Goal-Directed Resuscitation in Septic Shock: A Critical Analysis

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- Severe sepsis
- Septic shock
- Goal-directed therapy
- Resuscitation

A BRIEF HISTORY OF GOAL-DIRECTED RESUSCITATION

The term goal-directed resuscitation or goal-directed therapy is used to describe care that targets a physiologic or hemodynamic goals or endpoints. Although the approach is more recently associated with a treatment algorithm based on the 2001 study by Dr Rivers and colleagues for the care of patients with severe sepsis, the concept of goal-directed resuscitation perhaps began in high-risk surgical patients in the form of supranormal oxygen delivery. A 1988 single-center, 88 patient study by Shoemaker and colleagues found that patients treated with a pulmonary artery catheter protocol, aimed to facilitate supranormal oxygen delivery, had a 4% mortality compared with 23% for those receiving nonprotocolized pulmonary catheter care and 33% in a no pulmonary catheter group. These findings were replicated in a study by Boyd and colleagues of 107 high-risk surgery patients where a pulmonary catheter was used to target physiologic goals of supranormal oxygen delivery, demonstrating a significant mortality decrease compared with nonprotocolized care (5.7% vs 22.2%). Together these 2 studies ushered in an era of supranormal oxygen delivery titrated to targeted physiologic goals.

This treatment approach continued until 1995 whenGattinoni and colleagues published the results of a multinational 56 center study in 762 patients that failed to find mortality benefit when supranormal oxygen delivery was targeted. In fact, in a subsequent 1994 study by Hayes and associates that included 100 patients at 2 centers, the treatment arm actually had a higher mortality compared with the control arm (54% vs 34%; \( P = .04 \)). Thus, the practice of targeting supranormal oxygen delivery fell out of favor.

A subsequent metaanalysis was performed to assess the hemodynamic optimization studies. Interestingly, when stratified by interventions...
occurring “before” or “at” the onset of organ dysfunction, as opposed to “after” organs began to fail, studies with treatment initiated early showed mortality benefit, whereas those initiated after onset of organ failure did not. A similar meta-analysis by Jones and colleagues conducted later had similar findings.

This is perhaps the point in history for the Rivers trial of early goal-directed therapy (EGDT), which operationalized the early implementation of goal-directed resuscitation in emergency department patients with sepsis. Published in 2001, the Rivers study found a 16% absolute mortality reduction in patients with severe sepsis and septic shock resuscitated using goal-directed therapy, and it established a new expectation that the mortality of this patient population could be improved with early, focused interventions. A number of subsequent pre–post trials supported these findings and quality assurance initiatives such as the Surviving Sepsis Campaign’s guidelines endorsed widespread implementation of EGDT.

Although the Rivers trial was a single-center trial, a prospective, multicenter, randomized validation trial was not immediately pursued. In 2014, 13 years after the Rivers trial, the first of 3 large randomized controlled clinical trials comparing EGDT with standard care was published. These trials all used similar inclusion and exclusion criteria as the Rivers trial. The Protocol-Based Care for Early Septic Shock (ProCESS) trial, performed in the United States (1351 patients, 31 sites), showed no difference in 60-day in-hospital mortality among patients randomized to EGDT (21.0% mortality), a noninvasive protocol targeted to physiologic goals (18.2% mortality), or usual care (18.9% mortality; P = .52). Later in 2014, results from the ARISE trial (1600 patients, 51 sites), conducted in Australia and New Zealand, were published, which did not demonstrate a difference in 90-day all-cause mortality between EGDT and standard care groups (18.6% vs 18.8% mortality; P = .90). Last, in early 2015, the Protocolised Management in Sepsis (ProMISe) trial (1260 patients, 56 sites), conducted in England, likewise failed to show a significant difference in all-cause 90-day mortality rates between treatment and usual care (29.5% vs 29.2%; P = .90).

A final metaanalysis evaluating the randomized, controlled studies of EGDT versus standard care seems to be the last argument that EGDT does not confer a mortality benefit over usual care.

