Evidence-Based Management of Severe Sepsis and Septic Shock

Joseph M. Kontra, M.D.
Infection Specialists of Lancaster

ABSTRACT

Sepsis remains a frequent and deadly diagnosis in hospitals across the United States. It continues to exact a heavy toll in morbidity, mortality, and resource consumption despite decades of intense research and technological advances. In the last few years, however, scientific endeavor has begun to define intervention strategies that impact outcome. This article summarizes the current literature and expert opinion on this important topic, and suggests a specific approach to the management of sepsis in 2006.

INTRODUCTION

Over 750,000 cases of sepsis occur in the United States annually, a rate of 3 cases per 100,000 population. In comparison, there are 900,000 cases of acute myocardial infarction per year, and 700,000 cases of acute stroke (1). Crude mortality rates of sepsis (29%), AMI (25%), and stroke (23%) are comparable as well. Mortality rates for patients who progress to severe sepsis or septic shock are bleaker still, at 40% and 50% respectively (1). The excess cost attributable to the development of sepsis is $22,100, which translates to an annual national cost of $16.7 billion (1).

DEFINITIONS

Definitions established in 1992 by the American College of Chest Physicians and the Society for Critical Care Medicine Consensus, have withstood the test of time. The ***Systemic Inflammatory Response Syndrome (SIRS)*** is a clinical syndrome that results from an exogenous stimulus that causes dysregulation of the body's homeostatic balance of pro- and anti-inflammatory mechanisms. It can be triggered by such diffuse causes as trauma, burns, toxins, ingestions, pancreatitis, pulmonary barotrauma, and infection (2). The diagnostic criteria for SIRS are summarized in Table 1. ***Sepsis*** is defined as SIRS resulting from a suspected or identified infection. ***Severe Sepsis*** requires, in addition, evidence of hypotension or organ dysfunction, examples of which are listed in Table 2. ***Septic shock*** occurs when severe sepsis is refractory to fluid resuscitation, or when pressor agents are required.

TABLE 1: DIAGNOSTIC CRITERIA FOR SIRS

- core temp ≥ 38°C (100.4°F) or ≤36°C (96.8°F)
- heart rate ≥ 90 beats per minute
- respiratory rate ≥ 20 breaths per minite or $PaCO_2$ ≤ 32 mmHg
- wbc ≥ 12,000/mm^3 or ≤4,000/mm^3 or >10% bands

TABLE 2: CRITERIA FOR THE DIAGNOSIS OF SEVERE SEPSIS

- BP ≤ 90 mmHg or MAP ≤ 70 mmHg for over 1 hr.
- Urine Output ≤ 0.5 ml/kg/hr or acute renal failure
- PaO_2/FiO_2 ≤ 250
- Hepatic dysfunction
- Altered Mental Status
- Platelet count ≤ 80,000/mm^3 or DIC
- pH ≤ 7.30 and plasma lactate ≥ 4 mmol/L

PATHOPHYSIOLOGY

Sepsis results when an infectious agent or its biochemical products cause the host's normal protective inflammatory response to become dysregulated and pervasive. This immunologic dissonance results in widespread tissue injury, and leads to a pro-inflammatory and pro-coagulant milieu (2). It has perhaps been best described as malignant intravascular inflammation, as it is unregulated, spreads beyond the original portal of entry, and is self-sustaining.

The result of the inflammatory storm of sepsis is progressive multi-system organ damage. This results from a unique and complex derangement of tissue perfusion and cellular dysfunction. In cardiogenic or hemorrhagic shock, a fall in cardiac output causes hypotension, hypo-perfusion, and anaerobic cellular metabolism.

In septic shock there is a far more complex interplay of pathologic vasodilation, altered flow distribution, relative and absolute hypovolemia, depression of myocardial function, and direct mitochondrial and cellular toxicities (3).

MONITORING AND ENDPOINTS

The pathophysiology outlined above translates into clinical and laboratory parameters that provide the clinician with indicators of a patient's hemodynamic and perfusion status. These parameters also provide potential end points for resuscitation efforts, and serve as indicators of overall response to treatment.

