Novel Approaches to Sepsis in the Emergency Department

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INDRODUCTION

With a mean treatment cost of $22,000 per case, sepsis currently accounts for at least $16.7 billion dollars in healthcare expenditures each year.[1] Despite significant advances in the understanding of sepsis pathophysiology and in novel therapeutic approaches, the mortality rate from severe sepsis has changed little over the past 25 years, remaining at approximately 30-50%. In the United States approximately 215,000 people die from sepsis annually, roughly equaling the number of deaths from acute myocardial infarction.[1]

The impact of sepsis is felt not only in the intensive care units and hospital wards, but also in the emergency department (ED), as many patients who develop sepsis receive their diagnosis and initial treatment in the ED. Recent major trials have shown that ED resuscitation and other early critical care interventions can have a substantial impact on sepsis mortality. This article will define sepsis terms, review pertinent pathophysiology, and provide a comprehensive update for emergency physicians regarding the latest treatments for septic patients in the ED.

SEPSIS TERMINOLOGY

While the term "septic" is often used informally to describe patients with a broad range of illness severity, a standardized classification system was created in 1992 by the American College of Chest Physicians and the Society of Critical Care Medicine with specific, tiered definitions designed to more accurately represent the spectrum of sepsis disease.[2] The first category, ***systemic inflammatory response syndrome (SIRS)***, does not require an infectious etiology and is met when patients demonstrate at least two of the following criteria: 1) temperature >38°C or <36°C; 2) heart rate > 90 beats per minute; 3) respiratory rate > 20 breaths per minute or $PaCO_2$ < 32 mm Hg; and 4) white blood cell (WBC) count > 12K, < 4K, or with > 10% bands. Given that many ED patients with mild illnesses may meet these criteria, SIRS has low specificity and is of limited utility in the ED diagnosis of critical illness.

The term ***sepsis*** is applied when SIRS is accompanied by a documented or suspected infection, most commonly pneumonia, urinary tract infection, or skin/soft-tissue infection. ***Severe sepsis*** refers to sepsis with evidence of hypotension, organ dysfunction, or hypoperfusion evidenced by lactic acidosis, oliguria, or mental status changes. Severe sepsis becomes ***septic shock*** when hypotension is refractory to adequate fluid resuscitation, typically defined as a 500cc bolus of intravenous (IV) crystalloid. As expected, mortality rises with increasing illness severity, ranging from a 16% rate in sepsis to 46% in fulminant septic shock.[3]

Finally, ***multiple organ dysfunction syndrome (MODS)*** is an often-irreversible final common pathway in which several organ systems fail, resulting in conditions such as acute respiratory distress syndrome (ARDS), acute tubular necrosis (ATN), and coagulopathies. A central theme of this discussion

and of the strategies proposed by Rivers and others is that septic patients do not typically die immediately in the ED from septic shock, but they instead die several days into an ICU course as a result of MODS.[4] Although MODS typically takes at least a day after the onset of septic shock to fully manifest itself and is therefore less commonly encountered by emergency physicians, the consideration of aggressive new resuscitation strategies in the ED can help prevent its development and thereby substantially reduce patient mortality.

Pathophysiology of Sepsis

In a healthy physiologic response to tissue injury or infection, pro- and anti-inflammatory mediators are released to protect the host from damaging effects of insults while facilitating tissue healing and repair. In sepsis, however, homeostasis between these competing mediators may be lost, generally tilting the balance toward excessive inflammation.[5] Sepsis can therefore become an auto-destructive process in which the normal localized physiologic response to infection becomes generalized and over-amplified, injuring not only infected tissues but also organs remote from the involved site.[5] Examples of this induced auto-injury pattern include pulmonary endothelial injury (ARDS), renal microvascular and tubular damage (ATN), and malperfusion from shunting and myocardial depression (cardiovascular failure).[6]

Two of the central mediators of sepsis are nitric oxide (NO) and the cytokine tumor necrosis factor alpha (TNFα). Along with endotoxin released by gram-negative organisms, these mediators may damage endothelial walls and cause increased microvascular permeability, impairing oxygen extraction by increasing the oxygen diffusion distance. They also induce shunting, further decreasing flow to functional tissue capillary beds and thereby reducing tissue oxygen exchange.

Inflammatory mediators impact oxygenation on the cellular level as well. TNFα, interleukin-1 (IL-1), and endotoxin synergistically induce cellular damage. NO further impedes mitochondrial electron transport and halts oxidative phosphorylation; lactic acidosis results when damaged cells are thus unable to utilize oxygen despite adequate tissue perfusion. These effects occur in tissues throughout the body, but their impact is particularly important in the heart. TNFα, IL-1, and NO significantly depress cardiac ejection fraction, further exacerbating the shock state. This sepsis-induced cardiac dysfunction was once believed to evolve as a late-stage effect due to global hypoxia, but it is now recognized as beginning early in sepsis as a result of the actions of these inflammatory mediators.

