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Original Research Article

Comparative Effectiveness of Early Goal-Directed Therapy versus Standard Care in the Management of Septic Shock in Emergency Settings

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Abstract

Background: Septic shock remains a leading cause of mortality in critically ill patients. Early Goal-Directed Therapy (EGDT), a structured resuscitation protocol, was historically advocated, but its superiority over contemporary standard care is debated, especially in non-academic emergency department (ED) settings.

Methods: We conducted a pragmatic, multi-center, randomized controlled trial in 10 community hospital EDs. A total of 350 adult patients with septic shock were randomly assigned to either EGDT (n=175) or standard care (n=175). The EGDT group followed a 6-hour protocol targeting central venous pressure (CVP), mean arterial pressure (MAP), and central venous oxygen saturation ($ScvO_2$). The standard care group received resuscitation guided by the treating physician's judgment, adhering to current sepsis guidelines but without mandated invasive monitoring targets. The primary outcome was all-cause mortality at 28 days.

Results: Baseline characteristics were similar between the groups. There was no significant difference in the primary outcome of 28-day mortality: 24.6% (43 of 175 patients) in the EGDT group versus 21.7% (38 of 175 patients) in the standard care group (relative risk, 1.13; 95% CI, 0.77 to 1.66; p=0.48). Patients in the EGDT group received a significantly greater mean volume of intravenous fluids in the first 6 hours (4.8 ± 1.2 L vs. 4.1 ± 1.1 L; p<0.001) and had a higher incidence of central venous catheter placement (100% vs. 62.3%; p<0.001). The use of vasopressors (85.1% vs. 76.6%; p=0.04) and dobutamine (16.6% vs. 7.4%; p=0.009) was also higher in the EGDT group. There were no significant differences in secondary outcomes, including ICU length of stay (8.1 ± 4.2 days vs. 7.5 ± 3.9 days; p=0.19) or duration of mechanical ventilation.

Conclusion: In community emergency department settings, a strict protocol of Early Goal-Directed Therapy did not confer a survival advantage over contemporary standard care for patients with septic shock. However, EGDT was associated with greater use of invasive procedures and resuscitation therapies, indicating higher resource utilization without a discernible clinical benefit.

Keywords: Septic Shock, Early Goal-Directed Therapy, Standard Care, Emergency Medicine, Mortality, Critical Care.

Introduction

Sepsis, a life-threatening organ dysfunction caused by a dysregulated host response to infection, and its most severe form, septic shock, represent a major global health challenge [1]. Septic shock is associated with profound circulatory, cellular, and metabolic abnormalities, carrying an in-hospital mortality rate that can exceed 40% [2].

The initial hours of management, typically occurring in the emergency department (ED), are critical and have a profound impact on patient outcomes [3]. Consequently, significant research has focused on optimizing early resuscitation strategies. For over a decade, the cornerstone of early sepsis resuscitation was Early Goal-Directed Therapy (EGDT), a complex, protocolized algorithm introduced by Rivers et al. in a single-center trial in 2001 [4].

This landmark study demonstrated a dramatic 16% absolute reduction in mortality by using a 6-hour protocol to guide fluid, vasopressor, and inotrope administration to achieve specific physiological targets: a central venous pressure (CVP) of 8–12 mmHg, a mean arterial pressure (MAP) of ≥65 mmHg, and a central venous oxygen saturation ($ScvO_2$) of ≥70% [4]. Based on these compelling results, EGDT was widely adopted and

incorporated into international guidelines, including those of the Surviving Sepsis Campaign [5]. However, the universal applicability and superiority of EGDT have been questioned in recent years. Three large, multi-center, international randomized controlled trials—ProCESS in the United States, ARISE in Australia and New Zealand, and ProMISe in the United Kingdom—failed to replicate the mortality benefit of EGDT [6-8]. These trials demonstrated that patients treated with less invasive, protocol-based standard care or even usual care had outcomes similar to those treated with the strict EGDT protocol. This has led to a paradigm shift in sepsis management, with subsequent guidelines de-emphasizing the mandatory use of CVP and $ScvO_2$ monitoring in favor of a more flexible approach focusing on core principles: early recognition, prompt antibiotic administration, adequate fluid resuscitation, and vasopressor support [9, 10].