Hypotension is a cardinal manifestation of sepsis. Mean arterial blood pressure (MAP) below 65 mmHg portends inadequate perfusion and tissue hypoxia. Nonspecific clinical manifestations of tissue hypoxia can include altered mental status, oliguria, ileus, and cutaneous changes.

Central venous pressure (CVP) is an important indicator of the adequacy of fluid resuscitation. Failure to rapidly achieve or maintain a CVP >8 mmHg has been correlated with a poor prognosis in severe sepsis and septic shock (3). A target CVP range of 8-12 mmHg is ideal. In mechanically ventilated patients on positive end expiratory pressure (PEEP), the target should be adjusted to at least 12-15 mmHg to compensate for increases in intra-thoracic pressure.

Oxygen-derived variables such as central venous oxygen saturation (S_VO_2) or mixed venous oxygen saturation ($S_{MV}O_2$) may also provide evidence of tissue hypoxia. These measures, however, represent the algebraic sum of oxygenation in all venous return, and may therefore not reflect relative distributive hypo-perfusion of certain organs. Nonetheless, saturations below 70% correlate with global tissue hypoxia and a poor prognosis in severe sepsis and septic shock (4).

Biochemical indicators of tissue hypoxia and anaerobic metabolism include metabolic acidosis and elevated plasma lactate levels. Hyperlactatemia, in fact, can precede a fall in blood pressure in patients who are transitioning from sepsis to severe sepsis, and is therefore an important screening parameter in the febrile normotensive patient. It can result not only from anaerobic metabolism due to hypo-perfusion, but also from direct failure of cellular mitochondrial metabolism, increased glycolysis, and decreased clearance from the liver. In severe sepsis, blood lactate levels are of greater prognostic value than oxygen-derived measures, and a plasma lactate > 4 mmol/L indicates a poor prognosis.

THE SURVIVING SEPSIS CAMPAIGN

In 2004, a consensus committee representing 11 professional organizations published the Surviving Sepsis Campaign (SSC) Guidelines for the management of severe sepsis and septic shock (5). This included 47 specific graded recommendations, based on a review of the then current literature. What follows is a review of selected recommendations, with updated references and discussion.

ANTIBIOTICS AND INFECTION MANAGEMENT

Sepsis is by definition a consequence of infection. Efforts to identify and manage the clinical site of infection and to establish the microbiology are of critical importance. Although this seems intuitively obvious, studies indicate a surprising frequency of inadequate or absent workup, and suboptimal or inappropriate antibiotic therapy. In one large prospective trial of over 2,000 patients, treatment with antibiotics to which the offending organism was later shown to be resistant occurred in 32% of patients (6). Mortality is reduced from 34% to 18% when appropriate antimicrobials are prescribed at the onset of sepsis (7).

The choice of antibiotics is based on the patient's history and physical exam, data collection including imaging studies, Gram stain data, and a knowledge of local and regional resistance patterns and epidemiology. The major sites of infection in severe sepsis and septic shock, however, remain either intra-abdominal (includes urinary) or pulmonary in over 90% of cases.

The optimum timing of administration of antibiotics remains nebulous. SCC guidelines suggest that an antimicrobial regimen should be started within one hour of a diagnosis of sepsis. There are, however, no published data that establish a crucial 'time to antibiotic' interval. SSC also recommends that antibiotics be re-evaluated after 48-72 hours to determine the adequacy of the antimicrobials, and to wean those drugs not required (5).

In addition to antimicrobial treatment, management of the infection source is crucial. Drainage of abscesses,

debridement of devitalized tissues, and removal of potentially infected vascular catheters are examples of appropriate interventions.

VOLUME RESUSCITATION

Sepsis is characterized by capillary leak, a greatly expanded volume of fluid distribution, and both absolute and relative hypovolemia. A critical early step in management of the septic patient is therefore aggressive volume expansion. Isotonic crystalloid with an initial infusion of 20 ml/kg has been advocated, with repeated boluses to rapidly achieve a CVP of 8-12 mmHg. Rates of 1-2 liters per hour in the first 6 hours may be required in patients whose underlying cardiac status can tolerate such volumes. Notably, colloid offers no advantage over crystalloid, and the role of blood products is under debate. A hematocrit of >30%, however, has been shown to be a predictor of survival in septic shock. Another advantage of aggressive volume repletion is the possibility of reducing the need for vasopressor agents, and thus limiting their adverse effects.

