Early goal-directed therapy in severe sepsis and septic shock: a contemporary review of the literature

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Purpose of review

Aggressive approaches to acute diseases such as acute myocardial infarction, trauma, and stroke have improved outcomes. Early goal-directed therapy for severe sepsis and septic shock represents a similar approach. An analysis of the literature assessing external validity and generalizability of this intervention is lacking.

Recent findings

Eleven peer-reviewed publications (1569 patients) and 28 abstracts (4429 patients) after the original early goal-directed therapy study were identified from academic, community and international settings. These publications total 5998 patients (3042 before and 2956 after early goal-directed therapy). The mean age, sex, APACHE II scores and mortality were similar across all studies. The mean relative and absolute risk reduction was $0.46 \pm 26\%$ and $20.3 \pm 12.7\%$, respectively. These findings are superior to the original early goal-directed therapy trial which showed figures of 34% and 16%, respectively. A consistent and similar decrease in healthcare resource consumption was also found.

Summary

Early goal-directed therapy modulates systemic inflammation and results in significant reductions in morbidity, mortality, and healthcare resource consumption. Early goal-directed therapy has been externally validated and is generalizable across multiple healthcare settings. Because of these robust findings, further emphasis should be placed on overcoming logistical, institutional, and professional barriers to implementation which can save the life of one of every six patients presenting with severe sepsis and septic shock.

Keywords

bundles, early goal-directed therapy, hemodynamic optimization, protocols, resuscitation, sepsis, septic shock, severe sepsis

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Introduction

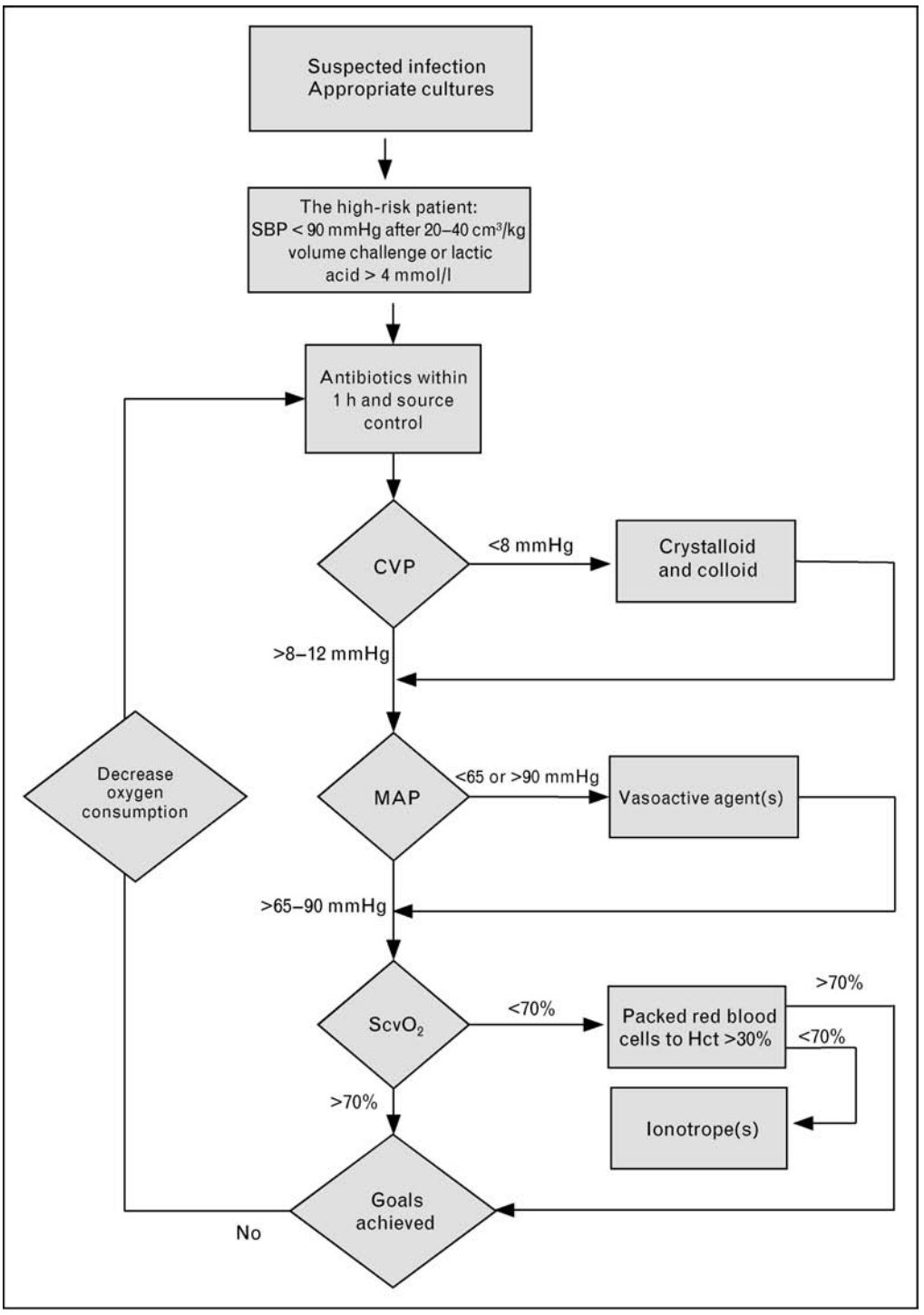
Improvements in survival for acute myocardial infarction, trauma, and stroke have been realized through early identification and implementation of time-sensitive therapies at the most proximal stage of disease presentation. Similar to these diseases, the emergency department (ED) is the portal of entry for over 600 000 patients with sepsis per year in the US. In spite of waiting times averaging 5 h and increasing for sepsis patients in the ED, a similar approach was lacking for early sepsis management [1]. In response, early goal-directed therapy (EGDT) was conceived as a multifaceted continuous quality improvement initiative (CQI) which included assessment of the hospital's preexisting sepsis incidence and mortality rate; methods for early identification of high-risk patients; mobilization of resources for intervention; aggressive reversal of early hemodynamic abnormalities using available best practice; assessment of compliance; dedicated education of healthcare providers; quantification of healthcare resource consumption; and assessment of outcomes.

