OBJECTIVES:
1. Quantify the prevalence and magnitude of sepsis mortality as it relates to Emergency Medicine.
2. Understand the pathogenesis of early sepsis which provides the therapeutic rationale for early goal-directed therapy.
3. Understand the components of a sepsis quality initiative and its salutary impact on patient outcomes and health care resource consumption.

INTRODUCTION
A Change in the Paradigm of Treating Severe Sepsis and Septic Shock
Improvement in mortality for acute myocardial infarction, trauma and stroke have been realized by a coordinated team approach, beginning in the emergency department (ED), to provide early identification of high risk patients and time sensitive evidence-based therapies. Over 500,000 patients present each year to the ED with severe sepsis and septic shock, having a resulting mortality ranging from 20%-60%. The same approach provided for acute myocardial infarction (AMI), trauma and stroke has been lacking for early sepsis management until recently. Early goal-directed therapy (EGDT) was developed as a quality initiative which includes 1) assessment of the hospital sepsis prevalence and mortality, 2) early identification of high-risk patients, 3) mobilization of resources for intervention, 4) reversal of early hemodynamic perturbations, 5) assessing compliance, 6) dedicated education of health providers, 7) quantifying health care resource consumption and 8) assessing outcomes (Figure 1).

The Early Hemodynamics of Sepsis
The early stages of sepsis can manifest as a hypodynamic state of oxygen delivery dependency causing elevated lactate concentrations and low venous oxygen saturations. Depending on the stage of disease presentation and the extent of resuscitation, however, a hyperdynamic state, where oxygen consumption is independent of systemic oxygen delivery having normal to increased lactate concentrations and high venous oxygen saturation, may be more commonly recognized. Thus, sepsis evolves as a progression of hemodynamic phases where lactate and central venous oxygen saturation ($ScvO_2$)/mixed central venous oxygen saturation ($SvO_2$) represent the balance between systemic oxygen delivery and demands and quantifying the severity of global tissue hypoxia. The hypodynamic phase in particular is associated with the generation of inflammatory mediators with increased morbidity and mortality if unrecognized or left untreated. This phase also can be present with normal vital signs. Thus, the hemodynamic derangements of sepsis can be hypovolemia, vasodilatation, myocardial depression and impairment of oxygen utilization. These derangements

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may exist alone or in combination beginning upon hospital presentation (Table 1 and Figure 2).

**Previous Hemodynamic Optimization Trials**

Early work by Shoemaker *et al.*\(^{13}\) observed that survivors of critical illness had supra-normal levels of oxygen delivery compared to non-survivors. This prompted some clinicians to target supra-normal levels in all critically-ill patients without outcome benefit.\(^{14, 15}\) The relatively later timing of the intervention in the intensive care unit (ICU) setting, and absence of a delivery-dependent phase of systemic consumption with decreased \(SvO_2\) and increased lactate, differentiates these studies from EGDT. A meta-analysis of hemodynamic optimization trials by Kern suggested early, but not late, hemodynamic optimization reduced mortality.\(^{16}\) It has since become increasingly evident from multiple subsequent studies the six hour time interval used in the EGDT trial was not only important from a diagnostic perspective, but had outcome implications based on adequacy of care.\(^{17-21}\) EGDT was performed for these patients in the pre-ICU or ED phase of the disease, within hours of patient presentation.

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**Table 1. The hemodynamic stages of sepsis**

<table>
<thead>
<tr>
<th>MAP</th>
<th>CVP</th>
<th>(SvO_2)</th>
<th>Lactate</th>
<th>Cardiac Index</th>
<th>Systemic vascular resistance</th>
<th>Treatment and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemia</td>
<td>Variable</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Compensated &amp; vasodilatory</td>
<td>↓</td>
<td>Normal</td>
<td>↑</td>
<td>Variable</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Myocardial suppression</td>
<td>Variable</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>Normal or ↓</td>
<td>Normal or ↑</td>
</tr>
<tr>
<td>Impairment of tissue (O_2) utilization</td>
<td>Variable</td>
<td>Normal</td>
<td>↑</td>
<td>↑</td>
<td>Variable</td>
<td>↓, Normal or ↑</td>
</tr>
</tbody>
</table>

r-APC = recombinant activated protein C
Early Recognition of the High Risk Patient

