



Early Goal-Directed Therapy in Severe Sepsis and Septic Shock Revisited*

Concepts, Controversies, and Contemporary Findings

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Studies of acute myocardial infarction, trauma, and stroke have been translated into improved outcomes by earlier diagnosis and application of therapy at the most proximal stage of hospital presentation. Most therapies for these diseases are instituted prior to admission to an ICU; this approach to the sepsis patient has been lacking. In response, a trial comparing early goal-directed therapy (EGDT) vs standard care was performed using specific criteria for the early identification of high-risk sepsis patients, verified definitions, and a consensus-derived protocol to reverse the hemodynamic perturbations of hypovolemia, vasoregulation, myocardial suppression, and increased metabolic demands. Five years after the EGDT publication, there has been much discussion generated with regard to the concepts of EGDT, as well as debate fueled regarding diagnostic and therapeutic interventions. However, during this time period further investigations by the primary investigators and others have brought additional contemporary findings. EGDT modulates some of the components of inflammation, as reflected by improved organ function. The end points used in the EGDT protocol, the outcome results, and the cost-effectiveness have subsequently been externally validated, revealing similar or even better findings than those from the original trial. Although EGDT is faced with challenges, a coordinated approach to sepsis management is necessary to duplicate the progress in outcomes seen in patients with conditions such as acute myocardial infarction, stroke, and trauma. (CHEST 2006; 130:1579–1595)

Key words: biomarkers; brain natriuretic peptide; early goal-directed therapy; implementation; lactate; sepsis bundle; sepsis outcomes; septic shock; severe sepsis

Abbreviations: ALI = acute lung injury; APACHE = acute physiologic and chronic health evaluation score; BNP = brain natriuretic peptide; CVP = central venous pressure; ED = emergency department; EGDT = early goal-directed therapy; ESRD = end-stage renal disease; HFH = Henry Ford Hospital; IL = interleukin; MAP = mean arterial pressure; PAC = pulmonary artery catheter; ScvO₂ = central venous saturation; SvO₂ = mixed venous saturation; V̇O₂ = oxygen uptake

Conditions such as acute myocardial infarction,¹ trauma² and stroke³ have seen improvements in outcome by the application of early diagnosis and time-sensitive therapies at the most proximal stage of hospital presentation. A similar approach has been previously lacking for early sepsis management. The study, using early goal-directed therapy (EGDT) in the treatment of patients with severe sepsis and septic shock, began as a quality initiative that challenged the paradigm of sepsis

management at a large urban tertiary care hospital. EGDT is essentially a comprehensive strategy for evaluating septic patients that includes the following: (1) assessment of the sepsis prevalence and mortality at the hospital; (2) identification of high-risk patients based on early pathogenesis; (3) mobilization of resources for intervention; (4) performance of a consensus-derived protocol to reverse early hemodynamic perturbations; (5) appraisal of the quality indicators to assess compli-

ance; (6) quantification of health-care resource consumption; and (7) assessment of outcomes (Fig 1).

Since the publication of the original study of EGDT (see the study by Rivers et al¹²), much discussion has been generated in regard to the concepts underlying the early pathogenesis of sepsis, the conceptualization of the study, controversies over the treatment algorithm, the salutary effects of EGDT on morbidity and mortality, as well as the generalization and implementation of EGDT. Further data have been generated from the original study by the primary investigators as well as by investigators at other centers who have adopted EGDT. This state-of-the-art review will revisit these aforementioned issues by addressing key concepts, controversies, and contemporary findings regarding EGDT.

CONCEPTS: THE EVOLUTION AND PHYSIOLOGIC RATIONALE OF EGDT

Early and Late Sepsis: A Hemodynamic Comparison

Sepsis represents a continuum from an inciting infectious event and host-pathogen interaction to the hemodynamic consequences caused by the relationship among proinflammatory, antiinflammatory, and

apoptotic mediators.⁴ The early stages of sepsis can be accompanied by circulatory insufficiency resulting from hypovolemia, myocardial depression, increased metabolic rate, and vasoregulatory perfusion abnormalities. As a consequence, a variety of hemodynamic combinations create a systemic imbalance between tissue oxygen supply and demand, leading to global tissue hypoxia and shock (Fig 2).

Increases in oxygen extraction, or decreases in the central venous saturation ($ScvO_2$) or mixed venous saturation ($S\bar{v}O_2$) signal falling venous oxyhemoglobin saturation. These parameters provide a compensatory mechanism for mitigating the imbalance of maintaining tissue oxygen needs. However, when the limits of this compensatory mechanism are reached, lactate production ensues as an indicator of anaerobic metabolism. In this delivery dependency phase, lactate concentration increases and may be inversely correlated with systemic oxygen delivery and $S\bar{v}O_2$ or $ScvO_2$ (Fig 2).⁵ This phase that is characterized as *global tissue hypoxia* is an important transition from sepsis to severe disease. While this phase is associated with increased morbidity and mortality if unrecognized or left untreated, it can occur with the patient displaying normal vital signs.⁶⁻⁸

The transition to septic shock can range from a hypodynamic state of oxygen delivery dependency (*ie*, elevated lactate concentrations and low venous oxygen saturations) to the more commonly recognized hyperdynamic state where oxygen consumption ($\dot{V}O_2$) is independent of oxygen delivery (*ie*, normal to increased lactate concentrations and high venous oxygen saturation), depending on the stage of disease presentation and the extent of hemodynamic optimization (Fig 2, 3).⁹ The observation of a hypodynamic state as shown by mean lactate levels of 6.9 and 7.7 mmol/L, respectively, combined with $ScvO_2$ values of 49.2% and 48.6%, respectively, at baseline in the standard and EGDT groups was not a novel finding. Astiz et al¹⁰ noted similar observations of a mean (\pm SD) lactate level of 5.3 ± 0.5 mmol/L and an $S\bar{v}O_2$ of $57 \pm 2\%$ (range, 28 to 73%) in septic patients who were immediately monitored on ICU admission (Table 1). Thus, sepsis evolves as a series of hemodynamic phases in which lactate and $ScvO_2/S\bar{v}O_2$ levels can serve as surrogates for monitoring the balance between systemic delivery and demands, and for quantifying the severity of global tissue hypoxia (Fig 2).^{5,10-12}

Lactate as a Metabolic Marker of High-Risk Patients

Although hypotension is currently used to define the transition from severe sepsis to septic shock, it is not sufficiently sensitive as a screening tool for tissue perfusion deficits occurring in patients with early

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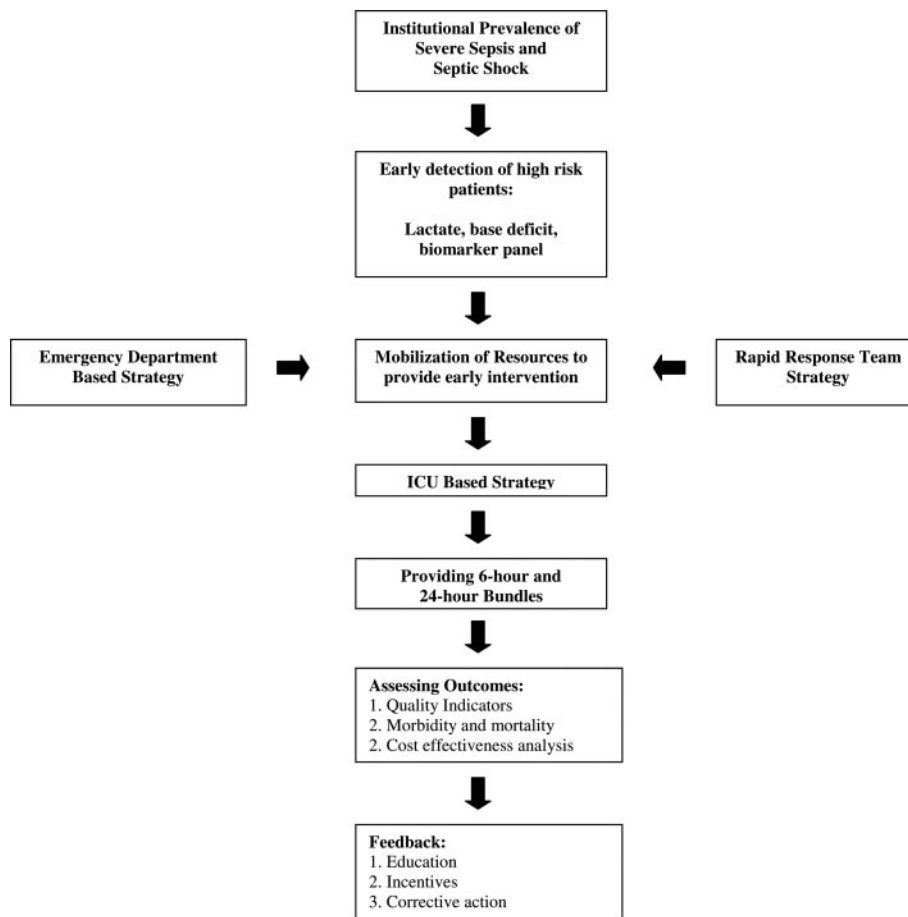