The ProCESS, Australasian Resuscitation in Sepsis Evaluation (ARISE), and ProMISe trial of studies do not establish the superiority of standard care over EGDT. However, although these trials sought primarily to assess the mortality benefit of EGDT compared with standard care, they also provide a window to understand the care currently being provided by acute care providers across 3 continents. Likewise, in establishing the equivalence between EGDT and standard care groups, these trials provide new data to update the clinical care of patients with septic shock. By examining the processes of care used across these studies, we can identify the practice patterns, in both treatment and usual care groups, now associated with mortality rates recognized as lower than previously realized.

**Early Identification, Intravenous Fluid Resuscitation, and Empiric Antibiotics**

An important note about the conduct of the trials is that the inclusion criteria mandated early enrollment (and thus, early identification, namely, within 2.5 hours), an initial fluid bolus of roughly 1 L or 20 to 30 mL/kg of intravenous fluids before randomization, and the majority of patients received early antibiotics as well. Thus, the usual care arms in the 3 validation studies should be interpreted in the backdrop of early identification, early fluid loading, and early antibiotics.

**Early identification**

Identifying patients with severe sepsis and septic shock in the early stages of their disease has become increasingly emphasized because septic shock is categorized as a time-critical disease. Even the protocol name—early goal-directed therapy—emphasizes the expected timing of interventions. However, identifying patients with septic shock is often difficult because different disease processes can cause an inflammatory response, resulting in overlapping clinical presentations. For instance, fever may occur in patients without infection, and many patients with septic shock will not exhibit hyperthermia or hypothermia. Owing to the high frequency of sepsis as the cause for shock, clinicians should have a low threshold for suspecting sepsis as a cause of shock and initiating appropriate care so that critical interventions are not delayed.

**Intravenous fluid resuscitation**

A trial of intravenous fluids to correct hypoperfusion (hypotension or increased lactate) has become the standard of care for septic shock. An early resuscitation with intravenous fluids, which may be regarded as “vigorous,” is supported by the practice patterns seen in the ProCESS, ARISE, and ProMISe trials, where the average intravenous fluid given to each patient from before randomization fluids out to 6 hours after randomization was slightly more than 4 L.
In fact, in these studies and the Rivers trial, patients were not enrolled until they demonstrated persistent hemodynamic or lactate abnormalities after this step had been completed, making each studies’ findings contingent on a trial of fluid resuscitation first. Although the volume of intravenous fluids will vary by clinical scenario, the average show in Fig. 1 provides a general appreciation of the intravenous fluid volume a patient received during early resuscitation in the trials.

Although an initial dose of intravenous fluid has become commonplace, and there seems to have been a movement toward a more vigorous resuscitation, there is scarce outcomes-based evidence to support the practice. In fact, there remains an ongoing debate as to whether aggressive or restrictive fluid administration strategies will yield the best outcomes, with data emerging that suggest that overresuscitation may have detrimental effects. For example, using patients from the Vasopressin and Septic Shock Trial (VASST) trial, all of whom had vasopressor-dependent septic shock, Boyd and colleagues found that patients within the upper 2 quartiles of fluid balance at 12 hours after presentation had higher mortality rates. Similarly, in a single-center retrospective review of 325 patients with septic shock, Micek and colleagues found that patients within the highest quartile of fluid balance at 24 hours after presentation had significantly higher 28-day mortality compared with lowest quartile of fluid (P < .001). These studies advocate for a more restrictive fluid administration strategy. On the other hand, a retrospective, 24-center study by Waechter and colleagues suggested that lower intravenous fluid volumes, in particular less than 0.5 L in the first hour and less than 1 L in hours 1 to 6 of resuscitation, were associated with higher mortality. Unfortunately, these studies are not the randomized trials, which will be needed to truly test the impact of intravenous fluid quantity or fluid balance on patient outcomes. The initial approach fluid resuscitation will continue to be a refined, yet for now, providing 20 to 30 mL/kg (or the more pragmatic 2 L) of intravenous fluids remains the clinical expectation for septic shock.