The use of lactate ≥ 4 mmol/L as a marker for severe tissue hypoperfusion and as a predictor of mortality is supported by a number of studies. Although there is some controversy regarding other potential mechanisms underlying lactate accumulation in severe sepsis, serial lactate levels can assess lactate clearance or changes in lactate over time. Nguyen et al. has also reconfirmed work by others showing increased lactate clearance rates during the first 6 hours of sepsis presentation are significantly associated with preserved organ function and improved survival. Lactate levels can be performed by venipuncture.

The Components of EGDT

EGDT allows emergency physicians to diagnose and treat each of the hemodynamic perturbations urgently (Figure 2) using recommendations and endpoints supported by consensus statements from both critical care and emergency medicine. The titration of intravenous fluid to a central venous pressure (CVP) of 8-12 mmHg provides an objective endpoint for preload optimization while preventing volume overload. As a result, more fluid administration can be given initially and safely, leading to a 14% reduction in vasopressor, steroid use and mechanical ventilation.
While there is debate regarding whether ScvO₂ is a numeric equivalent to SvO₂, it has clinical utility and reflects outcome. The Surviving Sepsis Campaign recommends an SvO₂ of 65% and an ScvO₂ of 70% as resuscitation endpoints. Given the challenges of using a pulmonary artery catheter (PAC) in an early setting such as the ED, the ScvO₂ represents a convenient surrogate, but not a replacement, for SvO₂. While continuous monitoring allows for a more rapid adjustment of hemodynamic variables from rapid feedback, intermittent values will suffice.

Acute anemia and global tissue hypoxia provide potent stimuli for erythropoietin production to increase marrow production of red blood cells (RBCs). Severe sepsis and septic shock patients who have both an impaired marrow response and variable erythropoietin levels may lack this compensatory ability to increase hemoglobin concentrations. The combination of anemia and presence of global tissue hypoxia represent the physiologic rationale to transfuse RBCs in these patients. Volume resuscitation results in hemodilution. The threshold for transfusion is based on consideration of a physiologic rationale such as low ScvO₂ and increased lactate or global tissue hypoxia, a high-risk patient population, and expert consensus. These are important considerations when comparing EGDT patients to those enrolled in ICU transfusion studies. Hebert et al., Marik et al. and others have shown a restrictive strategy of red-cell transfusion (7-9 mg/dl) was “at least as effective and possibly superior to a liberal transfusion strategy in critically ill patients.” However, these studies did not specifically address patients with severe sepsis and septic shock. Patients with co-morbidities including atherosclerotic heart disease, congestive heart failure, and renal failure are substantially represented in the EGDT study. Excluding such patients limits the generalizability of prior transfusion studies for patients with severe sepsis and septic shock.

In previous studies, dobutamine therapy has been associated with increased mortality. Not only did the resuscitation endpoints of these studies include supra-physiologic oxygen delivery, but also some patients received doses of dobutamine as high as 200 mcg/kg/min. The selection of patients in a delivery dependent state, lower dose, timing of therapy, and endpoints of resuscitation were different between the EGDT study and previous studies. In the EGDT study, patients were treated using a lower dobutamine dose (average dose 10.3 mcg/kg/min to maximum 20 mcg/kg/min), which was titrated upward to achieve ScvO₂ ≥ 70%.

Cerra et al. and Spronk et al. noted hemodynamic improvement in the microcirculation for septic patients with the use of nitroglycerin. Vasodilator therapy was used in 9% of EGDT patients who met protocol criteria. These patients had median baseline ScvO₂ of 46% and a previous history of hypertension and congestive heart failure. It is becoming increasingly evident disordered microcirculatory flow is associated with systemic inflammation, acute organ dysfunction, and increased mortality. Using new technologies to directly image microcirculatory blood flow may help define the role of microcirculatory dysfunction in oxygen transport and circulatory support.