FIGURE 1. An implementation model of EGDT.

sepsis. The employment of lactate levels of ≥ 4 mmol/L as a marker for severe tissue hypoperfusion as a univariate predictor of mortality is supported by a number of studies.^{13–16} By carefully avoiding long tourniquet times, peripheral venous lactate levels can be used as a substitute for arterial lactate levels.^{17,18} Early measurement of elevated lactate levels may also be accomplished with the use of point-of-care devices during emergency department (ED) triage, with a capillary measurement of lactate levels having a turnaround time of < 2 min.^{19,20}

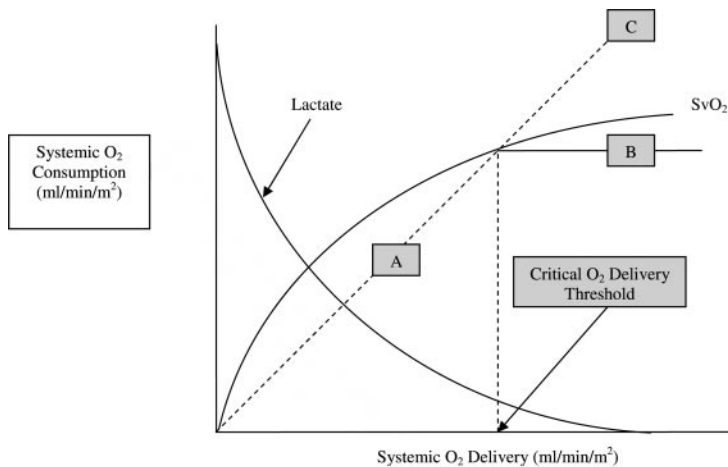
The question of whether to use anion gap or base deficit as a surrogate for lactate level is a valid one because of the availability of this parameter in routine laboratory assessments. In the EGDT study,²¹ a normal bicarbonate level or anion gap was observed in 22.2% and 25.0%, respectively, of patients with lactate levels of 4.0 to 6.9 mmol/L. The combination of a normal serum bicarbonate level and anion gap was observed in 11.1% of these patients. At higher lactate levels, this observation (mixed acid-base disorder) became less common and

was not present in any patients with lactate levels of > 10 mmol/L, all of whom had marked metabolic acidosis.

Although there is some controversy regarding other potential mechanisms underlying lactate accumulation in patients with severe sepsis,²² serial measurements of lactate levels can assess lactate clearance or changes in lactate level over time. Nguyen et al²³ have shown that increased lactate clearance rates during the first 6 h after sepsis presentation are significantly associated with preserved organ function and improved survival.^{23,24}

Previous Hemodynamic Optimization Trials: Why Is EGDT Different?

Early work by Shoemaker et al²⁵ produced observations that survivors of critical illness had supranormal levels of oxygen delivery compared to nonsurvivors. This prompted some clinicians to target supranormal levels in all critically ill patients. Hayes et al²⁶ targeted patient hemodynamics to supranormal values (*ie*, cardiac index, > 4.5 L/min/m²; oxy-



	MAP	CVP	ScvO2	Lactate	Cardiac Index	Systemic Vascular Resistance	Treatment and Comments
Hypovolemia	Variable	↓	↓	↑	↓	↑	Volume
Compensated and vasodilatory	Normal or ↓	Normal	↑	Variable	↑	↓	Vasopressors, low dose corticosteroids
Myocardial Suppression	Variable	↑	↓	↑	Normal or ↓	Normal or ↑	Increased BNP levels, Inotropic Therapy
Impairment of tissue O ₂ utilization	Variable	Normal	↑	↑	Variable	↓, Normal or ↑	Vasodilators, r-APC

FIGURE 2. Hemodynamic patterns of early severe sepsis and septic shock. Lactate levels and $\text{S}\bar{\text{v}}\text{O}_2/\text{ScvO}_2$ values can serve as surrogate markers for global tissue hypoxia during the delivery-dependent phase (A), delivery-independent phase (B), or pathologic delivery-dependent phase (C). Therapeutic patterns during each phase are shown in the table below the graph. r-APC = recombinant activated protein C; ↓ = decrease; ↑ = increase.

gen delivery, $> 600 \text{ mL}/\text{min}/\text{m}^2$; $\dot{\text{V}}\text{O}_2$, $> 170 \text{ mL}/\text{min}/\text{m}^2$). They found that achieving these target levels increased mortality compared with those in patients for whom more physiologic (*ie*, normal) goal levels were targeted. Gattinoni et al²⁷ similarly targeted critically ill patients by using optimization goals of cardiac index and $\text{S}\bar{\text{v}}\text{O}_2$, and found no mortality benefit in achieving supranormal values for cardiac index. The timing of intervention in the ICU setting and the absence of a delivery-dependent phase of systemic consumption (*ie*, decreased $\text{S}\bar{\text{v}}\text{O}_2$ and increased lactate level) differentiates these studies from EGDT. These studies are summarized and compared in Table 1.

A key element in the failure of these resuscitation trials is not only the magnitude of the end points but the timing of intervention. A metaanalysis of hemodynamic optimization trials by Kern and Shoemaker²⁸ suggested that early, but not late, hemodynamic optimization reduced mortality. EGDT was performed in the pre-ICU or ED phase of the disease,

within hours of patient presentation. It has since become increasingly evident from multiple subsequent studies^{23,29–32} that the 6-h time interval used in the EGDT trial was important not only from a diagnostic perspective but also in evaluating the effects of therapy and the resultant outcomes.

The Conceptualization of EGDT

The early pathogenesis of sepsis frequently begins prior to ICU admission and frequently in patients whose vitals signs fail to reflect the severity of global tissue hypoxia. Preliminary evidence,⁶ which laid the foundation for EGDT, has shown that this time period has significant implications for morbidity and mortality. Exploratory work³³ examining 1,067 patients presenting to the ED at Henry Ford Hospital (HFH) prior to the trial established lactate level as an appropriate screen for illness severity. Additionally, a prevalence study³⁴ conducted prior to the EGDT trial revealed a baseline mortality rate of 51%