PRESSORS AND INOTROPES

A MAP <65 mmHg *despite an adequate CVP* is an indication for pressor support. Premature prescription of pressor agents prior to adequate fluid resuscitation may have deleterious effects on regional blood flow, and further compromise tissue oxygenation. If pressor support is required emergently due to profound hypotension, an attempt to wean pressors after volume expansion and achievement of the target CVP should be undertaken (3).

Four agents with vasopressor activity are commonly utilized in the management of septic shock: dopamine (DA), norepinephrine (NE), epinephrine (EP), and phenylephrine (PE). Table 3 summarizes the relative cardiovascular effects of these agents. While there are no well-controlled trials comparing them, some conclusions can be drawn from the available literature.

NE and DA are the first line pressor agents of choice (3). NE increases MAP due to vasoconstriction with little or no change in heart rate or cardiac output. Unlike hemorrhagic shock, in which NE may have deleterious effects on renal and splanchnic blood flow, this does not appear to be the case in the hyperdynamic state of early sepsis. In septic shock NE can raise MAP with a neutral or positive effect on organ perfusion, tissue oxygenation, and renal function (3). The well studied effects of DA in septic shock are a rise in MAP due to an increase in stroke volume and heart rate, with a resultant increase in cardiac index, but a minimal effect on SVR. The effects of DA at pressor doses on splanchnic circulation, however, are less predictable. In addition, DA has been shown to have multiple potentially deleterious endocrine effects (3). In a small, randomized crossover study, NE was more effective than DA in reversing hypotension in patients with septic shock who had received adequate volume resuscitation (8). The use of low dose DA for renal and splanchnic protection is *not* recommended by the SSC, based on both a large randomized trial (9), and meta-analysis (10), both of which demonstrated lack of efficacy.

Combination pressor therapy has also been studied. The goals of improving tissue oxygenation and reversing shock are best achieved by the combination of dobutamine and NE (3,5), which is superior to NE and DA, and to DA alone. EP and PE should not be used as first line pressors in septic shock as they both have marked adverse effects on splanchnic blood flow and oxygen delivery.

Attempts at providing supranormal oxygen delivery as an adjunct to sepsis management are not recommended

TABLE 3. RELATIVE CARDIOVASCULAR EFFECTS OF VASOACTIVE AGENTS

Drug	Vasoconstriction	HR	Contractility
Dopamine	++	++	++
Norepinephrine	+++	++	++
Epinephrine	++	+++	+++
Phenylephrine	+++	0	0
Dobutamine	dilates	+	+++

by the SSC (5), the American Thoracic Society, or by expert opinion (3). The concept of trying to override impaired oxygen delivery by increasing cardiac output to levels above normal with dobutamine was addressed by two large prospective clinical trials in septic patients (11,12). Both demonstrated no benefit from this strategy; instead, the goal in this patient population should be to achieve normal oxygen delivery.

VASOPRESSIN

Vasopressin (VP) causes arterial smooth muscle contraction through a non-catecholamine mechanism. In contrast to patients with cardiogenic shock, patients in septic shock have a relative deficiency in circulating VP in the later stages of sepsis, and infusion of VP improves their hemodynamics. In a randomized controlled study of catecholamine-resistant vasodilatory septic shock, the combined infusion of VP and NE produced superior hemodynamic results compared to NE alone (13). There are no current data that support the use of VP as a first line pressor in patients with septic shock, though published data seem to support its possible use at a dose of 0.01-0.04 units/min in combination with traditional catecholamines (5).