Despite this high-level evidence, a significant research gap persists. The ProCESS, ARISE, and ProMISe trials were predominantly conducted in large, well-resourced academic medical centers where "usual care" is often highly sophisticated and delivered by teams with extensive critical care expertise [11]. It remains uncertain whether these findings are generalizable to community hospital EDs, which manage a substantial portion of sepsis cases but may have different resource availability, staffing models, and practice patterns. In such settings, a structured protocol like EGDT could theoretically provide a valuable framework to standardize care and prevent therapeutic omissions. Conversely, it could also impose an unnecessary burden of invasive procedures and resource consumption without improving outcomes.

Therefore, the aim of this study was to conduct a pragmatic comparison of the effectiveness of a strict, protocol-driven EGDT approach against contemporary standard care on 28-day mortality in patients presenting with septic shock to a network of community hospital emergency departments. We hypothesized that there would be no significant difference in mortality between the two approaches.

Materials and Methods

Study Design and Setting: This was a pragmatic, multi-center, parallel-group, randomized controlled trial conducted across 10 community hospital EDs within a single regional health system between July 2022 and June 2024.

Study Population: Eligible participants were adults (≥18 years of age) presenting to the ED who met the Sepsis-3 criteria for septic shock. This was defined as a suspected or confirmed infection, a need for vasopressors to maintain a MAP ≥65 mmHg, and a serum lactate level >2 mmol/L after an initial intravenous fluid challenge of at least 20 mL/kg of crystalloid.

Key exclusion criteria included: age <18 years; pregnancy; an advance directive precluding aggressive resuscitation (e.g., Do-Not-Resuscitate order); a condition where the study interventions would be contraindicated or interfere with standard care (e.g., acute coronary syndrome, acute pulmonary edema, major trauma); or transfer from another acute care facility.

Randomization and Blinding: Patients were randomly assigned in a 1:1 ratio to either the EGDT group or the standard care group. Randomization was performed using a centralized, secure, web-based system with permuted blocks of varying sizes, stratified by study site. Due to the nature of the interventions, blinding of the treating clinicians was not feasible. However, the data analysts and the committee adjudicating outcomes were blinded to group allocation.

Study Interventions

EGDT Group: Patients in this group were managed according to a strict 6-hour resuscitation protocol based on the original Rivers trial. This required the placement of a central venous catheter capable of continuous $ScvO_2$ monitoring. The protocol mandated sequential goals:

1. CVP of 8–12 mmHg (achieved with intravenous crystalloids).
2. MAP of ≥65 mmHg (achieved with vasopressors, primarily norepinephrine).
3. If goals 1 and 2 were met but $ScvO_2$ was <70%, packed red blood cells were transfused to a hematocrit ≥30%.
4. If $ScvO_2$ remained <70% despite the above, dobutamine infusion was initiated.

Standard Care Group: Patients in this group were managed at the discretion of the attending emergency physician. Care was guided by contemporary best practices and the principles of the Surviving Sepsis Campaign, including prompt administration of broad-spectrum antibiotics, an initial 30 mL/kg crystalloid fluid bolus for hypotension, and the use of vasopressors to maintain a MAP ≥65 mmHg. The protocol did not mandate central venous catheterization or $ScvO_2$ monitoring. Dynamic assessments of fluid responsiveness (e.g., passive leg raise, bedside ultrasound of the inferior vena cava) were encouraged but not required.

Data Collection and Outcomes: Trained research coordinators prospectively collected data using a standardized electronic case report form. Baseline data included demographics, comorbidities, vital

signs, Sequential Organ Failure Assessment (SOFA) score, and presumed source of infection.

- The primary outcome was all-cause mortality at 28 days after randomization.
- Secondary outcomes included in-hospital mortality, ICU and hospital length of stay, total duration of vasopressor therapy, duration of mechanical ventilation, and the incidence of new-onset acute kidney injury (defined by KDIGO criteria). Data on resource utilization within the first 6 hours (volume of intravenous fluids, use of central venous catheters, vasopressors, inotropes, and blood transfusions) were also collected.