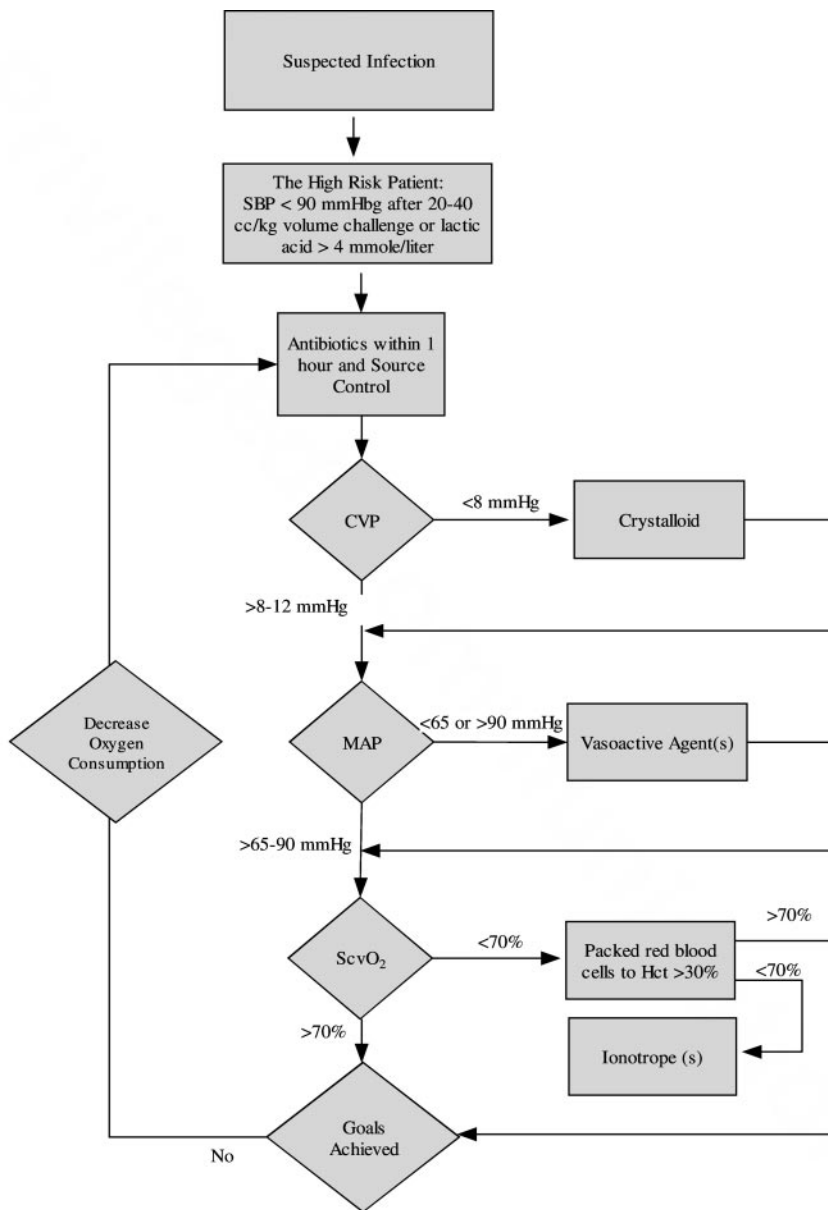


FIGURE 3. Algorithm of EGDT. Hct = hematocrit.

for patients with severe sepsis and septic shock at HFH. Due to these findings, the level of care provided in the standard arm of the EGDT study was mandated by the HFH institutional review board for human research as ethical management rather than a “wild-type” or no-care treatment arm.

Despite the fact that the care provided in the initial hours of the EGDT study was unblinded, it comprised a mean duration of 6.3 ± 3.2 h compared to 8.0 ± 2.1 h ($p < 0.001$), respectively, in the standard-care and EGDT groups. This time period comprised a mean duration of 9.9 ± 19.5 days compared to 7.2 ± 12.0 days ($p = 0.20$), respectively, of overall hospital stay for groups receiving the standard

care compared to those receiving EGDT. Thus, $> 90\%$ of the total hospital stay occurred after transfer from the ED to the ICU and was provided by health-care practitioners who were blinded to the randomization order performed in the ED.

CONTROVERSIES OF EGDT

The Therapeutic Components of EGDT

Since the publication of the EGDT study, numerous questions have been raised regarding specific components of treatment. While the trial began patient enrollment in 1997, the protocol goals were

Table 1—Comparison of Hemodynamic Optimization Studies*

Variables	Astiz et al ¹⁰ /1988†	Gattinoni et al ²⁷ /1995	Hayes et al ²⁶ /1994	Rivers et al ¹² /2001
Setting	Early ICU	ICU	ICU	ED or Pre-ICU
Enrollment time, h	< 6	Up to 72	Up to 24	< 2
Lactate, mmol/L	5.3 ± 0.5	NA	2.2–3.5	6.9–7.7
MAP, mm Hg	68 ± 2	NA	NA	74–76
SvO ₂ , %	57 ± 2	67.3	NA	48.6–49.2
CVP, mm Hg	NA	10.6	Optimized	5.3–6.1
Cardiac index, L/min/m ²	2.7 ± 0.2	3.7–3.8	3.2–3.4	1.7–1.9
SVRI, dyne · s · cm ⁻⁵ · m ²	2,394 ± 178	708–735	NA	1,181–1,192

*NA = not applicable; SVRI = systemic vascular resistance index.

†Values are given as the mean ± SE.

consistent with the practice parameters for hemodynamic support of sepsis recommended by the American College of Critical Care Medicine in 1999 (Table 2).³⁵ More recently, these recommendations have been updated,³⁶ but the therapeutic tenets remain the same.

Scvo₂ vs SvO₂: Does it Matter?³

An SvO₂ gives an estimate of the oxygen saturation of blood returning to the right side of the heart, which indirectly correlates with tissue oxygen extraction, and the balance between systemic oxygen delivery and demand. Given the challenges of using a pulmonary artery catheter (PAC) in the early setting such as the ED, the Scvo₂ represents a convenient surrogate for, but not a replacement for, SvO₂ or the PAC. Reinhart et al³⁷ have shown a significant correlation of SvO₂ with Scvo₂ using either intermittent or continuous measurement. Debate continues regarding whether Scvo₂ is a numeric equivalent to SvO₂.^{37–41} However, these studies have largely compared SvO₂ and Scvo₂ in the normal to high range, which is found in the latter stages of sepsis and in ICU patients.^{40,42}

The more important issue is whether there is equal clinical utility and correlation in the lower ranges where this value is most clinically useful.⁴³ The presence of a low Scvo₂ level in patients with early sepsis portends increased morbidity and mortality,^{32,44} and correcting this value according to a consensus-derived algorithm improves morbidity and mortality.¹² Thus, the clinical utility of this parameter has been calibrated in the early setting of severe sepsis and septic shock. Whether it equals SvO₂ is less relevant. The Surviving Sepsis Campaign has acknowledged the numeric difference between SvO₂ and Scvo₂, but recognizes the evidence-based clinical utility by recommending an SvO₂ of 65% and an Scvo₂ of 70% in the resuscitation portion of its severe sepsis and septic shock bundle.^{39,45}

Fluid Therapy

As stated in the practice parameters³⁵ for the treatment of the adult patient with sepsis, “the early, hypovolemic, hypodynamic phase of sepsis is treated by providing appropriate, high volume resuscitation. . . crystalloid solutions (6 to 10 L) are usually required during the initial resuscitation.” The phys-

Table 2—Selected Recommendations From the 1999 SCCM Practice Parameters for Hemodynamic Support of Sepsis in Adult Patients Compared to EGDT*

1999 SCCM Recommendation	EGDT
Fluid infusion should be titrated to a level of filling pressure associated with the greatest increase in cardiac output and stroke volume; for most patients, this will be a PAOP in the range of 12–15 mm Hg	Fluid infusion was titrated incrementally based on CVP monitoring; CVP target, 8–12 mm Hg substituted for PAOP
Hemoglobin concentrations should be maintained above 8–10 g/dL. In patients with low cardiac output, SvO ₂ , lactic acidosis, widened gastric-arterial PCO ₂ values, or coronary artery disease, transfusion to a higher level of hemoglobin may be desired	Transfusion trigger was set for a target hemoglobin level of 10 g/dL if Scvo ₂ was < 70% after CVP of 8–12 mm Hg was achieved; patients uniformly had lactic acidosis, as well as a widened arterial-venous PCO ₂ gradient
In patients with evidence of tissue hypoperfusion, the addition of dobutamine to therapy may be helpful to increase cardiac output and improve oxygen perfusion	If MAP, CVP, and hemoglobin level were at goal values, and Scvo ₂ was still < 70%, dobutamine infusion was initiated
A strategy of routinely increasing cardiac index to predefined supranormal levels (<i>ie</i> , > 4.5 L/min/m ²) has not been shown to improve outcome	Scvo ₂ provided an indirect measurement of the oxygen delivery consumption ratio; Scvo ₂ was used to titrate therapies, rather than routinely increasing cardiac index

*SCCM = Society of Critical Care Medicine; PAOP = pulmonary artery occlusion pressure.

ologic and clinical utility of central venous catheterization used for this monitoring purpose continues to be debated.⁴⁶ There are data from a recent study⁴⁷ suggesting that there is no clinical advantage of the PAC over the central venous catheter for fluid management in patients with acute lung injury (ALI) derived from various critical illnesses including sepsis.

