm Hg	Transfusion PRBC if hematocrit <30% Then inotropes until Scv_{O2} >70%

SBP, Systolic blood pressure; *MAP,* mean arterial blood pressure; *SCV,* central venous oxygenation saturation; *CVP,* central venous pressure; *PRBC,* packed red blood cells.
*Table adopted from discussion of the SSC Guidelines Steering Committee and the SSC Guidelines Writing Committee in Catania, Italy, September 13, 2004.

to the guidelines before they were formally endorsed by ACEP.

Each recommendation is graded by the level of evidence available. The levels of evidence ranged from randomized controlled clinical trials to expert opinion. Of the recommendations graded as lower levels of evidence, some require further study, and others will most likely not be studied, because of perceived harm to the control group. For example, because there are no outcome studies on the use of physiologic vasopressin in refractory septic shock, it was graded at a lower level, and further information is anticipated that will assist with revisions of this guideline. Although data about the use of source control are limited, it is unlikely that patients would be randomized to a study arm that did not include source control, which leads to a low level of evidence but is appropriately recommended.

Specific recommendations pertinent to the emergency physician included resuscitation; appropriate antibiotics, cultures and source control; lung protective strategies and use of drotrecogin alfa and steroids when appropriate. The primary resuscitation component included hemodynamic optimization using early goal-directed therapy. Early goal-directed therapy is an organized approach at hemodynamic optimization performed upon detection of severe sepsis or septic shock. The original randomized controlled trial[13] identified a 16% absolute mortality benefit in patients receiving early goal-directed therapy. This therapeutic strategy results in outcome benefits greater than any treatment evaluated by previous sepsis trials. Candidates for EGDT are described as those who are hypotensive despite a fluid challenge or those with a lactate ≥4 mmol/L. The utility of lactate as a biomarker demonstrating oxygen debt and as a predictor of mortality when not aggressively addressed is well established.[14-16] EGDT also resulted in significant financial benefits at the study institution due to decreased ICU and hospital days in survivors. Additional financial benefit resulted from decreased use of vasopressors, pulmonary artery catheters, and decreased use of mechanical ventilation. Reduced hospital resource utilization decreased yearly hospital costs at the study institution by $26,359,350 (E. P. Rivers, personal communication, October 2004). Preliminary work at the University of Pittsburgh on a formal cost-effectiveness analysis suggests that early goal-directed therapy is extremely cost-effective throughout a wide range of assumptions. Early goal-directed therapy remained cost-effective even if its 60-day mortality effectiveness was only 20% of that reported by Rivers et al.[13,17]

The SSC guidelines for management of severe sepsis and septic shock[7] are meant to be recommendations for the practicing bedside physician. Although many of the guidelines are targeted for the ICU, several recommendations are pertinent to clinicians with acute resuscitation expertise, such as the emergency physician who treats acutely presenting severe sepsis and septic shock patients. An article reviewing the SSC guidelines that pertain to ED practice and contemporary management strategies for the ED patient with severe sepsis and septic shock is being developed and may be forthcoming in a future issue of *Annals of Emergency Medicine*. Resource limitations may prevent some physicians from accomplishing these goals, and no recommendation takes the place of sound clinical judgment as individual patient presentations must be taken into account.

Phase III: Implementation: In Progress

The SSC and collaborators recognized that a focused implementation plan would be required to demonstrate measurable improvement in severe sepsis and septic shock outcomes. To assist in accomplishing this goal, the SSC formed a partnership with the Institute for Healthcare Improvement. The Institute for Healthcare Improvement is a nonprofit organization dedicated to accelerating the improvement of health care by advancing quality and value of health care resources.[18]

The 2 organizations are working together to incorporate a relatively new concept called "treatment bundles" in the management of severe sepsis and septic shock. A treatment bundle is a group of interventions that, when administered together, may be more efficacious than when administered individually. A treatment bundle, as defined by the Institute for Healthcare Improvement, incorporates a few key elements from the guidelines that, when combined and performed within the same time and space, enhance the guidelines, generating improved outcomes.[19]

ACEP representatives had significant input into developing a 6-hour resuscitation bundle and a 24-hour subacute care bundle. The 6-hour bundle focuses on identifying high-risk patients, as well as quantifying and administering early aggressive resuscitation with specific endpoint goals. Therapies involve the correction of hypovolemia, hypotension, and myocardial

depression, which all contribute to global tissue hypoxia in severe sepsis and septic shock. ACEP and other US representatives convened with international representatives in Italy in September 2004. Global agreement on the 6-hour and 24-hour bundles were solidified, and plans to facilitate implementation were discussed.