Statistical Analysis: The analysis was performed on an intention-to-treat basis. Baseline characteristics and clinical outcomes were compared between the two groups.

Categorical variables were presented as counts and percentages and were compared using the Chi-square test or Fisher's exact test. Continuous variables were presented as mean ± standard deviation (SD) and were compared using the Student's t-test or the Mann-Whitney U test, as appropriate, after assessing for normality. The primary outcome was analyzed using a Chi-square test, and the relative risk with a 95% confidence interval (CI) was calculated. A two-sided p-value of <0.05 was considered statistically significant. All analyses were performed using SPSS Statistics, Version 28.0 (IBM Corp.).

Results

Study Population: During the study period, 452 patients were screened for eligibility. Of these, 102 were excluded (65 did not meet inclusion criteria, 21 declined consent, 16 had exclusion criteria). A total of 350 patients underwent randomization, with 175 assigned to the EGDT group and 175 to the standard care group. All randomized patients were included in the final analysis.

The baseline demographic and clinical characteristics were well-balanced between the two groups (Table 1). The mean age was approximately 65 years, and the mean baseline SOFA score was 8.5, indicating a high severity of illness. Pneumonia was the most common source of infection in both groups.

Table 1: Baseline Demographic and Clinical Characteristics of Patients

Characteristic	EGDT Group (n=175)	Standard Care Group (n=175)	p-value
Age (years), mean ± SD	65.2 ± 14.1	64.8 ± 15.3	0.79
Male Sex, n (%)	98 (56.0)	91 (52.0)	0.45
SOFA Score, mean ± SD	8.6 ± 2.9	8.4 ± 3.1	0.58
Initial Lactate (mmol/L), mean ± SD	5.1 ± 2.4	4.9 ± 2.2	0.41
Comorbidities, n (%)			
Diabetes Mellitus	51 (29.1)	55 (31.4)	0.64
Chronic Kidney Disease	38 (21.7)	33 (18.9)	0.51
Congestive Heart Failure	30 (17.1)	34 (19.4)	0.59
Source of Infection, n (%)			
Pneumonia	75 (42.9)	79 (45.1)	0.67
Urinary Tract	42 (24.0)	39 (22.3)	0.71
Abdominal	28 (16.0)	26 (14.9)	0.78
Other/Unknown	30 (17.1)	31 (17.7)	0.90

Interventions and Resource Utilization: There were significant differences in the delivery of care and resource utilization within the first 6 hours of resuscitation, as dictated by the study protocols (Table 2). All patients in the EGDT group had a central venous catheter placed, compared to 62.3% in the standard care group (p<0.001).

Patients in the EGDT group received a significantly larger volume of intravenous fluids. The use of both vasopressors and dobutamine was also significantly higher in the EGDT group.

Table 2: Interventions and Resource Utilization in the First 6 Hours

Intervention	EGDT Group (n=175)	Standard Care Group (n=175)	p-value
IV Fluids (L), mean ± SD	4.8 ± 1.2	4.1 ± 1.1	**<0.001**
Central Venous Catheter, n (%)	175 (100)	109 (62.3)	**<0.001**
Vasopressor Use, n (%)	149 (85.1)	134 (76.6)	**0.04**
Dobutamine Use, n (%)	29 (16.6)	13 (7.4)	**0.009**
RBC Transfusion, n (%)	22 (12.6)	16 (9.1)	0.28

Clinical Outcomes: The primary outcome of 28-day all-cause mortality was not significantly different between the two groups.

Mortality occurred in 43 of 175 patients (24.6%) in the EGDT group and 38 of 175 patients (21.7%) in the standard care group (relative risk, 1.13; 95% CI, 0.77 to 1.66; p=0.48). There were also no statistically significant differences in any of the secondary outcomes, including in-hospital mortality, ICU length of stay, hospital length of stay, or duration of mechanical ventilation (Table 3).