**Empiric antibiotics**

Empiric antibiotics, similar to intravenous fluids, were a standard aspect of care in the 3 EGDT studies. Although the rates of antibiotics administration were not reported in the ARISE or ProMISe trials, the ProCESS trial reported antibiotics administration rates of 97.5% and 97.2% for the EGDT and standard care groups, respectively. As with intravenous fluids, these trials cannot assess the usefulness of early antibiotics, but the broad use of empiric antibiotics does reflect a pattern of practice seen in the care of most patients with septic shock, and this practice has been reinforced by a number of observational studies showing an association between early, appropriate antibiotics and improved survival as well as the Surviving Sepsis Campaign. These data withstanding, a recent metaanalysis by Sterling and colleagues failed to find a mortality benefit based on a specific time threshold for antibiotics; however, this does not mitigate the importance of administering appropriate antibiotics as early as possible.
Optimizing Preload

The first goal within EGDT involved achieving a central venous pressure (CVP) of 8 to 12 mm Hg to ensure adequate preload. This was accomplished in the EGDT trial by administering sequential 500-mL boluses of crystalloid every 30 minutes until this target was met. Whether the CVP truly reflects preload, total intravascular fluid, or fluid responsiveness has been contested intensely, and limitations surrounding CVP have been extensively reviewed in the literature.

Although rates of CVP measurement were not assessed directly in the ProCESS, ARISE, and ProMISe trials, central venous catheters were placed in 57% of patients in the standard care group, precluding the ability to measure CVP in a large proportion of patients (Fig. 2). The lines were placed typically for vasopressor administration as opposed to titrate therapy. Of note, this selective rate of central venous catheter placement also supports the ability of clinicians to select patients for central access, given that mortality remained the same between groups in each of these studies.

There are other alternatives to targeting CVP goals as a method for optimizing preload that have been proposed. These alternatives are sought perhaps owing to the inconsistent relationship between CVP and fluid responsiveness and relating a CVP of less than 8 mm Hg to lower mortality. Such alternative strategies for guiding fluid administration include inferior vena cava ultrasonography and dynamic measures of volume responsiveness through passive leg raises or fluid loading. Especially in light of the potential harms of overresuscitation with intravenous fluids, using such measures to determine fluid responsiveness is emphasized increasingly in early resuscitation. Although assessing fluid responsiveness is an intuitive strategy for optimizing preload while mitigating potential harm, none of these modalities have been shown to reduce mortality in large outcomes based clinical trials.

Vasopressor Support

Hypotension occurs in sepsis as a result of the relative hypovolemia typically caused by a combination of vasoplegia, capillary leak, and myocardial depression. If hypotension persists despite optimizing preload, then vasopressor agents are used to augment vasomotor tone, thereby addressing pathologic vasodilation. Reestablishing a blood pressure adequate for perfusion is critical to maintaining organ function.

The second step of EGDT stipulates that vasopressors are initiated to maintain a mean arterial pressure (MAP) of greater than 65 mm Hg. In the original EGDT trial, vasopressor administration rates in the standard care and EGDT groups were equivalent (30.3% vs 27.4%; P = .62) in the first 6 hours after randomization. Interestingly,

![Fig. 2. Rates of central venous catheterization in early goal-directed therapy (EGDT) and standard care groups by study. Rates for central venous oxygen saturation (ScvO2) and any central venous catheter placement are shown.](image)
vasopressor administration rates among the both
the EGDT standard care groups in ProCESS, ARISE, and ProMISE were much higher than in
the Rivers trial (Fig. 3), although the total average
of vasopressor use across these studies in the
EGDT arm (59.4%) was more frequent than in the
standard care arm (51.7%). Overall, the increase
in vasopressor use compared with the original
EGDT study may represent a lower tolerance for
hypotension or increased comfort with using vaso-
active medications. This comparison also sug-
gests a minimal clinically important difference
when vasopressor use was determined by proto-
col versus clinical discretion.