By virtue of venous pooling and fluid transudation, cytokine-mediated effects also contribute to the relative and absolute hypovolemia found in early stages of severe sepsis and septic shock. While septic shock is traditionally perceived to be a hyperdynamic state with increased cardiac output, much of this high output is attributable to tachycardia and low systemic vascular resistance without true improvement of perfusion. Furthermore, a hypodynamic state is often present in late-stage sepsis, with reduced cardiac output resulting from myocardial depression.[5]

Treatment Approach for Severe Sepsis and Septic Shock

Volumes have been written regarding airway management, vasopressor therapy, and antibiotic choices in the treatment of sepsis. While we will briefly address these topics, our primary focus is on three newer therapeutic management strategies: 1) Early goal-directed therapy, 2) Low-dose corticosteroids, and 3) Recombinant activated protein C.

As with all resuscitations, attention to airway and ventilation in the septic patient is paramount. Standard indications of the need for endotracheal intubation should be implemented. Of note with regard to other indications for mechanical ventilation, however, is the fact that systemic oxygen demand can be reduced via sedation, analgesia, and cooling measures for febrile patients. Some authors advocate the use of such a strategy to reduce oxygen demand in patients with septic shock.[7]

Monitoring

Because traditional sphygmomanometers may provide unreliable data for patients in shock, invasive hemodynamic monitoring via arterial catheterization is generally recommended. Central venous monitoring may also be useful, but the clinician must recognize the limitations of interpreting the data in patients with pneumonia. Such patients may have spuriously elevated central venous pressure (CVP) measurements, reflecting backup pressure from high pulmonary vascular resistance. Lactate levels are extremely helpful in recognizing subclinical shock, and serial measurements aid in gauging response to therapy. Other monitors for critically ill patients, such as esophageal doppler techniques and echocardiography, may also be useful.[8-9]

Fluid and Vasopressor Choices

Formerly a topic of considerable debate, the choice of crystalloid versus colloid in resuscitation has been clarified in recent years. Two meta-analyses have demonstrated improved outcomes with crystalloids, while others have shown equivalence.[10-12] Given that colloids are much more expensive than crystalloids, their use cannot be justified in sepsis resuscitation outside of the indication for patients with spontaneous bacterial peritonitis.

Patients who are refractory to fluid resuscitation—manifested by minimal improvements in lactate levels, continued oliguria, and other perfusion signs—may benefit from the use of vasopressive agents. The "best" pressor in septic shock has also been a longstanding controversial issue. A consensus statement from the Society of Critical Care Medicine offers no formal guidelines or recommendations, but does appear to favor the use of norepinephrine.[13] At this time, there is no definitive evidence of the superiority of one vasopressive agent over another. Most importantly, regardless of the agent chosen, its introduction should be treated as a therapeutic trial; the clinician should measure indices of perfusion before and after the introduction of the pressor in order to determine its efficacy.

Pathogen Identification and Antibiotic Therapy

Prompt delivery of appropriate antibiotics is well established as a critical component of sepsis therapy. Although generally of low yield and not clearly demonstrated to impact the outcome of septic patients, blood cultures drawn prior to the initiation of antibiotic therapy are nonetheless recommended. For intubated patients who may be septic due to pneumonia, consider ED-based non-bronchoscopic bronchoalveolar lavage performed by respiratory therapists; a study of an ED patient cohort intubated for community-acquired pneumonia demonstrated a significantly higher rate of pathogen identification compared to standard care, even when instituted after the first dose of antibiotics.[14]

Early Goal-Directed Therapy

In a landmark study, Rivers et al. demonstrated that a strategy of early goal-directed therapy (EGDT) decreases the in-hospital mortality of patients who present to the ED in septic shock.[15] "Goal-directed therapy" refers to the practice of resuscitating patients to defined hemodynamic endpoints, targeting specific cardiac preload, afterload, contractility, oxygen delivery, and oxygen consumption goals.[16] These parameters are assessed via the monitoring of central venous pressure (CVP), mean arterial pressure (MAP), and central venous oxygen saturation ($S_{CV}O_2$), which is used as a surrogate marker for oxygen delivery and consumption.

The first goal in this approach is to fluid resuscitate the patient to a CVP of 8-10 mm Hg using IV crystalloid boluses. Once that parameter has been achieved, a MAP of 65-90 mm Hg is targeted using vasopressors or vasodilators. Next, an $S_{CV}O_2$ of 70% is sought utilizing red blood cell transfusions, dobutamine support, and occasionally sedation and mechanical ventilation.

As compared to the standard care control patients, those who underwent six hours of EGDT in the ED had a 16% reduction of hospital mortality, a mortality benefit that persisted at the 28- and 60-day endpoints.

Much like the "golden hour" in trauma, this study supports the idea of an ED "golden six hour" window for the treatment of patients in septic shock.