The 3 components of the 6-hour resuscitation bundle are early identification, early antibiotics and cultures, and early goal-directed therapy (Table 3). The 24-hour bundle includes administration of drotrecogin alfa (Xigris) per hospital guidelines, administration of steroids if vasopressors are required for 6 hours, administration of glucose control (150 mg/dL) and lung protective strategies (maximum plateau pressure of 30 cm/H_2O).

Additional resources, which the SSC and Institute for Healthcare Improvement have made or plan to make available to interested practitioners, are listed below.[20]

Getting started: Information about how to set up a quality sepsis program, including PDF files with sample physician orders, nurse flow sheets, quality indicators, and quality measurement forms, among others.

Web-based database: A free Web-based database called "improvement tracker" is currently available online (available at: http://www.ihi.org/ihi/workspace/tracker) to all participants to track their programs over time and to compare their quality progress to that of national and international programs.

Online support: Access to designated experts in the field is provided to further assist with problem solving.

Internet list-serve: A list-serve of ED-based sepsis programs is provided to facilitate dialogue and assist in problem solving.

More information can be found at the Institute for Healthcare Improvement Web site, available at http://www.ihi.org/IHI/Topics/CriticalCare/Sepsis. Additional links are provided through the ACEP Critical Care Section (available at http://www.acep.org; search "critical care section").

ACEP has taken an active role in representing the interests of the emergency medicine community nationally and internationally. World leaders in the fields of critical care and infectious disease support improving outcomes in severe sepsis and septic shock patients. A significant impact on morbidity and mortality is realized when these patients are identified and treated aggressively early in the disease process.

Other specialties within the United States and abroad are understanding why physicians choose emergency medicine: because the treatment choices emergency physicians make in the first few hours can make a life-or-death difference. Our colleagues and our patients are calling on emergency medicine to make that difference. The answer from emergency medicine, a specialty characterized as one that responds to crisis, as well as change, will be resounding. How will you choose to answer?

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REFERENCES

1. Dellinger RP. Cardiovascular management of sepsis shock. *Crit Car Med*. 2003;31:946-955.
2. Osborn TM, Tracy KJ, Dunne JR. Epidemiology of sepsis in patients with traumatic injury. *Crit Care Med*. 2004;32:2234.
3. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29:1303-1310.
4. Brun-Buisson C, Meshaka P, Pinton P, et al, and the EPISEPSIS Study Group. EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. *Intensive Care Med*. 2004;30:580-588.
5. Finfer S, Bellomo R, Lipman J, et al. Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units. *Intensive Care Med*. 2004;30:589-596.
6. Rivers EP, Nguyen HB, Huang DT, et al. Critical care and emergency medicine. *Curr Opin Crit Care*. 2002;8:600-606.
7. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Intensive Care Med*. 2004;30:536-555.
8. Poze MRG, Ramsay G, Gerlach H, et al. An international sepsis survey: a study of doctors' knowledge and perception about sepsis. *Crit Care*. 2004;8:R409-R413.
9. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis: the ACCP/SCCM Consensus Conference Committee: American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992;101:1644-1655.
10. Matot I, Sprung CL. Definition of sepsis. *Intensive Care Med*. 2001; 27(suppl 1):S3-S9.
11. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International sepsis definitions conference. *Crit Care Med*. 2003;31:1250-1256.
12. Nathens AB, Marshall JC. Sepsis, SIRS, MODS: What's in a name? *World J. Surg*. 1996;20:386-391.
13. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345:1368-1377.
14. Knoblich B RE, Nguyen B, Rittinger W, et al. Lactic acid clearance (Lactime) in the emergency department: Implications for the development of multisustem organ failure and death. *Academic Emergency Medicine*. 1999;6:479.
15. Nguyen HB, Rivers EP, Knoblich BP, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med*. 2004;32:1637-1642.
16. Shapiro NI, Howell MD, Talmor D, et al. Serum lactate as a predictor of mortality in emergency department patients with infection. *Ann Emerg Med*. 2005;45:524-528.
17. Huang DT, Angus DC, Dremiszov TT, et al. Cost-effectiveness of early goal-directed therapy in the treatment of severe sepsis and septic shock. *Crit Care*. 2003;7(suppl 2):232.
18. Institute for Healthcare Improvement. About Us. Available at: http://www.ihi.org. Accessed May 26, 2005.
19. Resar R. Sepsis bundle history. Available at: http://www.ihi.org. Accessed May 26, 2005.
20. Institute for Healthcare Improvement. Sepsis, Tools. Available at: http://www.ihi.org/IHI/Topics/CriticalCare/Sepsis. Accessed May 26, 2005.
21. Marshall JC, Cook DJ, Christou NV, et al. Multiple organ dysfunction score: A reliable descriptor of a complex clinical outcome. *Crit Care Med*. 1995;23:1638-1652.