The EGDT study has been considered by some to be a liberal fluid strategy as the EGDT group received significantly more volume therapy and packed RBCs in the first 6 h of treatment. An important distinction is that by 72 h there was no significant difference in total fluid resuscitation (EGDT group, 13.36 L; standard therapy group, 13.44 L). The Fluids and Catheters Treatment Trial⁴⁸ isolated the manipulation of volume therapy as a controlled intervention that began an average of 43 h after ICU admission and 24 h after the establishment of ALI. These patients were resuscitated to normal or hyperdynamic cardiac indexes and, thus, were homogenous in this respect. Although there was no difference in 60-day mortality rates, patients in the group treated according to a conservative strategy of fluid management had significantly improved lung function and CNS function, and a decreased need for sedation, mechanical ventilation, and ICU care. There was a statistically significant 0.3-day increase in cardiovascular failure-free days in the liberal fluid group compared to the conservative fluid group, suggesting that caution should be used in applying a conservative fluid strategy during the resuscitation phase.

In the EGDT study, there was no difference in PaO₂/fraction of inspired oxygen ratios between the standard-care group and the EGDT group from baseline to the subsequent 72 h (Fig 4). There was also no significant difference in the rate of intubation and mechanical ventilation during the first 6 h in the standard-care group (53.8%) group compared to the EGDT group (53%). However, over the period from 7 to 72 h, 16.8% of patients in the standard-care group required intubation, compared to only 2.6% of patients in the EGDT group ($p < 0.001$). Over the total length of the hospital stay, the cumulative rate of mechanical ventilation was 70.6% in the standard-care group compared to 55.6% ($p < 0.02$) in the EGDT group, who received less fluid and packed RBCs initially. These findings of a delayed need for mechanical ventilation in the standard-care group is consistent with observations that the need for mechanical ventilation is closely related to shock resolution within the first 24 h rather than to primary respiratory decompensation.⁴⁹ Thus, in regard to fluid management, it is important to recognize that EGDT and Fluids and Catheters Treatment Trial⁴⁸

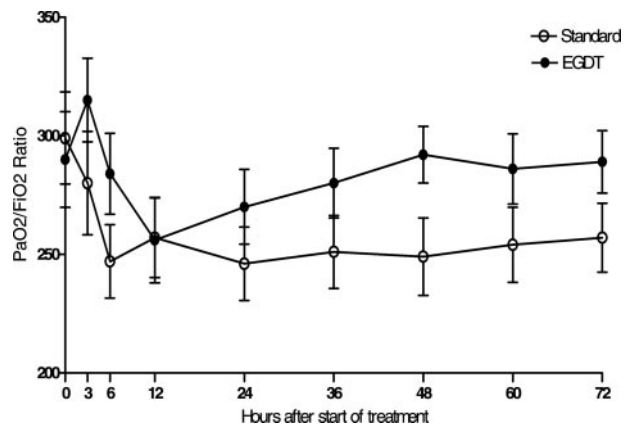


FIGURE 4. Comparing the PaO₂/fraction of inspired oxygen (FIO₂) ratios between the EGDT and standard-care groups. Despite more volume resuscitation in the EGDT group during initial 6 h, there was no net difference in PaO₂/FIO₂ ratio ($p = 0.34$).

are not at odds with each other but illustrate the fact that fluid management is a matter of timing.⁵⁰

Patients on Hemodialysis

Fluids are administered with understandable caution in patients with end-stage renal disease (ESRD). Due to concerns regarding the volume of fluids administered with EGDT, clinicians may have reservations in treating patients with ESRD. To address these concerns, a subset analysis of EGDT was performed. This subset consisted of 18 patients with ESRD who were receiving hemodialysis in the original study. In these patients (standard care, 10 patients; EGDT, 8 patients), intubation and mechanical ventilation rates were significantly greater (50% vs 29%, respectively; $p < 0.01$) and mortality rate was significantly higher (70% vs 14%, respectively; $p < 0.01$) in standard-care patients. Patients in the standard-care group received less fluid administration compared to EGDT patients.⁵¹

Vasopressor Therapy

The rates of vasopressor use were 30.3% vs 27.4% ($p = 0.62$), respectively, during the first 6 h, 42.9% vs 29.1% ($p = 0.03$), respectively, during the period from 7 to 72 h (ICU phase), and cumulatively 51.3% vs 36.8% ($p = 0.02$), respectively, over the first 72 h in the standard-care group compared to the EGDT group. These observations reveal not only that hypotension is more refractory to fluid administration at the later stage of disease presentation but that the later administration of vasopressors also correlates with outcome. Levy et al⁵² have shown that improvement in cardiovascular function, or the lack thereof, carries the greatest impact on survival compared to

any other organ dysfunction. In supporting cardiovascular function, the delayed need for vasopressor therapy is incrementally associated with a significantly higher mortality rate than that of any other organ failure beyond the first 24 h of sepsis.⁵²

Vasodilator Therapy

After adequate volume and hemoglobin targets were met, we surprisingly found that 9% of EGDT patients met the protocol criteria for afterload reduction for a mean arterial pressure (MAP) of > 90 mm Hg by utilizing nitroglycerin therapy. Nitroglycerin was chosen because of its effects on preload, afterload, and coronary vasodilation. All of these patients had a history of hypertension and congestive heart failure. The median baseline ScvO₂ was 46% in this subset of patients. Although the use of nitroglycerin was unexpected on study initiation, therapy with afterload reduction is not without precedent in treating sepsis patients. Cerra et al⁵³ provided vasodilator therapy to sepsis patients with low cardiac output and observed physiologic improvement. Spronk et al⁵⁴ found that nitroglycerin may improve microcirculatory flow in normotensive or even hypotensive patients with septic shock. It is becoming increasingly evident that 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 to define the role of microcirculatory dysfunction in oxygen transport and circulatory support.⁵⁵

Inotropic Therapy

In previous studies,^{27,56} dobutamine therapy has been associated with increased mortality. Patient selection, the dosage and timing of therapy, and the end points of resuscitation were different between the EGDT study and previous studies. Hayes et al²⁶ used dobutamine, up to 200 µg/kg/min, to reach a cardiac index of 4.5 L/min/m², which is considered to be a supraphysiologic end point. Almost half of the treated patients (24 of 50 patients) experienced complications from dobutamine therapy, including tachycardia (heart rate, > 130 beats/min), ECG signs of ischemia, and tachydysrhythmias. In the EGDT study, patients were treated using a lower dobutamine dose (average dose of 10.3 µg/kg/min to a maximum dose of 20 µg/kg/min), which was titrated upward to achieve an ScvO₂ of ≥ 70%. It appears that dobutamine therapy remains best reserved for those patients who are in a supply-dependent phase of their sepsis course.⁵⁷

Adequate preload is a requisite for optimal benefit from dobutamine therapy, and when titrated in a

goal-directed fashion, it has been shown to have outcome benefit.⁵⁸ Hypotension after dobutamine administration can often signal unrecognized hypovolemia. In the EGDT study, the titration of dobutamine began at 2.5 µg/kg/min and was systematically titrated upward by increments of 2.5 µg/kg/min every 15 to 20 min to mitigate sudden decreases in BP. The onset of sinus tachycardia (*ie*, heart rate, > 100 beats/min) is a criterion for discontinuing dobutamine therapy or decreasing its dose. When tachycardia develops in a patient while dobutamine is being administered after meeting EGDT goals, one must evaluate other concomitant vasopressors if they are being used. A switch from a β-agonist vasopressor to a more α-agonist-type vasopressor (*eg*, phenylephrine or norepinephrine) may decrease the heart rate and allow for dobutamine administration. This strategy may actually affect outcomes.⁵⁹ If tachycardia persists and an inotrope is needed, digoxin, 0.25 to 0.5 mg (with electrolytes corrected), may be administered to control the heart rate to a level of < 100 beats/min.^{60–63} Further investigation of volume assessment may be warranted using other invasive and noninvasive technologies at this juncture.