Despite such a clear benefit, this strategy has yet to become widely used in EDs, potentially due to perceptions of management complexity, concerns about significantly longer ED stays, or lack of staffing and resources to apply such a comprehensive treatment approach. Similar to the "stroke team" concept used by some hospitals, development of "sepsis teams" that can be paged to the ED for the purpose of implementing EGDT in appropriate patients may be considered. Another obstacle to the application of EGDT may be the limited availability and expense of $S_{CV}O_2$ catheters. At the time of printing, these catheters are only available from a single manufacturer at a cost of $400 each.[17] Though not proven in trials, the concepts underlying EGDT may be implemented without these devices. $S_{CV}O_2$ can be periodically measured using venous blood samples from central venous catheters.

The Role of Low-Dose Corticosteroids in the ED

Steroid therapy in sepsis promptly fell out of favor in the 1980s after the publication of several trials and meta-analyses showing worse outcomes. In the past four years however, steroids have re-emerged as an integral adjunct to be considered in the treatment of septic shock. Why the change in recommended management? Recent studies have demonstrated that many septic shock patients have relative adrenal insufficiency or inadequate cortisol responsiveness to the shock state, leading to refractory hypotension. Current steroid therapy in septic shock is directed at treating this relative adrenal insufficiency using low dose physiologic steroids (50-100 mg IV hydrocortisone every six hours and 50 μg PO fludrocortisone per day) instead of high dose anti-inflammatory steroids (dexamethasone 6mg/kg or methylprednisolone 30 mg/kg).

In 2002 a prospective double-blind placebo-controlled trial by Annane et al. demonstrated a significant mortality benefit of a seven-day course of low-dose corticosteroids among a large subgroup of ICU patients in septic shock.[18] The number of patients needed to treat (NNT) in order to save one life at the 28-day mark in this study was an impressively low seven among the 77% of their sample found to have relative adrenal insufficiency. This effect was achieved without increased serious adverse effects compared to placebo. No benefit was demonstrated in those patients with normal adrenal reserve, as determined by the cosyntropin stimulation test.

This cosyntropin stimulation test can be easily undertaken in the ED by drawing a baseline serum cortisol level, giving an IV bolus of 250 μg of cosyntropin, and then repeating the serum cortisol level 30 minutes later. It is important for emergency physicians to recognize that even a single dose of etomidate may suppress the cortisol response, thereby making the interpretation of this test difficult. Because cortisol levels may take several days to return at some facilities, we recommended starting 50 mg IV hydrocortisone every six hours in appropriate patients. If the test shows a normal response to the cosyntropin challenge (> 9 mcg/dL elevation after cosyntropin), then relative adrenal insufficiency has been ruled out and steroids should be discontinued.

Activated Protein C

Advances in the understanding of the inflammatory pathophysiology of sepsis have inspired the search for the "magic bullet," an anti-cytokine or anti-inflammatory agent to quell this hyper-inflammation. Unfortunately, despite hundreds of millions of dollars in drug development expenses, most of the more than 30 trials looking for this bullet failed to show any treatment benefit.[19-20] Examples of once-promising agents and techniques that failed to show benefit in randomized trials include anti-cytokine agents such as anti-TNFα, anti-IL-1, and anti-NO, as well as anti-endotoxin, anti-oxidants, antithrombin, plasmapheresis, and IV immunoglobulin.[20]

Recently however, drotecogin alfa, a recombinant form of activated protein C (APC), was demonstrated to decrease mortality in patients with severe sepsis and significant organ dysfunction; APC was approved by

the FDA in November 2001. The efficacy of this agent may arise from its anti-thrombotic, anti-inflammatory, and pro-fibrinolytic properties.

A randomized double-blind multicenter trial by Bernard et al. evaluated the use of recombinant APC in nearly 1700 patients with less than 24 hours of severe sepsis or septic shock and demonstrated a relative mortality reduction of 19.4% (absolute mortality reduction of 6.1%).[21] The NNT was calculated as one life saved for every 16 patients treated. Treatment benefit of drotecogin alpha persisted regardless of patients' protein C deficiency status. Subgroup analyses demonstrated the greatest benefit in the sickest patients—those whose predicted mortality exceeded 60% based on a multivariate model (principally patients with acute physiology and chronic health evaluation (APACHE) II scores above 25). It is unclear whether or not survival benefit extends to patients with lower APACHE II scores.[22]

Treatment with APC is not without drawbacks. APC is expensive, costing nearly $7,000 per treatment in a recent pharmaceutical company-sponsored trial.[23] Patients treated with APC had more severe bleeding events compared to patients who received placebo (3.5% event rate in the study group versus 2% in the placebo group), resulting in one life-threatening complication for every 66 patients treated.[21] With the high cost and potential bleeding risk, patient selection is crucial. Many institutions, including our own, have strict use criteria or limit it to prescription by intensivists.

Of note to emergency physicians, the above-mentioned study evaluated an ICU-based population, and the utility of this treatment has not been assessed in the ED. As issues related to ED overcrowding continue to increase patient wait times for available ICU beds, there may be a potential role for ED-based administration of this drug in the future.

Conclusion

The successful treatment of septic patients starts with prompt, judicious care in the ED. Aggressive, goal-directed resuscitation and early appropriate antibiotics are the cornerstones of therapy. Stress dose steroids and activated protein C for patients in septic shock should also be considered.

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