Early goal-directed therapy: physiological and pathogenic rationale for hemodynamic optimization

This best practice CQI was tested in a randomized, single center clinical trial comparing EGDT with standard therapy for patients with severe sepsis with evidence of tissue hypoperfusion (lactate > 4 mmol/l) or septic shock (systolic blood pressure < 90 mmHg after a volume challenge) [2–6]. The protocol resuscitation components of EGDT were largely derived from the practice parameters for the hemodynamic support of sepsis recommended by the American College of Critical Care Medicine in 1999 [7]. The EGDT protocol used central venous pressure (CVP) measurements instead of pulmonary capillary wedge pressure to address preload (Fig. 1).

Although patients treated with EGDT received a greater amount of fluid over the first 6 h than patients treated with standard therapy, these numbers equalized by 72 h as standard therapy patients received a larger volume

Figure 1 Algorithm for early management of the infected patient



CVP, central venous pressure; Hct, hematocrit; MAP, mean arterial pressure; SBP, systolic blood pressure; $ScvO_2$, surrogate central venous oxygen saturation.

between 6 and 72 h than did EGDT patients. After optimizing preload or CVP, EGDT resulted in a 13.8% reduction in vasopressor use during the first 6 h and a 14.5% reduction during the first 72 h when compared with standard care. This has outcome implications, as Levy *et al.* [8] noted, that in patients with severe sepsis and septic shock, the delayed need for vasopressor therapy has the strongest association with increased mortality when compared with any other organ failure beyond the first 24 h. An additional benefit of this reduction in

vasopressor use is the decrease in the number of patients who qualify for corticosteroid therapy, the benefit of which remains controversial [9].

After correcting CVP and mean arterial pressure (MAP), the EGDT protocol addresses the resolution of global tissue hypoxia. This is treated by reversing the imbalance between oxygen delivery and oxygen consumption, as measured by the surrogate central venous oxygen saturation ($ScvO_2$). The combination of anemia, global tissue hypoxia and the accompanying comorbidities (cardiovascular disease) provides the physiologic rationale for transfusion of red blood cells (RBCs) during the delivery-dependent (low-$ScvO_2$ and increased lactate) phase of the resuscitation of patients with severe sepsis and septic shock. Furthermore, the larger volume resuscitation during the first 6 h contributes to a 30% reduction in hematocrit in the EGDT group compared with the standard care group. After 72 h, the total amount of transfused red cell volume was only 102 ml or less than half a unit of red cells greater in the EGDT group than the standard therapy group. While transfusion therapy has received increasing scrutiny in critical illness, there are finding that suggest that the sublingual microcirculation is globally unaltered by RBC transfusion in septic patients and can improve in patients with altered capillary perfusion at baseline [10].

Vasodilator therapy was used in 9% of EGDT patients who met protocol criteria. All of these patients had a previous history of hypertension and congestive heart failure and their median baseline $ScvO_2$ was 46%. Although the salutary effects of nitroglycerin in sepsis remain to be proven, it is becoming increasingly evident that disordered microcirculatory flow is associated with systemic inflammation, acute organ dysfunction, and increased mortality [11].

In the EGDT trial, dobutamine was used to increase inotropy, optimize contractility and aid oxygen delivery in patients who remained in a hypodynamic, delivery-dependent phase, as identified by a low $ScvO_2$ after restoration of adequate intravascular volume (correction of CVP), perfusion (MAP), and oxygen-carrying capacity (by correcting anemia until the hematocrit is greater than 30%). The average dobutamine dose needed to achieve a $ScvO_2$ of at least 70% was 10.3 μg/kg/min; almost 15% of patients in the EGDT group required dobutamine. Dobutamine may also exert salutary effects on the microcirculation, independent of its systemic effects [12].

The greater resolution of occult shock by EGDT compared with standard care also has salutary consequences. A 100% reduction in sudden cardiopulmonary complications in the EGDT group during the first 72 h was associated with a decreased need for cardiopulmonary support, including mechanical ventilation and pulmonary artery catheterization. Consistent with these findings, Estenssoro *et al.* [13] found that the presence of shock on ICU admission day was the greatest prognostic indicator, even adjusting for severity of illness and hypoxemia for the delayed need for prolonged mechanical ventilation.

There is a pathologic link between the clinical presence of global tissue hypoxia, the generation of inflammatory mediators, and the mitochondrial impairment of oxygen utilization seen in septic ICU patients [14–16]. EGDT results in a statistically significant modulation of pro, anti-inflammatory, apoptotic and coagulation biomarkers in patients treated with EGDT versus standard therapy [17••]. This biomarker activity is significantly related to organ dysfunction [18–20]. While some wonder which components of EGDT made the difference, EGDT is simply a sequence of logical physiologic steps of a consensus-derived resuscitation. One isolated variable does not dictate or characterize the protocol as is the case in the treatment of many other acute diseases.

