A systems approach to the early recognition and rapid administration of best practice therapy in sepsis and septic shock
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Introduction
The successful treatment of acutely ill patients with a high risk of death is predicated on early recognition and treatment. The key role of early intervention has been recognized in the creation of the term ‘the golden hour’ as it relates to therapy of life-threatening conditions. Early accelerated treatment has been shown to improve outcome for a variety of acute, life-threatening illnesses including acute myocardial infarction (MI), stroke, trauma/hemorrhagic shock and, most recently, septic shock. Over the past 20 years, systems have evolved in order to better recognize patients with these acute illnesses and to accelerate appropriate treatment.

Septic shock has been reported to occur in 750,000 people annually in the United States with an associated mortality risk exceeding 30–40% [1]. Estimates place the total cost to society at $16 billion/year with an estimated consumption of 0.5–1.0% of the American gross domestic product (GDP) [2]. A primary difficulty with the management of patients with septic shock is ensuring early recognition of this disease state. Because of varying causes of sepsis and differing patient presentations and comorbidities, patients are often left undiagnosed or untreated or both for long periods of time and are often outside of their ‘golden hour’.

There is evidence to show that early application of basic therapies for sepsis reduces mortality [3, 4]. The early interventions that Rivers et al. and Sebat et al. performed in their respective academic and community emergency departments were, for the most part, simple to implement and applicable in numerous settings. This bundled approach of aggressive, goal-directed resuscitation included several therapeutic interventions. The interventions...
Early recognition of sepsis

The recognition of sepsis, in contrast to other conditions requiring immediate resuscitative efforts such as trauma, stroke and MI, can be difficult. Although clinical signs of the other conditions can be obvious and very specific, the symptoms and signs of severe infection and sepsis are much less so. Recognition of severe sepsis (sepsis with organ failure), by convention, has been tied to its defining criteria, which include elements of the systemic inflammatory response (tachycardia, tachypnea, fever, elevated white count or increased left shift), a suspected source of infection and at least one dysfunctional organ. These criteria require results of a complete blood count (CBC) and/or chest radiograph, urinalysis, blood cultures and computed tomography (CT) of the abdomen, which, because of their turn around time, may contribute to a delay in recognition and treatment. This delay can be avoided by utilizing easily measured bedside parameters to identify at-risk patients and immediately begin treatment while waiting for additional information. Hence, these bedside parameters are referred to as the 10 signs of vitality (10 SOV) (Table 1). When considered in combination, the 10 SOV can identify early patients at risk, many of whom are septic. This early identification of physiologic instability expedites basic resuscitation that is cause independent while collecting additional information. Operationally, this is accomplished by utilizing a significant abnormality in any one of the five conventional vital signs as a trigger (Table 1). Once a significant vital sign abnormality is recognized [facilitated by electronic alerts in the monitoring devices or electronic medical record (EMR)], a full 10 SOV assessment is performed at the bedside [14–17]. Nine of the 10 SOV can be assessed within several minutes; the 10th [base deficit or central venous oxygen saturation (ScVO2)] requires an arterial or central blood gas, a 15 min turn around time at many hospitals. Seven of the 10 SOV are key (bolded) in deciding if the patient has a perfusion deficit and is at risk. If two of these seven parameters are present, the patient is considered at high risk, often with decreased tissue oxygen delivery. This approach will identify early sepsis and other at-risk patients all of whom will benefit from the additional evaluation and treatment.

Early evaluation, triggered by a significant abnormality in one of the conventional vital signs, will maintain detection sensitivity, whereas a requirement of at least two of the seven key SOV will increase identification specificity. In one study of 500 consecutive patients, utilizing a similar approach, 50% were subsequently determined to be septic [13**].