RBC Transfusion Therapy

Anemia in patients with early severe sepsis and septic shock results from a combination of preexisting disease and acute volume resuscitation.⁶⁴ Acute anemia combined with global tissue hypoxia provides one of the most potent stimuli for erythropoietin production to increase marrow production of RBCs.^{65–67} Global tissue hypoxia is the stimulus for the elevated erythropoietin and hemoglobin concentrations observed in patients with more chronic illnesses such as cyanotic heart disease and COPD, and in persons residing at high altitudes. However, patients with severe sepsis and septic shock who have an impaired marrow response to RBC mobilization and variable erythropoietin levels may lack this acute compensatory ability to increase hemoglobin concentrations.^{68,69} The combination of anemia and the presence of global tissue hypoxia represents the physiologic rationale to transfuse RBCs in these patients.

In a seminal study, Hebert et al⁷⁰ concluded that a restrictive strategy of RBC transfusion, with corresponding hemoglobin concentrations of 7 to 9 mg/dL, was “at least as effective and possibly superior to a liberal transfusion strategy in critically ill patients.”^{70,71} However, Hebert et al⁷⁰ did not specifically address patients with severe sepsis, and septic shock patients who were hypovolemic and had clinical evidence of global tissue hypoxia. Furthermore,

comorbidities (*ie*, atherosclerotic heart disease and congestive heart failure), which have commonly served as exclusion criteria in prior transfusion studies, were highly prevalent in the EGDT study. Marik and Sibbald⁷² found that after the transfusion of 3 U of packed RBCs there was no increase in $\dot{V}O_2$ and an inverse association between the change in gastric intramucosal pH and the age of the transfused blood (*ie*, > 15 days) [$r = -0.71$; $p = 0.001$]. However, these patients were not delivery-dependent as the pretransfusion hemoglobin concentration was 9.9 ± 7.8 mg/dL, cardiac indices (4.6 ± 1.7 L/min/m²) and lactate levels (2.6 ± 2.1 mmol/L) were near to normal, and $S\bar{v}O_2$ levels (69.5 ± 8.1) were normal. Furthermore, septic shock and hemodialysis patients were excluded from the study (Table 3).⁷² Walsh et al⁷³ subsequently found that the transfusion of equally aged stored leuko-depleted RBCs to euvolemic, anemic, critically ill patients has no clinically significant adverse effects on gastric tonometry or global indexes of tissue oxygenation.

Hemoglobin thresholds in patients with critical illnesses have provoked passionate discussions warranting a reexamination of how effective transfusion therapy was in the EGDT group. There was a 30% greater reduction in hematocrit in the EGDT group at 3 h compared to that in the standard-care group, although the hematocrits in both groups were equal at baseline. The threshold for transfusion was based on the consideration of a physiologic rationale (*ie*, low $ScvO_2$ and increased lactate level), a high-risk patient population, and expert consensus.³⁵ These are important considerations when comparing

EGDT patients to those enrolled in transfusion studies of ICU patients (Table 3). Volume resuscitation as the initial therapy was sufficient to restore an $ScvO_2$ of >70% in 35.9% of patients. After fluid therapy, RBC transfusion in those patients with an hematocrit < 30% was successful in allowing an additional 50.4% of the patients to attain an $ScvO_2$ of > 70%. In those patients who met volume resuscitation and hematocrit goals, inotropic therapy was required in the remainder of patients (13.7%) to reach an $ScvO_2$ of 70%. Thus, despite the much-maligned inability of packed RBCs to carry oxygen, transfusion with RBCs had a physiologic effect in 79% of the patients in whom it was used. It remains unclear whether the lack of efficacy in the remaining 21% of patients was secondary to transfusing aged, ineffective blood, or whether the patients had persistent myocardial dysfunction. After RBC transfusion, the hematocrit at 6 h was statistically higher in the EGDT group compared to the standard-care group (33.3% vs 32.0%, respectively; $p = 0.03$). After 72 h, the actual difference in volume was a net difference of 102 mL more blood in the EGDT group. Although, this study was neither adequately powered nor designed to test the effect of transfusion therapy on morbidity and mortality; our favorable results were obviously not mitigated by our approach to RBC transfusion.

Antibiotic Therapy

Early and appropriate empiric antibiotic therapy has been associated with improved outcome in mul-

Table 3—Comparison of Transfusion Therapy Studies*

Variables	Rivers et al ¹² /2001	Hebert et al ⁷⁰ /1999	Vincent et al ⁷¹ /2002	Marik and Sibbald ⁷² /1993
Setting	ED	ICU	ICU	ICU
Time	< 1 h	24 h	> 2 wk	Up to 48 h
Age, yr	62–67	57–58	53–59	49.6
Hemoglobin, mg/dL	11.3–11.4	8.2–8.2	10.1–12.2	9.9
Lactate, mmol/L	6.9–7.7	1.8 ± 1.8 – 1.8 ± 2.1		2.6
$S\bar{v}O_2$, %	48.6–49.2			69.5
CVP, mm Hg	5.3–6.1			Resuscitated
Cardiac index, L/min/m ²	1.7–1.9			3.4
APACHE II score	20.4 ± 7.4–21.4 ± 6.9†	20.9 ± 3–21.3 ± 8.1†	16.5–13.5	
Mortality rate	30.5–56%	22.2–28.1%	10–18.5% (ICU) 17–22% (28 d)	Decreased pH _i
Comments	100% of patients enrolled had evidence of shock or global tissue hypoxia	13–16% of patients had evidence of shock; sepsis diagnosed in 6% of patients in restrictive transfusion cohort vs 4% of liberal transfusion cohort	20–23% of patients had evidence of shock	Excluded dialysis patients, patients likely to die in 24 h, and patients with septic shock (systolic BP, < 90 mm Hg)

*pH_i = mucosal pH.

†Values are given as the mean ± SD.

Myocardial Dysfunction and Brain Natriuretic Peptide

multiple studies.^{30,74–76} Although the EGDT study was not designed to evaluate the impact of time to antibiotic therapy on mortality, there were no significant differences in antibiotic therapy between the EGDT and standard-care groups in terms of the percentage of patients receiving antibiotics within 6 h (86.3% vs 92.4%, respectively), the percentage who received adequate antibiotics (96.7% vs 94.3%, respectively), and the mean duration of antibiotic administration (11.7 ± 16.2 vs 11.3 ± 15.8 days). While appropriate antibiotic therapy in septic shock patients has a significant impact on mortality, the outcome benefit of EGDT is not due to antibiotic inadequacy in the standard-care group.

Physiologic Scoring Systems: The Issues of Early Use

Equivalent enrollment of illness severity is a necessary characteristic of any randomized clinical trial. Physiologic scores are used to compare mortality probabilities and illness severity between groups of patients. In the EGDT study, physiologic scores were assessed to compare illness severity immediately on hospital arrival, a setting in which they have not been traditionally applied. The mean baseline acute physiology and chronic health evaluation (APACHE) II score, simplified acute physiologic score II, and multiple organ dysfunction score (20.4 ± 7.4 , 48.8 ± 11.1 , and 7.3 ± 3.1 , respectively) in the standard-care patients of the study would reflect a predicted mortality rate of approximately 40%, closely approximating the true mortality rate of 46.5% of the study population. Gao et al reported¹⁰⁹ similar APACHE II scores to the EGDT trial but actual hospital mortality rates of 29 to 55%.