The introduction of sepsis bundles

Recent landmark studies have led to a new era in the management of patients with severe sepsis and septic shock, resulting in the development of an international collaborative called the Surviving Sepsis Campaign (SSC). This organization has condensed management guidelines for severe sepsis into two bundles: an acute 'resuscitation bundle' and an ongoing 'management bundle' [21]. The sepsis resuscitation bundle is to be completed within the first 6 h while the management bundle is to be completed within the first 24 h of patient care. EGDT is only one of the components of these care bundles, but comprises one of the early steps in the resuscitation bundle and represents one of the critical early actions in the management of critically ill sepsis patients.

Since the creation of the SSC guidelines, a number of investigators at a variety of institutions, representing primary care, hospital medicine, critical care, and emergency medicine, have collected historic and prospective clinical data to examine survival benefits of SSC resuscitation and management bundle recommendations for the treatment of patients with severe sepsis and septic shock. To date, there has been no systematic review of the published literature to determine whether the outcome benefits of EGDT are being replicated at other institutions and whether the results are generalizable to a variety of hospital settings.

Contemporary analysis of the literature: methodology

The search engines used to examine the medical literature included Ovid, Pubmed, Athens, Medline, Google, Microsoft Network, Yahoo and Netscape. The search terms included bundles, early goal directed therapy, hemodynamic optimization, protocols, resuscitation, sepsis, severe sepsis, septic shock. Twelve peer-reviewed publications (including the original publication of EGDT) and 28 abstracts evaluating EGDT primarily or as part of a sepsis quality initiative were found since 2001. These investigations were comprised of the following: comparing retrospectively examined historical controls with patients who were prospectively examined after implementation; comparing a prospective collection of control patients before implementation during a defined period with patients receiving EGDT after a period of implementation; comparing patients who received the resuscitation bundle with those who did not complete the bundle; and comparing prospectively randomized controls with treatment patients.

Early goal-directed therapy: the outcome evidence

There was an international representation which included the US, Switzerland, Poland, Finland, Canada, Spain, the UK, Germany, Italy and Brazil. In the peer-reviewed publications, 748 patients were identified before and 821 patients after implementation (Table 1) [22–28,29••,30••,31,32••,33]. In the 28 published abstracts identified, there were 2294 patients identified before and 2135 patients after implementation (Table 2) [34–58]. When publications and abstracts were combined, 3042 patients were identified before and 2956 patients after implementation of sepsis bundles (Table 3). The Acute Physiology and Chronic Health Evaluation II (APACHE II) score, sex distribution, age, mortality before and after were consistently similar between publications, abstracts and the original publication (Table 3).

When peer-reviewed publications are compared, the relative risk reduction exceeds 0.25 (25%) and absolute risk reduction exceeds 9% in all studies (Figs 2 and 3). This shows effectiveness across a broad range of illness severity and mortality risks. When the original EGDT trial is compared with peer-reviewed publications only, abstracts only or a combination (publications and abstracts), the results are similar across all data comparisons (Table 3). The APACHE score is lower in the EGDT group because the calculation was made upon hospital arrival instead of at 24 h. The relative risk, odds ratio, relative risk reduction, absolute risk reduction, and number needed to treat were generally similar across publications, abstracts, and publication abstracts combined when compared with the original trial (Table 3).

Early goal-directed therapy: effects on healthcare resource consumption

A consistent finding was a significant reduction in healthcare resource consumption. This was realized through decreases in ICU length of stay, hospital length of stay, duration of mechanical ventilation, renal replacement therapy, and in some studies, vasopressor therapy, and pulmonary artery catheterization. At Henry Ford Hospital (HFH), a formal cost-effectiveness analysis found that EGDT can provide up to a 23.4% reduction in hospital costs related to severe sepsis and septic shock when compared with standard hospital sepsis management [59••]. The impact of EGDT was a $23.4 million reduction in the $100 million per year in sepsis-related costs at HFH.

EGDT is most cost-effective if patient volume exceeds 16 patients per year; cost savings are present regardless of whether the care is primarily provided by the ED, at various hospital locations by a rapid response team, or in the ICU. A mean reduction of 4 days per admission (32.6% reduction in hospital length of stay) for survivors and 13.9% reduction in pulmonary artery catheter use (both $P < 0.03$) was seen in the original EGDT study. Similar findings have been noted by other investigators [23,24]. Talmor *et al.* [23] showed that costs associated with treating a patient with EGDT were $33 337 ± 37 042 versus $29 683 ± 48 517 ($P = 0.595$) because of improved survival benefit. The increase in costs in the study cohort was largely driven by increased ICU costs associated with increased ICU length of stay; however, the cost per life saved by the protocol was $32 336, which compares very favorably with other commonly delivered acute care interventions [42]. Shorr *et al.* [59••] compared patients treated before the protocol with those cared for after the protocol was implemented. Even though there were more survivors following the protocol's adoption (70.0% versus 51.7%, $P = 0.040$), median total costs were significantly lower with use of the protocol ($16 103 versus 21 985, $P = 0.008$). The length of stay was also on average 5 days less among the postintervention population ($P = 0.023$). A Cox proportional hazard model indicated that the protocol was independently associated with less per-patient cost. Restricting the analysis to only survivors did not appreciably change our observations [18]. Barlotta *et al.* [60] performed a projected impact of EGDT over 2 years examining a clinical data repository of 1081 patients admitted from the ED. Cost reductions due to decreased hospital days and ICU days were noted for survivors. The total cost benefit favored EGDT and costs saving projected at $3.5 million per year for the institution. Becker