BLOOD PRODUCTS

The SSC guidelines make a number of recommendations regarding blood products (5). Although the ideal target hemoglobin for patients in septic shock has not been defined, transfusion of red blood cells (PRBC's) for a hemoglobin <7.0 g/dl is felt reasonable. This recommendation is independent of the use of PRBC's to augment CVP in the early resuscitation of severe sepsis (4). Erythropoietin is not recommended, nor is routine use of fresh frozen plasma to correct lab abnormalities such as an elevated prothrombin time unless clinical bleeding occurs, or an invasive procedure is planned. Similarly, platelet transfusions should be withheld until the platelet count is <5,000/mm^3, with the same exceptions.

EARLY GOAL-DIRECTED THERAPY

The critical importance of aggressive early management of patients with severe sepsis was addressed in a landmark study by Rivers (4). This single, urban center, prospective, randomized, controlled trial compared standard therapy (ST) to an aggressive early resuscitative protocol. Patients in the trial had severe sepsis as defined as SIRS, plus either hypotension unresponsive to an initial fluid bolus, or an elevated blood lactate of >4 mmol/L. Each arm contained approximately 130 patients. The early goal-directed therapy (EGDT) group was managed in the ER for the first 6 hours of care. They received a bolus of 20-30 ml/kg of crystalloid over 30 minutes, and repeated boluses until a CVP of 8-12 mmHg was attained. If the MAP was still low after the CVP target was reached, NE or DA was added as pressors, with a target MAP of 65-90 mmHg. When both CVP and MAP targets were reached, $ScvO_2$ was measured, and if <70%, dobutamine infusion was begun, and the patient was transfused to a hematocrit >30%.

Results of the trial are summarized in Table 4. Patients in the EGDT group had a significantly lower mortality, achieved their hemodynamic targets significantly more often, and had evidence for reversal of tissue hypoperfusion more often than the standard treatment (ST) group.

In the first 6 hours, patients in the EGDT group received an average of 5 liters of fluid versus 3.5 for the ST group, were more likely to have been transfused and to have received inotropic support ($p < 0.001$ for all comparisons).

TABLE 4. RESULTS OF EARLY GOAL-DIRECTED THERAPY (RIVERS, NEJM, 2001):

	EGDT	Standard	P Value
Mortality, %			
Hospital	31%	47%	p = 0.009
28 day	40%	61%	p = 0.01
60 day	50%	70%	p = 0.03
$ScvO_2$, > 70%	95%	60%	p < 0.001
Hemodynamic Goals Achieved	99%	86%	p < 0.001

In contrast, during hours 7-72 of the study, the ST group experienced higher APACHE II (Acute Physiology and Chronic Health Evaluation) scores, greater vasopressor requirements, and a greater rate of ventilator dependent respiratory failure and use of pulmonary artery catheters. This study emphasizes the importance of the first few hours of management in patients with severe sepsis.

It is worth also noting, however, the exclusion criteria for this study. These included age <18 years, pregnancy, cancer or immunosuppressive illness, transplantation, trauma or burn injury, drug overdose, GI bleeding, acute coronary syndrome, CHF, and acute CVA. Patients were, therefore, pre-selected to be those who would be more likely to tolerate the aggressive resuscitative measures of the protocol.

The study has also been criticized for its unusually high mortality rate (70% at 60 days) in the standard treatment group, compared to other sepsis studies with similar APACHE II scores. Finally, it is not clear which of the hemodynamic targets of treatment were most beneficial. Nonetheless, this study establishes that the first 6 hours of sepsis management are the key to reducing mortality, and challenges clinicians to more aggressively identify and treat those patients with severe sepsis.

CORTICOSTEROIDS

A cursory overview of the saga of steroids in septic shock might lead one to conclude that there is no clear answer among the plethora of papers with seemingly contradictory conclusions. Upon closer inspection, however, the evolution of a treatment strategy is apparent.

Published studies from the 1960's to the 1980's were reviewed in a meta-analysis by Cronin et al. (14). These trials were characterized by short-term treatment with high doses of anti-inflammatory steroids, with no demonstrable benefit in mortality or physiologic parameters. In addition, there was a clear increase in GI bleeding, risk of secondary infection, and blood sugar.