Thus, the physiologic scores obtained in the most proximal stage of disease presentation can be higher or lower than the scores obtained 24 h later in the ICU, depending on the resuscitation and the evolution of the disease being examined. If the same patients are assessed in the traditional time period after ICU admission, this lead-time bias before ICU admission may alter the actual mortality rate prediction. The APACHE II score and other physiologic scores are dependent on variables that reflect the progression or reversal of organ dysfunction and how optimal the resuscitation has been prior to the time of its calculation. Notwithstanding, physiologic scores such as the APACHE II score are recommended requisites for the administration of recombinant human activated protein C. For these reasons, the use of a physiologic score as an outcome predictor and as an indication for specific sepsis therapies requires further study.^{77–80}

At the hemodynamic juncture at which the goals of central venous pressure (CVP), MAP, and hematocrit are met, a low $ScvO_2$ implies decreased myocardial compliance or dysfunction. Previous work by Parillo et al⁸¹ has shown that 10 to 15% of patients with near-normal BP and preload optimization will continue to have significant myocardial depression, necessitating inotropic support. Similar findings were detected in the EGDT study with 13.7% of patients receiving inotropic therapy, which is not unlike findings in other studies.^{82–84}

The limitation of CVP is that it is a pressure measurement; thus, in the presence of an impaired ventricle, a pressure-volume discrepancy may exist as significant hypovolemia may be present with a normal to increased CVP.⁴⁶ This observation may lead to inappropriate manipulation of intravascular volume and its untoward consequences.⁸⁵ This was an unexpected observation in patients in the standard-care group in whom there was no indirect measure of cardiac function. Serum examined from a subset of patients during the EGDT trial shed light on the brain natriuretic peptide (BNP) levels in patients with early sepsis. In the EGDT study, clinicians treating the patient were blinded to the BNP levels. Receiver operating characteristic curve analysis revealed that the baseline BNP cutoff point that yielded the maximal sum of sensitivity and specificity for predicting dobutamine usage from hour 0 to hour 6 was 230 pg/mL.⁸⁶ Paradoxically, these patients had lower heart rates, higher CVP, higher blood lactate levels, a greater severity of renal failure (*ie*, increased BUN and creatinine levels), and lower glucose levels (all $p \leq 0.02$) than patients with low BNP levels. These patients also had significantly higher baseline illness severity scores and more chronic health conditions, especially cardiovascular disease ($p < 0.02$).⁸⁶ Similarly, a study by Tung et al,⁸⁷ found that at a BNP level of < 350 pg/mL few patients were found to be in cardiogenic shock or to have a low cardiac index (< 1.8 L/min/m²).

The clinical caveat in using an algorithmic approach when sepsis is complicated by myocardial dysfunction is that a reduction in systemic vascular resistance with the use of a preload and afterload reducer or the use of inotropes (in the absence of tachycardia) are more advantageous at this point.^{12,36} With improvements in stroke volume and myocardial compliance, CVP decreases to < 8 mm Hg, triggering the need for additional volume.¹² Thus, through optimizing this dynamic pressure-volume relationship, EGDT patients (especially those with myocar-

dial dysfunction) received significantly more volume in the first 6 h even though the CVP was similar to that in the standard-care group.¹²

Cryptic Shock

The progression of sepsis is often complicated by multisystem organ failure, including early cardiovascular insufficiency secondary to the hemodynamic perturbations, which are associated with increased mortality.^{4,7,88} These perturbations can go unresolved when hemodynamic management is guided by insensitive variables such as MAP and CVP.^{6,89} Eighty-six percent of patients in the standard-care group achieved the composite end points of CVP, MAP, and urine output compared to 95% of patients meeting these goals in the EGDT group. However, 39.8% of patients in the standard-care group compared to 5% of patients in the EGDT group continued to have global tissue hypoxia (*ie*, elevated lactate levels and decreased ScvO₂) despite 6 h of resuscitation to normalized vital sign goals (MAP, \geq 65 mm Hg; CVP, \geq 8 mm Hg; urine output, \geq 0.5 mL/kg/h). In this subset of patients, who had what is called *cryptic shock*,⁹⁰ the hospital mortality rate was 56.5%. When this was examined in the standard-care group, there was a twofold increase in cardiovascular collapse (*ie*, clinical incidents requiring cardiopulmonary support) as the cause of death in the first 24 h compared to the EGDT group. There was also a greater 60-day mortality rate compared to those who received EGDT (60.9% vs 20.0%, respectively; $p = 0.004$).⁹⁰

EGDT Effects on Inflammation: Pathogenic, Diagnostic, Therapeutic, and Prognostic Implications

The continued presence of supply dependency not only has pathologic significance *in vitro*,⁹¹ but may be the pathologic link among the clinical presence of global tissue hypoxia, the generation of inflammation, and the mitochondrial impairment of oxygen utilization seen in septic ICU patients.⁹² In addition to the primary stimulus of the systemic inflammatory response syndrome, global tissue hypoxia independently contributes to endothelial activation, the disruption of the homeostatic balance of coagulation, vascular permeability, and vascular tone.^{91,93}

One of the plausible explanations of why EGDT patients required less mechanical ventilation despite receiving more liberal fluid therapy during the first 6 h may be deduced from a reduction in interleukin (IL)-8 levels, which is associated with ALI (Fig 5).^{94,95} While equal at baseline, IL-8 was significantly reduced over the period of 12 to 72 h in the EGDT group compared to that in the standard-care group

($p = 0.045$) [Fig 5]. These results may be explained by the resolution of shock imparted by EGDT. Previous work by Estenssoro et al⁴⁹ demonstrated that the presence of shock on ICU admission day was the single most valuable predictor of prolonged mechanical ventilation, even after adjusting for severity of illness and hypoxemia.

The significant decrease in d-dimer levels in patients in the EGDT group compared to that in patients in the standard-care group over 72 h was similar to that observed in the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis trial⁸⁰ using recombinant human activated protein C in patients with severe sepsis (Fig 6). In addition, a significant inverse relationship between lactate clearance rates during the first 6 h of resuscitation and mean d-dimer concentrations over 72 h was also found (Fig 7), which is comparable to findings by Kobayashi et al.⁹⁶ These data regarding IL-8 and d-dimer suggest that part of the effectiveness of EGDT may be in mitigating another stimulus to inflammation, global hypoxia.⁹¹

The global tissue hypoxia stimulus to inflammation makes “hemodynamic heterogeneity” a potential source for “inflammatory heterogeneity.” This heterogeneity has not been accounted for in previous outcome trials of immunomodulation and may have future implications.⁹⁷ A multicenter trial⁹⁸ examining early biomarker patterns in patients with sepsis has suggested that this may be the case. Using a multi-marker panel of biomarkers, these data indicated significant predictive power in the transition from sepsis to severe disease and mortality. These biomarker patterns may one day serve as diagnostic, therapeutic, and prognostic adjuncts in the early management of patients with severe sepsis and septic shock, and in future outcome trials.

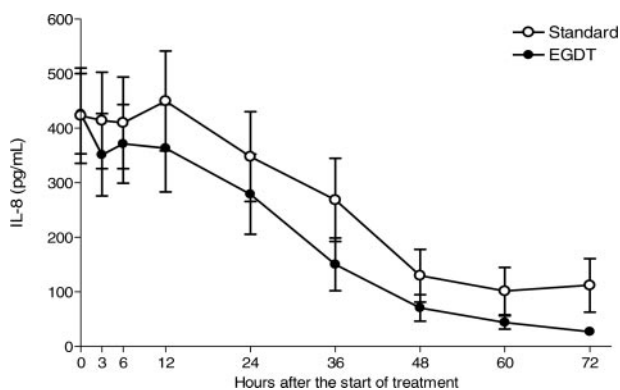


FIGURE 5. The effect of EGDT on inflammation. EGDT effects on inflammation (IL-8) associated with ALI. EGDT patients had a corresponding lower level of IL-8 and a decreased rate of mechanical ventilation in the subsequent 7 to 72 h time period ($p = 0.045$).