Table 1 Summary of peer-reviewed publications

Authors	Total	Pre	Post	Study protocol (EGDT)	Additional therapies or protocols	Primary endpoints (mortality)	NNT, *P*-value	Comments
Gao (2005) [22]	71	29	29	MAP > 65 Hgb 7–9	Glycemic control, low-dose steroids	In-hospital mortality RR = 0.50, OR = 0.29 RRR = 0.53, ARR = 26%	6, $P = 0.045$	No significant power for secondary endpoint
Sebat (2005) [23]	85	36	49	MAP > 70 $SvO_2 > 60$ Hgb > 9		In-hospital mortality RR = 0.73, OR = 0.49 RRR = 0.34, ARR = 17%	6, $P = 0.05$	Significant secondary endpoints were as follows: increase in pulmonary artery catheterization ($P = 0.02$). No statistical difference compared with control. Time to antibiotic, vasopressor therapy, ICU LOS
Kortgen (2006) [24]	60	30	30	CVP 8–12 MAP 65–90 $ScVO_2 > 70$ Hct > 24 Inotropes	Glycemic control (glucose 80–110 mg/dl), protective lung strategies, low-dose steroids, antibiotics given by 6 h, r-APC	28-day mortality RR = 0.63, OR 0.42 RRR = 0.49, ARR = 26%	4, $P < 0.05$	Significant secondary endpoints were as follows: decrease in vasopressor dosage ($P < 0.05$), increased in steroid administration ($P < 0.05$), increase in r-APC administration ($P < 0.05$). No statistical difference compared with control: mechanical ventilation days, ICU LOS, blood transfusion, glucose control, time to antibiotic
Shapiro (2006) [25]	167	51	116	CVP > 8 MAP > 65 $ScVO_2 > 70$ Hct > 30	Glycemic control (glucose 80–110 mg/dl), protective lung strategies, low-dose steroids, r-APC, empiric antibiotics	In-hospital mortality RR = 0.46, OR = 0.11 RRR = 0.31, ARR = 9%	11, $P = 0.3$	Significant secondary endpoints were as follows: increase in vasopressor therapy ($P < 0.01$), earlier time to empiric antibiotic therapy ($P < 0.01$). No statistical difference compared with control: mechanical ventilation days, blood transfusion, steroid therapy, r-APC
Trzeciak (2006) [26]	38	16	22	CVP 8–12 MAP > 65 ScVO2 > 70 Hct > 30		In-hospital mortality RR = 0.43, OR = 0.17 RRR = 0.58, ARR = 26%	4, $P = 0.09$	Significant secondary endpoints were as follows: increase in pulmonary artery catheterization ($P = 0.01$). No statistical difference compared with control: mechanical ventilation days, ICU LOS, vasopressor therapy, blood transfusion, time to antibiotic, steroid therapy, r-APC
Micek (2006) [27]	120	60	60	CVP 8–15 MAP > 65 $ScVO_2 > 70$ Hct > 30	Low-dose steroids, r-APC, empiric antibiotics	28-day mortality RR = 0.62, OR = 0.40 RRR = 0.38,ARR = 18%	6, $P = 0.04$	Significant secondary endpoints were as follows: decrease in vasopressor therapy ($P < 0.01$), decrease in steroid administration ($P < 0.01$), decreased in-hospital LOS ($P = 0.04$), earlier time to empiric antibiotic therapy ($P < 0.01$), increased blood transfusion ($P = 0.03$). No statistical difference compared with control: ICU LOS, mechanical ventilation days, r-APC
Shu-Min Lin (2006) [28]	224	116	108	CVP 8–12 MAP > 65 Urine output (>0.5 ml/hr)	Low-dose steroids, empirical antibiotics	In-hospital mortality RR = 0.43, OR = 0.50 RRR = 0.26, ARR = 17%	6, $P = 0.01$	Significant secondary endpoints were as follows: decrease in mechanical ventilation days ($P < 0.01$), decrease in ICU LOS ($P < 0.01$), decreased time to reversal of shock ($P < 0.01$), decrease in empiric antibiotic duration ($P = 0.03$), decrease complications of sepsis-associated CNS failure ($P < 0.01$), decrease in sepsis-associated renal failure ($P < 0.01$). No statistical difference compared with control: in-hospital LOS, blood transfusion, vasopressor therapy, steroid therapy. Compliance was 98% to the protocol