Respiratory rate and capillary refill are two vital signs whose value has been underappreciated [18–29]. Although both lack specificity, a respiratory rate of more than 20 bpm or a capillary refill of more than 3 s can be very sensitive in identifying at-risk patients. Because of their lack of specificity, it is important to evaluate them in the context of a full bedside assessment. For example, a patient with capillary refill of more than 3 s or with

### Table 1 The 10 signs of vitality

<table>
<thead>
<tr>
<th>Ten signs of vitality</th>
<th>Triggering parameter</th>
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<tbody>
<tr>
<td>Temperature</td>
<td>≤ 36°C</td>
</tr>
<tr>
<td>Pulse</td>
<td>&gt; 50 or &gt;100/min</td>
</tr>
<tr>
<td>Pain</td>
<td>New or significant increase</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>≤ 6 or &gt;20/min</td>
</tr>
<tr>
<td>SaO2</td>
<td>&gt; 90% and increased FiO2</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>SBP &lt; 90 mmHg, MAP &lt; 60 mmHg</td>
</tr>
<tr>
<td>Level of consciousness</td>
<td>Anxiety/lethargy</td>
</tr>
<tr>
<td>Capillary refill</td>
<td>&gt; 3 s</td>
</tr>
<tr>
<td>Urinary output</td>
<td>&lt; 30 ml/h × 5 h (&lt;100 ml/4 h – excluding renal failure)</td>
</tr>
<tr>
<td>ScvO2/base deficit</td>
<td>&lt; 85% or B deficit ≥ 5 or lactic acid &gt; 2.0</td>
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The seven signs of vitality in bold are key in deciding if the patient has a perfusion deficit and is at risk. MAP, mean arterial pressure; SBP, systolic blood pressure.
respiratory rate more than 20, who is otherwise stable, is not likely to be at risk or septic compared with a similar patient who also has an abnormality of one of the other key seven SOV. Once the patient is identified at risk, rapid administration of basic resuscitation is begun avoiding delay while differential diagnoses are considered.

The systematic early warning or rapid response system (RRS) for early identification of at-risk patients coupled with aggressive basic, but sometimes overlooked (AOVIPPPS, see ‘The early treatment of sepsis and goals of resuscitation’) resuscitation, is key to improving outcomes in sepsis. This is particularly true when comprehensive educational programs empower frontline providers to rapidly evaluate at-risk patients and to independently initiate basic treatment while institutional resources are mobilized. One study utilizing this approach looked at all patients who presented to the emergency department (ED) or were on hospital wards and met an early warning shock criteria; one half of those patients subsequently were determined to be septic. This generalized approach to shock identification and resuscitation, regardless of the cause, was able to decrease the mortality of septic shock from 50 to 10% over a 5-year period [13**]. This approach is being promoted by RRS throughout the world facilitated by the Society of Critical Care Medicine RRS courses and manual [30].

The early treatment of sepsis and goals of resuscitation

Sepsis causes progressive derangements in normal physiology resulting in inadequate delivery of oxygen to tissues, lactic acidosis and organ dysfunction. If left untreated, irreversible shock, multisystem organ failure and death ensue. The concept of irreversible shock [31] recognizes that delayed resuscitation and correction of hemodynamic instability, while providing physiologic improvement to isolated oxygen transport parameters, can still occur too late to prevent organ injury leading to inevitable deterioration and death. Thus, early restoration of end organ oxygen delivery and early elimination of the infectious source is paramount.

During septic shock, excessive production or decreased elimination or both of nitric oxide results in profound vasodilatation and relative hypovolemia. This results in hypotension and inadequate cardiac output [32]. Compounding this situation is microvascular clotting [33] due to activation of the inflammatory and coagulation cascades [34] along with activation of neutrophils at the endothelial surface. In aggregate, these processes result in migration of intravascular fluids into the interstitium, gross tissue edema, and often acute lung injury [35]. The latter increases VO₂resp (the oxygen cost of breathing) that normally accounts for approximately 5% of total body oxygen consumption, but in sepsis, can account for 40% of oxygen demand [36]. This increased work of breathing requires that blood flow be diverted from other vital organs at a time when total body oxygen consumption may be increased because of tachycardia or fever. One of the most important goals in early sepsis management is to reduce VO₂resp. Support of the respiratory system with noninvasive ventilation or early intubation is often overlooked and can be key to reducing mortality [3,37].

Early support of ventilation in septic and other forms of shock was first emphasized in the 1969 mnemonic VIP [38]. This mnemonic stands for Ventilatory support, Infuse volume aggressively and Pressors support of BP. It was later expanded by the same authors to VIPPS shock resuscitation adding Pharmacologic and Specific invasive interventions to resuscitation and most recently to AOVIPPS to emphasize Airway and Oxygenation issues [30].