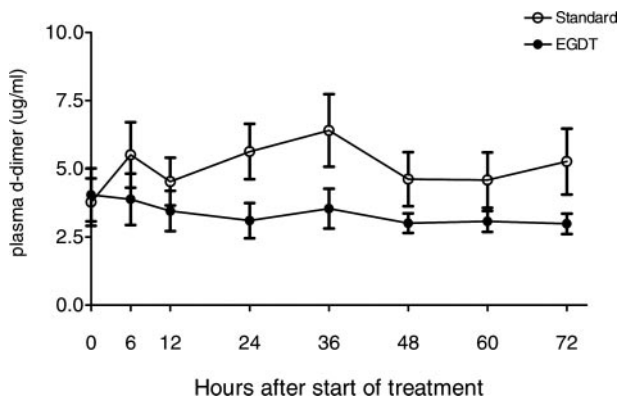


FIGURE 6. EGDT effect on coagulation defects (d-dimer). A significant decrease is seen in the level of d-dimer over 7 to 72 h in the EGDT group ($p = 0.01$).

Implementation Barriers and Successful Strategies

Sepsis has traditionally been viewed as an ICU disease rather than a hospital disease.⁹⁹ The successful implementation of protocols to improve morbidity and mortality in patients with other conditions such as acute myocardial infarction, trauma, and stroke have highlighted the fact that the care of the critically ill traverses geographic locations and must bridge care between specialties.¹⁰⁰ As the late Peter Safar noted, “critical care is a concept, not a location, which frequently begins with ED intervention, and culminates in ICU admission and continued management.”¹⁰¹ Dr. Safar’s vision included a model of care that provides objective criteria for defining the disease, mobilizes the appropriate resources to provide a level of care commensurate with illness sever-

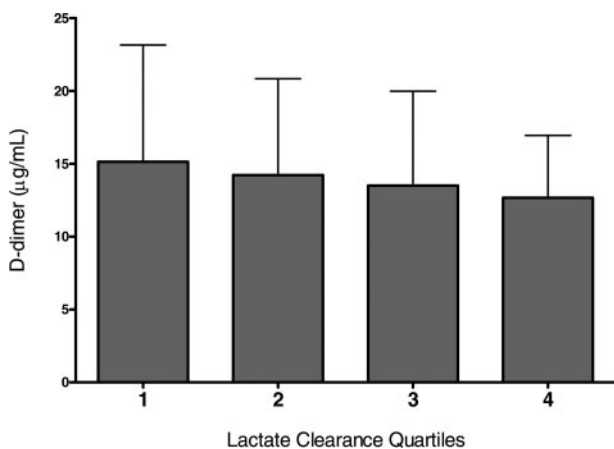


FIGURE 7. Lactate clearance and d-dimer. The lactate clearance is defined as the baseline or zero hour lactate minus the 6-h lactate divided by the baseline lactate; quartile 1, $-24 \pm 42\%$; quartile 2, $30 \pm 8\%$; quartile 3, $53 \pm 7\%$; quartile 4, lactate clearance $75 \pm 7\%$. D-dimer levels significantly decrease as lactate clearance increases ($p = 0.01$).

ity, standardizes management protocols, and provides outcome measures for compliance and quality improvement (Fig 1).

The provision of appropriate and prompt care while in the ED, general practice medical-surgical floors,³¹ or the ICU²⁹ has common but at the same time unique barriers to the implementation of EGDT for each location. From the ED perspective, the recent Institute of Medicine report from June 14, 2006, *Hospital-Based Emergency Care: At the Breaking Point*, concludes that ED overcrowding is a “national threat to quality, safety and timely care in the United States.” Patients may languish in the ED, as ICU “boarders” until a bed is available, for up to 24 h in the hands of an understaffed, overloaded work force that provides adverse nurse/patient ratios.¹⁰² Although the multitasking required of an ED clinician working in a busy ED limits the quality of intensive care provided, the amount of critical care provided in this environment has been quantitated to be up to 15% of the care provided during the entire hospitalization.¹⁰³ This issue has generated varying opinions regarding the role of the ED in sepsis management, especially in regard to EGDT.¹⁰⁴ While components of EGDT may be regarded as too resource-intensive and labor-intensive or beyond the skill set of some ED clinicians,¹⁰⁴ a coordinated patient care model that combines appropriate expertise and resource allocation may rectify such a situation. The American College of Emergency Physicians has taken a public stance representing the interests of the patient and the emergency medicine community by formally becoming full partners in the Surviving Sepsis Campaign, an international multidisciplinary collaborative designed to reduce sepsis mortality.¹⁰⁵

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 that utilizes mobile resources to descend on the patient irrespective of location.¹⁰⁶ The third concept is an ICU-based model that rapidly transfers the patient to the ICU, where EGDT is administered.¹⁰⁷ Each of these unique models must be tailored to the institution (Fig 1).

Best-Practice Guidelines

The Surviving Sepsis Campaign, which garnered support by the Institute of Healthcare Improvement, has condensed the management guidelines for severe sepsis into the *resuscitation bundle* and the *management bundle*.⁴⁵ The sepsis resuscitation bundle is to be completed within the first 6 h, and the

management bundle is to be completed within the first 24 h of patient care. EGDT, although only one of the components of these care bundles, comprises the earliest step in the implementation of the guidelines. Since the inception of these guidelines, many institutions and investigators in critical care and emergency medicine have begun collecting clinical data to confirm the benefit from embarking on these quality and care improvement initiatives.

An Outcomes Survey of Early Sepsis Management

A survey of centers that have instituted sepsis programs is summarized in Table 4.^{12,82,83,107–116} There were a total of 1,298 patients with a mean mortality rate prior to implementation of $44.8 \pm 7.8\%$ (range, 55.0 to 29.3%). After implementation, the mean mortality rate was reduced to $24.5 \pm 5.5\%$ (range, 33.0 to 18.2%) for an average reduction of 20.3% (Table 4). The limitations of this outcome survey relate to its use of some preliminary data published in abstract form; however, verification was made by direct communication with each center. There has been an underreporting of implementation results as many centers have begun incorporating EGDT as best practice or as a quality initiative, and thus the publication of data may not be forthcoming. Furthermore, implementation programs may include additional therapies such as aggressive hemodialysis, glucose control, recombinant activated protein C, corticosteroids, and protective lung strategies, which may add to the salutary effects of EGDT.

Although many of the studies in the survey were performed in a retrospective case-control manner, they consistently highlight several points. First, the rapid institution of interventions, often not provided until ICU admission, uniformly improves patient outcome. Second, when all centers are summarized, the baseline mortality rates for the preimplementation phase, the baseline mortality rate (survey, 44.8%; EGDT, 46.5%), and the absolute reduction in mortality (survey, 20.3%; EGDT, 16.5%) are very similar. A recent review¹¹⁷ of frequently cited clinical research found that it was not unusual for subsequent studies to find contradictory or less impressive results. Specific to EGDT, some investigators have expressed concern regarding the high baseline mortality rates of the study. In addition, the presence of the expert research team and staff with experience in the management of sepsis may be considered a confounding variable. The result of this survey not only contradicts the aforementioned review but also indicates significant generalizability. Third, these centers (both academic and community-based) demonstrated that a deliberate adaptation of the sepsis

bundles into standard care can be implemented through an organized multidisciplinary approach.

Cost-Effectiveness of EGDT

The potential benefits that can be realized through a program such as EGDT should demonstrate fiscal justification. An examination¹¹⁸ of EGDT included factors such as additional training, personnel, possible physical plant changes, and equipment necessary to screen patients, and concluded that EGDT is a cost-effective intervention. Huang et al¹¹⁸ in a formal cost-effectiveness analysis found that EGDT can provide up to a 23.4% reduction in hospital costs related to the treatment of patients with severe sepsis and septic shock. EGDT was found to be most cost-effective if the volume of patients exceed 16 patients per year. The cost-effectiveness was demonstrated in all models of care including whether the care was provided primarily by the ED, rapid response team, or the ICU. For HFH in particular, there was a mean reduction of 4 days per hospital admission (a 32.6% reduction in hospital length of stay) for survivors and a 13.9% reduction in PAC use (both $p < 0.03$). Similar findings have been noted by other investigators. Shapiro et al⁸³ have reported a cost per life saved of \$32,336, and Trzeciak et al⁸² found a reduction in median hospital facility charges from \$135,199 to \$82,233 (reduction, 39.2%; $p = 0.14$) and in PAC use from 43.8 to 9.1% ($p = 0.01$).