Nguyen (2007) [29••]	330	253	77	MAP > 65 CVP > 8 $ScVO_2$ > 70% Hct > 30%	Low-dose steroids, empiric antibiotics, glycemic control, r-APC	In-hospital mortality RR = 0.25, OR = 0.17 RRR = 0.47, ARR = 19%	5, $P < 0.01$	Significant secondary endpoints were as follows: increase in steroid administration ($P = 0.01$), earlier time to empiric antibiotics ($P = 0.04$), increase r-APC administration ($P = 0.01$). No statistical difference compared with control: mechanical ventilation days, ICU LOS, ED LOS, vasopressor therapy, blood transfusion
Jones (2007) [30••]	155	79	77	CVP > 8 MAP > 65 ScVO2 > 70 Hct > 30	Empiric antibiotics	In-hospital mortality RR = 0.26, OR = 0.08 RRR = 0.33, ARR = 9%	11, $P = 0.13$	Significant secondary endpoints were as follows: earlier time to empiric antibiotic therapy ($P = 0.02$), increase in vasopressor therapy ($P < 0.01$), increase in steroid administration ($P < 0.01$), increase in mechanical ventilation frequency ($P < 0.01$), increase in ICU LOS ($P < 0.05$). No statistical difference compared with control: mechanical ventilation days, blood transfusion, r-APC
Qu (2006) [31]	34	19	15	CVP 8–12 MAP > 65 $ScVO_2$ > 70 Hct > 30		In-hospital mortality RR = 0.25, OR = 0.11 RRR = 0.68, RR = 28.9%	3.5, $P < 0.05$	Qu *et al.* examined 34 patients in an ICU-based program. The incidence of repeated resuscitation was 73.7% in the late resuscitation group and 20.0% in the early resuscitation group ($P < 0.01$). The incidence of adrenal dysfunction, coagulopathy, and MODS was significantly greater in the late resuscitation group compared with the early resuscitation group ($P < 0.05$). Seven days after resuscitation, renal, pulmonary and cardiovascular failure were significantly greater in the late resuscitation group
Sebat (2007) [32••]	254	36	218	MAP > 70 SvO_2 > 60 Hgb > 9	Glycemic control, low-dose steroids, Xigris	28-day mortality RR = 0.6, OR = 0.11 RRR = 0.8, ARR = 40%	3, $P < 0.001$	Significant secondary endpoints were as follows: earlier time to empiric antibiotic therapy ($P < 0.05$). No statistical difference compared with control: ICU LOS
Rivers (2001) [33]	263	133	130	CVP 8–12 MAP > 65 $ScVO_2$ > 70 Hct > 30		In-hospital mortality RR = 0.65, OR = 0.51 RRR = 0.34, ARR = 15%	7, $P < 0.01$	Significant secondary endpoints were as follows: 28-day mortality decreased ($P < 0.01$), decrease in mechanical ventilation ($P = 0.02$), decrease in vasopressor therapy ($P = 0.02$), decrease in pulmonary artery catheterization ($P < 0.01$), increase in blood transfusion ($P < 0.01$). No statistical difference compared with control: total mechanical ventilation days, inotropic therapy, hospital LOS

EGDT, early goal-directed therapy; NNT, number needed to treat; MAP, mean arterial pressure; Hgb, hemoglobin; RR, relative risk; OR, odds ratio; RRR, relative risk reduction; ARR, absolute risk reduction; $ScvO_2$, surrogate central venous oxygen saturation; LOS, length of stay; CVP, central venous pressure; Hct, hematocrit; r-APC, recombinant activated protein C; CNS, central nervous system; MODS, multi-organ dysfunction syndrome.

Table 2 Summary of published abstracts

Total patients	Preimplementation mortality	Postimplementation mortality	Author and comments
45	73%	47%	Michaud *et al.* [34] in a retrospective cohort study examined a conservative fluid (CF) group (those receiving <60 ml/kg IVF in the first 6 h) and an aggressive fluid (AF) group (those receiving 60 ml/kg in the first 6 h). There were trends toward improved survival, ICU LOS (AF = 9 ± 8 versus CF = 16 ± 18 days, $P = 0.20$), hospital LOS (AF = 26 ± 23 versus CF = 33 ± 30 days, $P = 0.44$), and ventilator days (AF=10 ± 16 versus CF=22 ± 31, $P = 0.13$) all showed trends favoring the AF group.
54	47%	31%	Verceles *et al.* [35] examined a hospital-wide sepsis program. There were statistically significant decreases in time to antibiotic administration, CVP measurement, and attainment of MAP and $ScvO_2$.
131	43%	21%	Armstrong and Salfen [36] utilized a rapid response team in a community hospital. Significant reductions in time to intravenous fluid, ICU admission, and intensivist arrival.
188	32.5%	21.7%	Rogove and Pyle [37] conducted a pre and postimplementation study and found a decreased critical care admission, from 12.3% to 10.8% ($P = 0.403$), median critical care length of stay from 5.4 to 3.7 days and a significant ICU mortality reduction from 19.2% to 12.0% in addition to the hospital mortality shown in the table.
94	46.7%	23.2%	Stenstrom *et al.* [38] instituted EGDT in a pre and postimplementation strategy. There was no significant difference in time to ICU transfer.
38	55%	25%	Gaieski *et al.* [39] compared historic standard care for septic patients enrolled in the ED who qualified and received EGDT and evaluated 28 and 60-day mortality.
115	45.9%	23.1%	Fried *et al.* [40] prospectively examined septic shock patients receiving a protocol over 7 months and compared them to a historical control group of septic shock patients.
194	34%	40.3%	Mullon *et al.* [41] examined adherence to the 6 h bundle. A disease-specific order set for severe sepsis and septic shock improves adherence to some but not all evidence-based practices. No mortality benefit was noted due to poor rate of compliance.
120	50%	38%	Kubler *et al.* [42] found the rate of compliance with the 6 h resuscitation bundle was 11% and the 24 h management bundle was 36%. The mortality rate in patients compliant with the resuscitation bundle was 38% and noncompliant 50%. Mortality in patients compliant and noncompliant with the management bundle was 37% and 55%.
67	39%	0%	Nobre *et al.* [43] retrospectively analyzed 67 patients in severe sepsis and septic shock. 73% came from the ED, 18% from other wards, and 9% were in the ICU. Mortality was 0% among patients resuscitated (<6 h) according to the bundles (0/18) versus 39% (19/49) in patients in whom one or more of the goals were not achieved ($P = 0.004$).
314	40.75%	18.87%	Ikeda *et al.* [44] prospectively studied 266 consecutive patients over a 2-year period. The historical control cohort was 48 consecutive ICU patients admitted over 6 months. The ICU mortality was 40.07% in the control period, compared with 18.86% in the study period ($P < 0.001$).
135	58%	22%	Castellanos-Ortega *et al.* [45] examined consecutive episodes of septic shock with hospital mortality of 44.4%. The rate of compliance with the resuscitation bundle was 38%. There were significant differences in mortality between compliant and noncompliant groups ($P = 0.001$).
82	43.18%	23.6%	Hayatdavoudi *et al.* [46] examined 44 patients in the preimplementation phase and 38 patients consecutively afterwards. The protocol implemented the 6 and 24 h bundle guidelines ($P = 0.0662$). There was also a significant improvement in renal function in patient who received EGDT.
259	23%	16.7%	Kinsella *et al.* [47] performed a retrospective chart review over three periods: 2003 (prebundle, $n = 82$), 2004 (ICU phase, $n = 74$), and (C-4 phase, $n = 103$). In the prebundle phase, compliance with all resuscitation bundle measures and all management measures was 0% and mortality 23%. During the ICU phase, resuscitation compliance remained at 0%; compliance with the management bundle was approximately 45% and mortality was unchanged at 23%. In the C-4 phase, compliance with the resuscitation bundle was 29%, the management bundle was 59%, and mortality was 16.7%.
20	50%	16.7%	Gaieski *et al.* [48] examined 12 patients treated with EGDT and 8 patients received conventional therapy. In-house mortality in the EGDT group was 16.7% (2/12) while mortality in the conventional therapy group was 50% (4/8). All patients treated with EGDT survived to 28 days.