**EGDT Effects on Systemic Inflammation and Organ Dysfunction**

There is a pathologic link between the clinical presence of global tissue hypoxia, generation of inflammation, and the mitochondrial impairment of oxygen utilization seen in septic...
Table 2. Early goal-directed therapy (EGDT) decreases these components of care:

1. Mortality by 16-20%
2. Components of the inflammatory response
3. Morbidity of organ dysfunction
4. Need for vasopressor therapy
5. Need for mechanical ventilation
6. Sudden cardiopulmonary complications in the first 24 hours
7. Length of hospital stay
8. Health care resource consumption

The Effect of EGDT on Mortality
The baseline mortality of 51% prior to the study was reduced to 46.5% with standard care and 30.5% after the introduction of EGDT at the Henry Ford Health Center. Published programs of EGDT to date represent a cumulative total of over 3,000 patients. In these confirmatory studies, a mean mortality prior to implementation was 45.6 ± 7.9% (range 59.0 to 29.3%) and 25.8 ± 5.7% (range 29.0 to 18.0%) after implementation of EGDT for an average reduction of 19.6%, which is greater than the original study of 16%. In these studies which were performed in both academic and community hospital settings enrolled patients with similar age and APACHE II scores to the original trial. These studies provide external validity EGDT is generalizable and reproducible. While these implementation programs may include additional therapies such as aggressive hemodialysis, glucose control, recombinant activated protein C, corticosteroids and protective lung strategies, multivariate analyses reveal the EGDT contributes statistically significant mortality benefit when compared to these other interventions.
Implementation Strategies of EGDT

EGDT represents one of the first ED based therapies shown to improve outcome, however, it remains incompletely practiced. The reasons range from ED overcrowding, variation in skill levels among clinicians in the ED setting, and the lack of understanding of the continuum of care required to implement this therapy. A coordinated patient care model similar to the treatment of AMI, stroke and trauma is required. To achieve a consistent level of quality at various locations within the hospital, multiple models of care may be required. The first model of sepsis management is ED based. A second and increasingly popular model incorporates a multidisciplinary rapid response team which utilizes mobile resources to care for the patient irrespective of location. The third concept is an ICU based model which rapidly transfers the patient to the ICU where EGDT is performed in the ICU. Each of these unique models must be tailored to the institution.

A Cost Analysis of EGDT

EGDT can provide up to a 23.4% reduction in hospital costs related to severe sepsis and septic shock. EGDT is most cost-effective if patient volumes exceed sixteen patients per year and irrespective of whether the care is primarily provided by the ED, rapid response team, or the ICU. This volume of patients is easily seen in a 200-bed hospital. A mean reduction of 4 days per admission, or a 32.6% reduction in hospital length of stay, for survivors and 13.9% reduction in PAC use (both p<0.03) were seen in the EGDT study. Similar findings have been noted by other investigators.

Summary

EGDT results in significant reductions in morbidity, mortality, vasopressor use, and health care resource consumption. EGDT modulates some components of inflammation, which is reflected by improved organ function. The end-points used in the EGDT protocol, outcome results and cost effectiveness have subsequently been externally validated, revealing similar or even better findings than the original trial. Adherence to the principles of early recognition, early mobilization of resources, and multidisciplinary collaboration is imperative if improvements in the morbidity and mortality associated with sepsis are to parallel those seen with other severe disease states such as AMI, trauma and stroke.

References

42. Rivers E. Mixed vs central venous oxygen saturation may be not numerically equal, but both are still clinically useful. Chest. 2006;129(3):507-508.
50. Rivers E. Mixed vs central venous oxygen saturation may be not numerically equal, but both are still clinically useful. Chest. 2006;129(3):507-508.