More recent studies investigating the use of replacement doses of mineralocorticoids have revealed a clear therapeutic benefit. In a large, double-blinded, placebo-controlled trial (15), patients with septic shock were assigned to treatment with placebo or hydrocortisone (50 mg IV Q 6 hrs) and fludrocortisone (50 mcg daily). Patients were all subjected to a high dose (250 mcg) ACTH stimulation test, and stratified on the basis of their response to cortrosyn. In patients with inadequate adrenal reserve, as defined as an increase in blood cortisol from baseline of <9 mcg/dl in response to ACTH, hydrocortisone administration was associated with a significant decrease in 28 day mortality (63% to 53%), ICU mortality (70% to 58%), and hospital mortality (72% to 61%). Vasopressor withdrawal was achieved in 57% of ACTH responders compared to 40% of non-responders. The ACTH stimulation test seemed to be able to identify a group of septic patients with relative adrenal insufficiency. More surprising still was the fact that almost 70% of septic patients demonstrated relative adrenal insufficiency.

In a meta-analysis of 15 randomized, controlled trials including 2023 patients, steroid therapy was associated with increased shock reversal. In a sub-analysis of trials utilizing low dose hydrocortisone for more than 5 days, a significant reduction in 28 day, ICU, and hospital mortality was observed. Benefit from steroids is sepsis indeed occurs, but appears to be associated only with low dose regimens (16).

The SSC guidelines recommend that all septic shock patients who require pressors also receive hydrocortisone at 100-300 mg daily for seven days. But the more recent data above argue that there is indeed a role for the ACTH stimulation test. Current expert opinion favors a "start, stim, and stop" approach wherein all patients in septic shock on pressors receive empiric replacement hydrocortisone while awaiting the results of the ACTH stimulation test (17). Steroid therapy can then be discontinued in patients with adequate adrenal reserve.

Even for some ACTH non-responders, however, rapid withdrawal of pressors has been observed after the start of hydrocortisone therapy, which suggests a therapeutic response. In these rare patients, some experts favor continuation of the steroid to a full seven days irrespective of the ACTH response (17).

DROTRECOGIN ALFA (ACTIVATED)

Several large trials have demonstrated an important therapeutic role in septic shock for Drotrecogin alfa (activated), which is recombinant human activated Protein C (rhAPC, Xigris, Eli Lilly and Co.). This compound has been demonstrated to interfere with

the pro-inflammatory, pro-coagulant milieu of sepsis. Drotrecogin alfa inhibits endothelial cell activation and apoptosis, and is an inhibitor of tumor necrosis factor. It is administered as a continuous 96 hour infusion at a rate of 24 mcg/kg/hr.

The pivotal study for this compound was the PROWESS trial (18), a multi-national, blinded, randomized, placebo-controlled trial that evaluated 1690 patients with severe sepsis or septic shock. Patients were randomized to rhAPC or placebo within 24 hours of admission. Treated patients had lower 28 day mortality (24.7% vs. 30.8%, $p < 0.01$), demonstrated more rapid recovery from cardiovascular and pulmonary dysfunction ($p = 0.009$), and had significantly lower sequential organ failure assessment scores ($p = 0.022$). Post hoc analysis demonstrated benefit only for patients with APACHE II scores >25, as reflected in the initial FDA indication for this drug. There was an increased risk of serious bleeding, including fatal CNS hemorrhage in the treatment group that did not reach statistical significance.

This trial was criticized for a study protocol modification after 720 patients had been enrolled that excluded patients with certain co-morbidities, such as organ transplants, patients with metastatic cancer, and pancreatitis. In addition, the master cell line used to produce rhAPC was changed during the study, with a greater benefit in patients enrolled later in the study.

A second open label, single arm trial (ENHANCE) was subsequently performed (19), and a mortality benefit similar to PROWESS was again demonstrated. In addition, patients treated within 24 hours after the first sepsis-induced organ dysfunction had a lower mortality (22.9% vs. 27.4%).

The ADDRESS trial was an investigation of the use of rhAPC in lower risk patients (20), defined as having an APACHE II score of <25 or single organ dysfunction. It was designed to randomize 11,000 patients, but was stopped after 2,600 patients based on an interim analysis, which demonstrated no mortality benefit in the treatment arm. Of particular note, patients with recent surgery or failure of only one organ, demonstrated an *increase* in mortality (20.7% vs. 14.1%, $p = 0.03$). A significant risk of bleeding in the rhAPC group was again demonstrated (20).