(*continued overleaf*)

Table 2 (*continued*)

Total patients	Preimplementation mortality	Postimplementation mortality	Author and comments
79	64.3%	36.1%	Antro *et al.* [49] examined 51 patients, global mortality was 33.3% at discharge and 40.4% at 60 days. Adherence to all 6 h elements was in 27% of patients, with a hospital mortality of 21.4% versus 37.8% in the noncompliant group (*P* NS). The mortality at discharge in protocol-septic shock patients was 36.1% versus 64.3% in the control group (28 patients) with a statistically significant reduction of 28.2% ($P < 0.05$).
509	26%	13%	The Denver Collaborative [50] examined 509 patients from 10 hospitals (70% ED admissions) admitted over 16 months. Overall bundle adherence was low (5% for all SSC elements) and did not change significantly over time. Mortality was decreased by 65% for the 8.6% of patients treated with all applicable resuscitation bundle and 24 h or MB elements (9.1% versus 26% for partial bundle adherence. Mortality was halved for the 15% of patients treated with all resuscitation bundle elements (13% versus 26% for partial bundle adherence; $P < 0.05$; 80% power). Complete MB care (117 patients; 23%) was also associated with a trend to reduced mortality (18% versus 26% for partial bundle adherence; $P = 0.2$).
196	34.5	40.3	Mullon *et al.* [41] examined 72 patients prior and 124 after order set introduction. Age was higher (74 versus 66 years, $P < 0.01$) after order set implementation. The order set was utilized in 91 (73%) of eligible patients. There were no statistically significant differences in measurement ($P = 0.42$).
63	44%	29%	Varpula [51] examined 63 patients. In a multivariate analysis including all separate targets, delay for ICU admission and APACHE II score, the APACHE II value and measurement of lactate were independent predictors of mortality ($P = 0.001$ and 0.02).
120	50%	38%	Kubler *et al.* [42] examined the 6 h resuscitation and 24 h management bundles in the first 120 cases of bundle implementation. The rate of compliance with the 6 h resuscitation bundle was 11% and the 24 h management bundle, was 36%.
20	50%	16.7%	Gaeski *et al.* [48] examined patients who would have been excluded from the original trial. Twelve patients were treated with EGDT; 8 patients with conventional therapy. In-house mortality in the EGDT group was 16.7% (2/12) while mortality in the conventional therapy group was 50% (4/8). No patients in either group had a do not resuscitate order at the time of ED presentation.
176	42%	26%	Akinnusi *et al.* [52] prospectively examined 87 consecutive elderly patients managed according to a sepsis resuscitation and maintenance bundle. A high prevalence of adrenal insufficiency (86%) was identified in the study population. There were no significant differences between the treatment and control groups in the surviving patients with respect to the duration of mechanical ventilation, or ICU length of stay. Implementation of the sepsis bundle protocol was independently associated with 28-day improved survival.
96	73%	45%	Tanios *et al.* [53] examined 96 patients with severe sepsis (34 controls and 62 SSC group). EGDT was achieved in 86% of SCC groups versus 64% of controls ($P < 0.03$). Implementing SSC guidelines was an independent predictor for survival but none of the interventions individually reached statistical significance.
629	49.5%	41.4	Meredith and Simpson [54] examined before and after implementation of sepsis guidelines. Sepsis was diagnosed in 398 with 27.4% mortality, severe sepsis in 171 with 49.1% mortality, septic shock in 110 with 50.0% mortality. After implementation sepsis mortality was reduced to 25.2%, severe sepsis mortality reduced to 40.6% and septic shock mortality reduced to 42.8%.
892	26%	28.7%	Becker [55] performed a before and after retrospective analysis to determine if implementation of a sepsis bundle and continuous quality initiative can reduce patient mortality, length of stay or cost of care for septic patients. There were 490 patients in the first 6 months and 402 in the second 6 months admitted to the ICU from various locations in the hospital with a diagnosis of sepsis. The initial bundle element compliance in the ED was 0%. The hospital mortality rate was essentially unchanged (26% for the first 6 months compared with 28% for the second 6 months compared with 28.7%).