Mnemonic AOVIPPS stands for

1. Airway;
2. Oxygen;
3. Ventilation support;
4. Infuse volume aggressively;
5. Pressors support of BP;
6. Pharmacologic interventions, that is, antibiotics, activated protein C (APC) etc.;
7. Specific, invasive therapies.

Along with early support of ventilation/oxygenation, most authorities consider goal-directed rapid administration of fluids paramount. In the Rivers et al. study [3], early and aggressive fluid loading appeared to be the key intervention that led to the decrease in mortality. Several other studies have similarly suggested that early aggressive fluid resuscitation is associated with improved outcome in sepsis [3,39,40]. Maintenance of adequate tissue perfusion with early support of the respiratory system, aggressive volume resuscitation, and vasopressors or inotropes, if needed, is part of basic shock resuscitation and should begin immediately regardless of the cause [41,42].

For effective treatment of sepsis and, particularly, septic shock, early elimination of the pathogenic bioburden that drives the septic process and resuscitation are equally important. Administration of appropriate antibiotics along with source control should be done in parallel with the resuscitative therapy. Ibrahim et al. [43] looked at the result of inadequate antimicrobial therapy on outcome in patients with bacteremia. In this study, an inadequate antimicrobial agent was defined as one that did not have activity against that class of microorganism (e.g., antibiotics for fungal infection) or one to which the organism was resistant. They found that when patients were given inadequate therapy, their mortality was increased by
almost two-fold. Further, Kumar et al. [4**] have shown that the speed with which appropriate antimicrobials are initiated after onset of hypotension in patients with septic shock is one of the critical determinants in their survival [44]. Survival dropped approximately 7.5% per hour delay over the first 6h. Early drainage of abscesses or debridement of infected necrotic tissue is also vital in the treatment of sepsis [44,45].

When resuscitating a patient, the clinician has to decide when perfusion defects have been reversed. Wo et al. [46] have shown that resuscitation goals such as BP alone are unreliable markers of adequate blood flow to organs. Utilizing multiple resuscitation goals in combination has reduced mortality [3,5,13**]. The most easily measured and often useful goals of resuscitation are mental status, work and rate of breathing, urine output, cap refill or extremity temperature, BP and heart rate. However, these goals may or may not show the whole picture. Rivers et al. added ScVO2 more than 70% as a resuscitation goal and by doing so decreased septic shock mortality from approximately 40 to 30%. Frequently utilized resuscitation goals that are useful when evaluated together are listed below:

1. Improved or normalized mental status;
2. SaO2 > 90%;
3. Decreased work of breathing;
4. Mean arterial pressure (MAP) > 60–65%;
5. Capillary refill < 6 s;
6. Urinary output > 0.5 ml/h;
7. ScvO2 > 60%, lactate acid < 2.0 mmol/l.

One of the more controversial aspects of sepsis management is the role of blood transfusion to improve mixed venous oxygen saturation. In the Rivers study, red cell transfusions were initiated if the mixed venous oxygen tension was less than 70% after respiratory, fluid and vasopressor support and if the hematocrit was less than 30%. This seems to contradict other studies that showed no difference in mortality when red cells were given to critically ill patients [47] or, in fact, made them worse [48,49] because of infection and lung injury. As red cell transfusion was part of a ‘bundle’ of interventions, it is hard to discern what role individual parts had in the reduction of mortality. However, it is also notable that this intervention was performed early during the acute phase of illness whereas other studies examining RBC transfusion were performed later.

It cannot be overemphasized that there is almost no therapy that is more beneficial when administered later in the course of critical illness, whether one is talking about intubation, fluids, antibiotics or surgical intervention. In addition to effective antimicrobials and appropriate resuscitative efforts, drotrecogin-alpha is another example of a therapy whose benefits are maximal when administered early in the course of disease yet whose administration is often delayed [50,51].