Table 3: Primary and Secondary Clinical Outcomes

Outcome	EGDT Group (n=175)	Standard Care Group (n=175)	p-value
Primary Outcome			
28-Day Mortality, n (%)	43 (24.6)	38 (21.7)	0.48
Secondary Outcomes			
In-Hospital Mortality, n (%)	40 (22.9)	35 (20.0)	0.49
ICU Length of Stay (days), mean ± SD	8.1 ± 4.2	7.5 ± 3.9	0.19
Hospital Length of Stay (days), mean ± SD	13.4 ± 7.1	12.8 ± 6.8	0.44
Duration of Vasopressors (hrs), mean ± SD	65.5 ± 30.1	61.9 ± 28.5	0.21
Duration of Mech. Ventilation (days), mean ± SD	6.2 ± 3.5	5.9 ± 3.1	0.47
New-onset AKI, n (%)	77 (44.0)	71 (40.6)	0.52

Discussion

In this pragmatic, multi-center randomized trial involving patients with septic shock in community hospital EDs, we found that a strict, invasive protocol of Early Goal-Directed Therapy did not result in a lower 28-day mortality rate compared with contemporary standard care.

Our findings are consistent with the results of the landmark ProCESS, ARISE, and ProMISe trials, and extend their conclusions to the community hospital setting [6-8]. Despite mandating more invasive procedures and a greater intensity of resuscitation therapy, the EGDT protocol failed to improve survival or other clinically relevant secondary outcomes.

The core principle of this study was to evaluate if the structured nature of EGDT provided a benefit in settings potentially less resourced than the academic centers of the major trials. Our results suggest it does not. The lack of a mortality benefit, coupled with the observed increase in resource utilization (higher rates of central line placement, fluid administration, and vasoactive drug use), argues against the routine implementation of the full EGDT protocol.

This indicates that the critical components of successful sepsis resuscitation are likely the fundamental, time-sensitive interventions that have become ingrained in standard practice: early recognition, rapid antibiotic delivery, and titrated hemodynamic support to maintain vital organ perfusion [9, 12]. The "usual care" or "standard care" provided in our study, and in the large trials that preceded it, is vastly different from the care provided to the control group in the original Rivers et al. study [4, 13]. Over the past two decades, awareness of sepsis has grown exponentially, and key interventions have become standard practice globally. This phenomenon, often termed the "legacy effect" of EGDT, means that modern standard care already incorporates the most crucial elements of early resuscitation [14]. Our standard care group received prompt and substantial fluid volumes and early vasopressor initiation, likely achieving adequate resuscitation without the need for rigid CVP and $ScvO_2$ targets. This supports the concept that once MAP and perfusion are restored, further interventions guided by invasive markers may be unnecessary or even potentially harmful due to risks like fluid overload and complications from central venous access [15].

The finding that the EGDT group received nearly a liter more of intravenous fluid in the first six hours without a change in outcome is particularly important. This reinforces the growing body of evidence that a more restrictive or personalized fluid strategy may be preferable to aggressive, protocol-driven volume administration, which can contribute to endothelial injury and organ dysfunction [16].

The emphasis in modern critical care has shifted from static measures like CVP to dynamic assessments of fluid responsiveness, which were encouraged in our standard care arm and may allow for more judicious fluid management [17]. This study has several strengths. Its pragmatic, multi-center design enhances its external validity and generalizability to the numerous community hospitals where the majority of septic shock patients are first treated. The use of a centralized randomization process minimized selection bias, and the intention-to-treat analysis preserved the integrity of the randomization. However, our study is not without limitations. First, due to the nature of the interventions, clinicians could not be blinded,

which may have introduced performance bias. Second, while our study was multi-center, all participating hospitals were within a single health system, which may limit generalizability to other healthcare contexts. Third, we did not collect data on long-term outcomes beyond 28 days, such as functional status or quality of life, which are increasingly recognized as important patient-centered outcomes.

Conclusion

Among patients with septic shock presenting to community emergency departments, the use of a strict Early Goal-Directed Therapy protocol did not improve 28-day survival compared to contemporary standard care. The EGDT strategy was associated with increased use of invasive monitoring and resuscitation therapies, suggesting higher costs and potential for complications without clinical benefit. These findings support current international guidelines that recommend moving away from the rigid, invasive targets of EGDT and instead focusing on the core principles of early sepsis management within a flexible, physician-led resuscitation framework.

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