(*continued overleaf*)

Table 2 (*continued*)

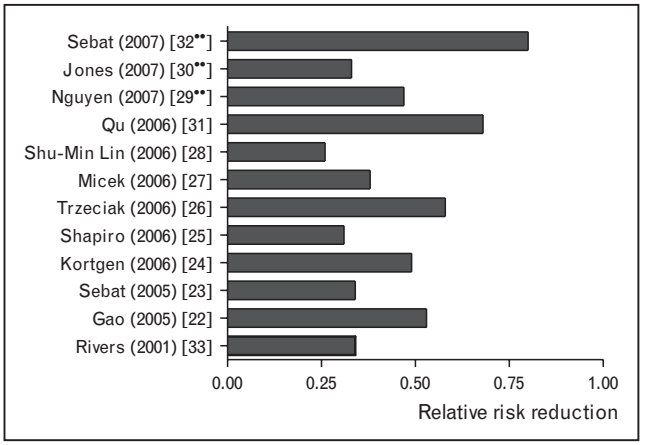
Total patients	Preimplementation mortality	Postimplementation mortality	Author and comments
193	n/a	n/a	McGrath *et al.* [56] evaluated time to antibiotics and patient outcomes before and after implementation of an EGDT protocol for sepsis. There was poor compliance to bundle requirements. Performance to resuscitation bundle elements was less than 30% for before and after except for antibiotics, 47% before versus 45% within 2 h of triage ($P < 0.88$). Implementation of an EGDT protocol through education, cards, and web-based ordering did not reduce mortality in septic patients admitted to ICU. Further study is needed to improve adherence to this protocol. No after mortality was given.
67	50%	18.5%	Victorino *et al.* [57] performed a prospective cohort study of consecutive patients with severe sepsis ($n = 67$) admitted to medical–surgical ICU.
38	43.2%	15.1%	Venkatram *et al.* [58] examined the connection between compliance and outcomes with the use of EGDT in a university-affiliated inner city hospital. Among the 38 patients examined, in 33 (87%) patients, all goals of EGDT were achieved within 6 h of onset of severe sepsis or shock. Among the remaining 5(13%) patients, mean duration to achieve all goals of EGDT was 9 h. Observed hospital mortality when the components of EGDT were met within 6 h was 15.15% against a predicted mortality of 43.2%. Reductions in mortality appear to be sustained (observed mortality of 20% compared with a predicted mortality of 41.6%).

IVF, intravenous fluid; LOS, length of stay; CVP, central venous pressure; MAP, mean arterial pressure; $ScVO_2$, surrogate central venous oxygen saturation; ED, emergency department; EGDT, early goal-directed therapy; RB, resuscitation bundle; SSC, surviving sepsis campaign, MB, maintenance bundle.

et al. [55] performed a retrospective analysis to determine if implementation of a sepsis bundle can effectively reduce patient mortality, length of stay or cost of care for septic patients. Length of stay decreased from 18.4 to 15.7 days while cost decreased from an average of $9346.60 per patient. This would result in average cost savings of $4 million every 6 months.

Joffe and Lidsky [61] showed that poor patient response to EGDT may lead to earlier end of life discussions such that nonsurvivors of a septic episode will undergo withdrawal of therapy sooner resulting in cost savings. In this manner EGDT was associated with a significant decrease in duration of mechanical ventilation (2.8 days, $P = 0.02$), strong trends toward reduction in ICU and hospital resources, and cost savings.

Figure 2 A comparison of relative risk reduction of peer-reviewed publications



Implementation strategies for early goal-directed therapy and continuous quality improvement

Due to the salutary findings of EGDT and the logistical issues regarding its implementation, several approaches to implementing an EGDT protocol have been utilized. To achieve a consistent level of quality at various locations within the hospital, multiple models may be required. The first model of sepsis management is ED based, with the ED team performing the initial algorithmic resuscitation. A second, increasingly popular model utilizes a multidisciplinary rapid response team, efficiently mobilizing resources to resuscitate an unstable sepsis patient irrespective of location [62]. A third model is ICU based, emphasizing rapid transfer of critically ill sepsis patients from their initial location (ED, medical or surgical floor, operating room) to the ICU, where the ICU team initiates EGDT [23]. Each of these models can be tailored to the unique needs of individual institutions, but each has the potential to be implemented in a clinical and cost-effective manner.