CONCLUSION

EGDT results in significant reductions in morbidity, mortality, vasopressor use, and health-care resource consumption. Five years after its publication, this study has generated much discussion with regard to the concepts of early sepsis, and has fueled debate regarding diagnostic and therapeutic interventions. Further investigations by the primary investigators and others have brought additional contemporary findings. EGDT modulates some components of inflammation, which are 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 those of the original trial. While many challenges remain before EGDT is universally implemented, 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 conditions such as acute myocardial infarction, trauma, and stroke.

Table 4—An Outcome Survey of Sepsis Initiatives With EGDT Legend*

Program	Total Patients, No.	Patients, No. (Mortality %) [95% CI]		Comments
		Preimplementation	Postimplementation	
Loma Linda University (6-h bundle) ¹⁰⁸	330	253 (39.5) [0.33–0.45]	77 (20.8) [0.13–0.31]	Nguyen et al ¹⁰⁸ implemented EGDT and the 6-h sepsis bundle over a 2-yr implementation period; there was no statistical difference in ED LOS or ICU LOS (for mortality: $p \leq 0.01$; RR, 0.53; OR, 0.4; RRR, 46.9%; ARR, 18.4%; NNT, 5)
Birmingham Heartlands ¹⁰⁹	101	52 (49) [0.36–0.62]	49 (23) [0.13–0.37]	Gao et al ¹⁰⁹ reviewed daily admissions for severe sepsis and septic shock from ED to ICU settings; the rates of compliance with these sepsis bundles were 52% at 6 h and 30% at 24 h (for mortality: $p = 0.045$; RR, 0.7; OR, 0.49; RRR, 30%; ARR, 17.6%; NNT, 6)
Friedrich-Schiller (SOP) ¹¹⁰	60	30 (53) [0.36–0.70]	30 (27) [0.14–0.45]	Kortgen et al ¹¹⁰ examined outcomes in patients before and after implementing an SOP for patients with severe sepsis (for mortality: $p < 0.05$; RR, 0.51; OR, 0.33; RRR, 49%; ARR, 26.0%; NNT, 4)
Redding Medical Center (shock team) ¹⁰⁷	85	36 (50) [0.35–0.66]	49 (33) [0.21–0.47]	Sebat et al ¹⁰⁷ compared preimplementation and postimplementation results in a community hospital shock program; 1 yr after implementation, a significant reduction was seen in mortality, time until patients received central line placement, 2-L infusion of fluids, and antibiotic administration (for sepsis patients in particular: $p = 0.05$; RR, 0.65; OR, 0.48; RRR, 34.7%; ARR, 17.4%; NNT, 6)
Beth Israel Deaconess (sepsis team) ⁸³	167	51 (29.3) [0.19–0.43]	116 (20.3) [0.14–0.29]	Shapiro et al ⁸³ implemented a multidisciplinary sepsis team, utilizing an SOP procedure for sepsis; a statistically significant improvement in appropriate empiric antimicrobial coverage and tighter glycemic control was found; there was a nonstatistical trend toward decreased mortality ($p = 0.3$; RR, 0.7; OR, 0.62; RRR, 31%; ARR, 9.0%; NNT, 11)
University of Medicine and Dentistry of New Jersey-Camden (EGDT) ⁸²	38	16 (43.8) [0.17–0.6]	22 (18.2) [0.73–0.39]	Trzeciak et al ⁸² implemented a collaborative ED and ICU quality improvement initiative utilizing EGDT; they found that 91% of patients with severe sepsis achieved the EGDT hemodynamic end points of MAP > 65 mm Hg and ScvO ₂ > 70% in < 6 h; nonstatistical decrease in mortality ($p = 0.09$; RR, 0.51; OR, 0.4; RRR, 48.9%; ARR, 17.4%; NNT, 6)
University of Pennsylvania (EGDT) ¹¹¹	38	22 (55) [0.35–0.74]	16 (25) [0.10–0.50]	Gaieski et al ¹¹¹ compared historical standard care for septic patients admitted to the ED who qualified and received EGDT, and evaluated 28-d and 60-d mortality ($p = 0.1$; RR, 0.46; OR, 0.27; RRR, 54.6%; ARR, 30.0%; NNT, 3)
Hahnemann University (SSC/IHI) ¹¹²	54	20 (47) [0.27–0.68]	34 (31) [0.18–0.48]	Vereceles et al ¹¹² examined a hospital-wide program similar to that of Sebat et al ¹⁰⁷ ; there were statistically significant decreases in time to antibiotic administration, CVP measurement, and attainment of MAP and ScvO ₂ goals (for mortality: p value, not reported; RR, 0.66; OR, 0.5; RRR, 34.3%; ARR, 16.1%; NNT, 6)
Good Samaritan (shock team) ¹¹³	131	68 (43) [0.39–0.63]	63 (21) [0.18–0.39]	Armstrong et al ¹¹³ utilized a rapid-response team in a community hospital; significant reductions in time until administration of IV fluids, ICU admission, and intensivist arrival; APACHE II scores were 21.9 and 23.0, respectively, for preimplementation and postimplementation (for mortality: $p < 0.03$; RR, 0.53; OR, 0.35; RRR, 47.1%; ARR, 24%; NNT, 4)
Barnes Jewish Hospital (EGDT) ¹¹⁴	120	60 (48.3) [0.36–0.61]	60 (30) [0.20–0.43]	Micek et al ¹¹⁴ found a significant mortality benefit when all components of this protocol including education, standing orders, and equipment were available; there was a decreased use of vasopressor and steroids ($p = 0.04$; RR, 0.63; OR, 0.46; RRR, 37.8%; ARR, 18.2%; NNT, 6)
Hoag Hospital ¹¹⁵	78	12 (32.5) [0.13–0.60]	66 (21.7) [0.13–0.33]	Rogove ¹¹⁵ conducted a preimplementation and postimplementation study, and found decreased rate of critical care admission (12.3–10.8%; $p = 0.403$), a decreased median critical care LOS (5.4–3.7 d), and decreased critical care mortality reduction (19.2–12.0%; $p = 0.132$) (for overall mortality: $p = 0.060$; RR, 0.67; OR, 0.57; RRR, 33.3%; ARR, 10.8%; NNT, 9)
St. Paul's Hospital, Vancouver ¹¹⁶	96	51 (46.7) [0.34–0.60]	45 (23.2) [0.13–0.37]	Stenstrom et al ¹¹⁶ studied 50 patients admitted to the ICU from the ED; mean APACHE II score was 24; there was no significant difference in time to ICU transfer (for mortality: $p < 0.018$; RR, 0.49; OR, 0.34; RRR, 50.4%; ARR, 23.5%; NNT, 4)
Summary of all above centers†	1,298	671 (44.8) ± 7.8 [0.41–0.49]	627 (24.5) ± 5.5 [0.21–0.28]	For all centers reporting mortality data: RR, 0.54; OR, 0.39; RRR, 45%; ARR, 20.3%; NNT, 5
Henry Ford Hospital (EGDT) ¹²	263	130 (46.5) [0.36–0.53]	133 (30.0) [0.22–0.38]	Survivors in standard-care group had a significantly longer LOS (18.4 d) those in EGDT group (14.6 d) (in-hospital mortality: $p < 0.01$; RR, 0.65; OR, 0.51; RRR, 34.1%; ARR, 15.1%; NNT, 7)

*RR = relative risk; OR = odds ratio; RRR = relative risk reduction; ARR = absolute risk reduction; NNT = number needed to treat; CI = confidence interval; LOS = length of stay; SOP = standard operating procedure; IHI = Institute for Health Improvement.
 †Values are given as (total No. of patients) mean ± SD [95% CI].

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