The SSC guidelines recommend rhAPC for patients with APACHE II scores >25 and multiple organ failure who do not meet any of the extensive exclusion criteria for this drug. Limitation of use in patients with only one organ dysfunction or recent surgery also seems prudent.

GLUCOSE CONTROL

Hyperglycemia and insulin resistance are common in ICU patients, even in the absence of underlying diabetes mellitus. In a study of intensive insulin therapy in post-operative surgical patients, aggressive control of hyperglycemia to maintain values of 80-110 mg/dl utilizing a continuous insulin drip demonstrated a reduction in mortality from 8.0% to 4.6% for treated patients (21). In addition, reductions were observed in the prevalence of progression of renal failure to dialysis, ICU polyneuropathy, transfusion requirements, need for ventilator support, and blood stream infections. Significant hypoglycemia, however, complicated the intensive therapy group. Post hoc analysis demonstrated that a significant benefit was still accrued in patients with less aggressive glucose target values <150 mg/dl (5). More recently, Van den Berghe has published a study on intensive insulin therapy in medical ICU patients (22) which demonstrated that in the first 72 hours of ICU admission, the intensive insulin therapy group experienced an *increase* in mortality from 19% to 27% ($p = 0.05$). Like the previous study, criticism has been directed at the high intensity of glucose control. These studies suggest that tight insulin control should target glucose values <150 mg/dl, and should be implemented only after initial stabilization of the patient (5).

VENTILATOR MANAGEMENT

Acute lung injury and the adult respiratory distress syndrome may accompany septic shock. Ventilator barotrauma may in fact contribute to SIRS. Mortality in ventilated ICU patients can be reduced by limiting tidal volume and ventilator pressures. A large trial demonstrated a reduction in mortality from 40% to 31% in patients managed with tidal volumes of 6 ml/kg of lean body weight, accompanied by peak inspiratory plateau pressures of <30 cm water (23). Additional strategies such as permissive hypercapnia, PEEP to maximize compliance, semi-recumbent positioning, and the use of weaning protocols and protocol-driven interruption of sedation are also supported in the literature, and recommended in the SSC guidelines (5).

TABLE 5: A STAGED APPROACH TO SEPSIS MANAGEMENT

Diagnosis (Rapid Response Team)

1. Screen patients with SIRS clinically for organ hypoperfusion
2. Obtain plasma lactate, blood cultures, and other appropriate studies.
3. Initiate appropriate antibiotics within 1 hour
4. Transfer patients with severe sepsis to ICU

Resuscitation (SIRS plus hypotension or plasma lactate > 4mmol/L)

1. Place central venous or pulmonary artery catheter
2. Institute Early Goal Directed Therapy Protocol with targets:
   a. CVP 8-12 mmHg, utilizing volume expansion
   b. MAP > 65 mmHg, utilizing pressors
   c. SvO_2 > 70%, utilizing dobutamine and transfusions
3. Achieve targets within 6 hours

Septic Shock Management (ICU)

1. Empiric hydrocortisone after ACTH stimulation test
2. APACHE II score and evaluation for rhAPC
3. Glucose control protocol with target BS < 150 mg/dl
4. Ventilator management protocol TV < 6 cc/kg, EIPP < 30 cm H2O

CONCLUSION

The management of severe sepsis and septic shock is a burgeoning and evolving field. Based on this current review, the staged recommendations summarized in table 5 provide a sound, evidence-based approach to sepsis management. The call for implementation of these guidelines, particularly the EGDT protocol, is paramount, and is a challenge to both physicians and hospital administrators. To the cardiologist, "time is muscle." To the neurologist, "time is brain." To the physician caring for the septic patient, "time is survival."

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Joseph M. Kontra, M.D.
Infection Specialist of Lancaster
2106 Harrisburg Pike, Suite 301
Lancaster, PA 17601
717-544-3517
jmkontra@lancastergeneral.org