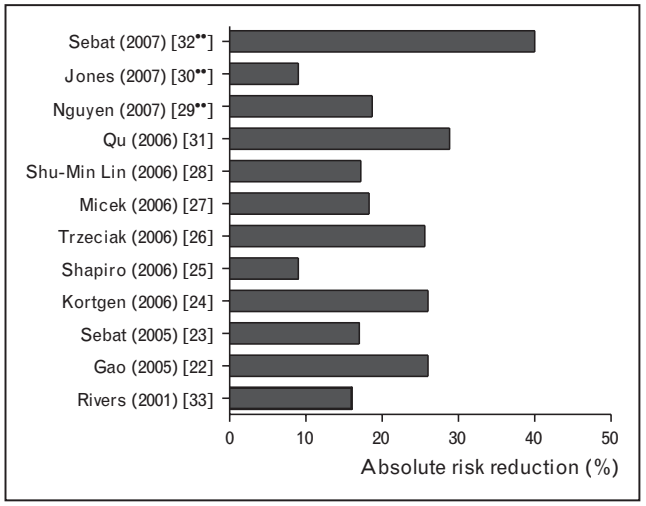
Nguyen *et al.* [29••] showed that a continuous quality initiative is important to realize the outcome benefit. Most recently, at HFH, a 2-year clinical quality indicator (CQI) of the resuscitation bundle revealed a baseline compliance of 28%. Upon implementation of this CQI, a relative mortality reduction of 28% was noted with improving resuscitation bundle compliance to 60%. The

Table 3 Comparison of studies

	APACHE II score	Sex, % male	Age	Patients before	Mortality before	Patients after	Mortality after	RR	OR	RRR	ARR	NNT
Publications												
Mean	25.9	53.8	65.4		45.4		23.96	0.56	0.40	0.47	21.42	5.66
SD	8.84	4.81	3.04		10.7		9.2	0.07	0.12	0.19	9.9	0.95
Maximum	35.0	63.5	72.0		67.2		50.0	1.43	2.05	0.8	40.0	11.11
Minimum	20.76	41.7	57.6		27.0		10.0	0.25	0.08	0.26	9.0	2.5
n				748		821						
Abstracts												
Mean	24.3	58.96	63.4		44.5		25.1	0.87	0.77	0.45	19.72	7.25
SD	7.8	5.31	4.10		12.5		10.2	0.12	0.19	0.23	12.66	6.02
Maximum	28.0	66.0	74.5		73.0		45.0	5.0	6.28	0.9	36.1	37.04
Minimum	21.44	48.0	50.0		18.0		0.0	0.08	0.05	0.09	0.40	2.77
n				2294		2135						
Publications and abstracts												
Mean	25.5	55.4	64.5		44.8		24.7	0.77	0.65	0.46	20.27	6.72
SD	8.7	4.30	4.3		10.3		12.98	0.24	0.28	0.26	12.66	6.02
Maximum	35.0	66.0	74.5		73.0		50.0	5.0	6.28	0.9	40.0	37.04
Minimum	20.8	41.7	50.0		18.0		0.0	0.08	0.05	0.09	0.4	2.5
n				3042		2956						
EGDT, 2001												
Mean	21.4	50.4	64.4	130	46.5	133	30.5	0.61	0.38	0.34	16.0	6.25
SD	6.9		17.1									
n				130		133						

APACHE II, Acute Physiology and Chronic Health Evaluation II; RR, relative risk; OR, odds ratio; RRR, relative risk reduction; ARR, absolute risk reduction; NNT, number needed to treat; EGDT, early goal-directed therapy.

Figure 3 A comparison of absolute risk reduction of peer-reviewed publications



$CVP/ScvO_2$ component of the bundle carried the greatest impact on survival than any other bundle element (lactate, blood culture, and antibiotics). These findings suggest that 100% compliance, while a laudable attainment, is not necessary for the realization of mortality benefit. There is a critical threshold for total protocol compliance, however. Of the publications (abstracts) that showed no survival benefit, the compliance to bundle elements was less than optimal [41,56,57]. Thus, the effectiveness of EGDT as with any intervention is significantly related to a critical compliance effort.

Limitations

This analysis of the literature represents both abstracts and peer-reviewed publications. The rationale for including abstracts is because some centers presented their data as quality initiatives and have no intention of publishing the results as scientific investigations. Many of these institutions have elected to establish sepsis improvement as a quality initiative and have presented their data to organizations such as the Institute for Health Improvement, Volunteer Hospital Association, Keystone Initiative, Leapfrog, and other quality improvement forums. Thus, the actual magnitude of these quality initiatives is under-represented in the literature. Many of these centers have taken the position that it would have been unethical to consider a control or wild type care as an intentional comparison group. To knowingly or prospectively provide or observe less than best practice to a vulnerable and high-risk patient population would be unethical as a scientific investigation.

The EGDT implementation programs in the published articles and abstracts identified are heterogeneous in some respects and the level of care in the preimplementation period varies from institution to institution. Due to the variability of data available, it is not possible to compare exact similarities and differences between patient populations. This variability, however, is also true when comparing published sepsis outcome trials [63]. These shortcomings do not deter from the obvious and robust changes seen in mortality between pre and post-implementation groups across the studies comprising over 6000 patients. A further limitation is that some of the studies initiated EGDT in isolation but others implemented it as part of a more inclusive sepsis treatment strategy. While these implementation programs may incorporate additional therapies, including renal replacement therapy, tight glucose control, recombinant activated protein C, low-dose corticosteroids for relative adrenal insufficiency, and protective lung strategies; multiple institutions have shown that EGDT carries the greatest mortality benefit compared with the other interventions [29••].

Conclusion

EGDT modulates inflammation and results in significant reductions in morbidity, mortality, and healthcare resource consumption. The findings of the original EGDT trial have been externally validated and have been consistently shown to be generalizable. Due to these robust findings, further emphasis should be placed on overcoming logistical, institutional, and professional barriers to the implementation of EGDT, which can save the life of one of every six patients presenting with severe sepsis and septic shock.

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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 World Literature section in this issue (pp. 248–249).

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