**Institutional systems can improve earlier recognition and treatment of sepsis**

Early recognition and rapid application of best practice in sepsis as in other critical illnesses is often delayed or inadequate [5,40,52–54]. Insufficient knowledge of frontline providers or lack of their empowerment to initiate basic resuscitative therapy independently or to mobilize additional institutional resources substantially compounds this problem. Resistance to change by healthcare providers or inability to break down barriers to improve process or both further contributes to delays in the adoption of best practice [5,33,40,55]. Developing institution-wide systems that address these issues will and has improved outcomes [3,10,11,13**,40,56–64].

The key to improving sepsis outcomes is implementation of a prehospital and hospital-wide system that recognizes at-risk or septic patients early and rapidly administers effective therapy. This is best accomplished by identifying physicians, nurses, administrators and quality-assurance personnel that can be champions of a sepsis RRS (Fig. 1) [30,65]. This system should emphasize education, as well as policies and procedures that empower frontline providers to recognize sepsis early, and independently institute basic resuscitation as additional resources are mobilized. Creation of an RRS for sepsis requires not only various champions to drive it, but also needs an effective structure for its development, education of staff, implementation and continuous process improvement.

Providing substantial education and training to the bedside nurses and respiratory therapists increases the chance of early identification and resuscitation (by protocol) of septic patients while activating the sepsis or rapid response team early enough to make a difference. Early recognition of sepsis, which is 90% of the battle, is labor intensive because, in contrast to other conditions, such as massive hemorrhage, stroke and MI, the manifestations of sepsis can be relatively nonspecific. As a consequence, an institutional capacity for early recognition requires intense education and training of nearly all healthcare providers. However, once this is accomplished, assuring rapid administration of best practice therapy is easier as it requires educating a much smaller number of response team members. Attention to both the afferent and efferent arms of the RRS is critical and has been demonstrated to decrease time to recognition and treatment and improve outcomes [13**].

The RRS administrative, afferent, efferent and quality assurance arms are essential components for success
They provide for system design, education of bedside clinicians and team responders, implementation, team response including treatment, data collection/analysis and process improvement. The sepsis RRS functions should include:

1. Administrative arm: coordinates development, education and implementation of the RRS. This includes development of hospital policy and procedure that defines brisk best practice resuscitation to be initiated by bedside providers, continued by the response team followed by rapid triage to the most appropriate location (i.e. remain at current location, diagnostic suite, operating room or ICU). The administrative arm is also responsible for process change based on data and recommendations from the quality assurance arm.

2. Afferent arm (bedside clinicians): should receive a formalized and comprehensive educational program that facilitates early recognition of at-risk and septic patients along with tools and systems that increase recognition such as lanyard cards or electronic alerts as vital signs are measured or charted and mock sepsis drills are conducted.

3. Afferent arm that through cognitive recognition or conventional vital sign EMR alerts assess further at-risk patients utilizing 10 SOV or three of the classic sepsis criteria. Once preestablished criteria are recognized by bedside personnel, or are met by preprogrammed logic within the EMR, alerts activate the efferent arm (response team).

4. Efferent arm or rapid response sepsis team should include critical care nursing, respiratory therapy,
pharmacy, sepsis lab panel radiograph and nursing supervisor for triage assistance.

(5) Quality assurance arm is responsible for collecting and analyzing demographics (incidence, location), outcome data [length of stay (LOS), vent days] and surrogates for outcomes [i.e. time to mobilization of the rapid response team (RRT), antibiotics, 21 of fluids, drotrecogin-alpha, source control].

**Summary**

For decades, healthcare workers faced the challenge of how to adequately treat sepsis and septic shock. Several recent studies have conclusively shown that the early recognition and treatment of sepsis reduce mortality. The challenge that hospitals must now face is how best to implement systems to facilitate this goal. This is accomplished by involving all members of the healthcare team, including physicians, nurses, respiratory therapists and pharmacists. The role of administrators is in identifying champions of the concept of an RRS and then facilitating the development of the necessary infrastructure to educate and train staff on the recognition and treatment of sepsis. The need for continuous data collection and analysis by members of a quality assurance team will ensure that best practices are followed and that there is ongoing focus on process improvement. Only with this team approach will healthcare providers be able to reduce the mortality of this deadly disease.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current Literature section in this issue (pp. 369–370).

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Garrard C, Young D. Suboptimal care of patients before admission to intensive care is caused by a failure to appreciate or apply the ABCs of life support. BMJ 1998; 316:1841–1842.