The therapeutic goal of vasopressor support
from the EGDT trial was a MAP of 65 mm Hg,
meant to meet the requirements to achieve renal
perfusion. However, vasopressors also increase
systemic vascular resistance and may impede
perfusion in patients with a low cardiac output. A
recent study did compare MAP goals of 65 to
70 mm Hg versus 80 to 85 mm Hg, and showed
no difference in mortality at 28 days. This sug-
gests that increasing the systemic blood pressure
with vasopressors does not increase perfusion
beyond the limit of autoregulation. This concept
was demonstrated in a study showing that sublin-
gual microvascular perfusion remained constant
across systolic blood pressures beyond 90 mm
Hg. As in EGDT, the most recent evidence sup-
ports the use of a MAP above renal arteriole autor-
egulation, 65 mm Hg, as a target in vasopressor
use. In patients with chronic hypertension, this
level may be higher, but otherwise, target levels
higher than the autoregulation threshold has not
shown benefit.

The use of vasopressors has become a com-
mon indication for establishing central venous ac-
cess, although many patients will be started on
peripheral vasopressors before central line place-
ment. However, a recent metaanalysis of case re-
ports of central and peripheral vasopressor
adverse events suggests that shorter duration
and more proximal peripheral intravenous lines
are associated with a low rate of complications
and supports the use of a peripheral line for
short-term vasopressor administration. Although
further confirmatory studies are needed, this
approach is potentially practice changing.

Assessing Oxygen Delivery and the Use of
Packed Red Blood Cells and Dobutamine

The final step of EGDT and major component
tested within the Rivers Trial involves measuring
a central venous (or superior venous) oxygen satu-
ratio ($S_{CV}O_2$) to assess whether oxygen delivery
was meeting the metabolic needs of the tissues.

Fig. 3. Rates of vasopressor administration. ARISE, Australasian Resuscitation in Sepsis Evaluation; EGDT, early
goal-directed therapy; ProCESS, Protocol-Based Care for Early Septic Shock; ProMISE, Protocolised Management
in Sepsis.
The physiologic premise assumes that patients with low $S_{\overline{CV}O_2}$ have increased oxygen extraction compared with delivery, and thus require interventions to increase oxygen delivery. For patients with an $S_{\overline{CV}O_2}$ of less than 70%, signifying a need to increase oxygen delivery, the first intervention is transfusion of packed red blood cells to achieve a hematocrit of at least 30% to ensure adequate oxygen-carrying capacity. The second intervention, once all other EGDT criteria are fulfilled, is to administer dobutamine to increase cardiac output until $S_{\overline{CV}O_2}$ is raised above the 70% threshold. In the Rivers trial, $S_{\overline{CV}O_2}$-guided interventions occurred frequently: EGDT patients received far more blood transfusions (64.1% vs 18.5%; $P<.001$) and dobutamine infusions (13.7% vs 0.8%; $P<.001$) compared with standard care in the first 6 hours after randomization. Although these interventions tended to be used more frequently in the protocol versus control groups of the triad of validation studies, the degree to which they were used in either group tended to be much less compared with the original EGDT trial (Figs. 4 and 5).

In 2010, Jones and colleagues assessed the usefulness of $S_{\overline{CV}O_2}$ versus lactate clearance to trigger red blood cell transfusion and dobutamine in the form of a randomized trial. This trial found no differences for in-hospital mortality between patients randomized to $S_{\overline{CV}O_2}$ measurements versus those randomized to serial lactate levels. This finding supports the use of lactate clearance as an alternative to using $S_{\overline{CV}O_2}$ monitoring. Interestingly, despite using the same inclusion and exclusion criteria as Rivers, the number of patients meeting criteria for either packed red blood cells ($S_{\overline{CV}O_2}$ 3% vs lactate clearance 7%) or dobutamine ($S_{\overline{CV}O_2}$ 5% vs lactate clearance 3%) were far below the rates in the original EGDT trial, and the mortality rate in both the lactate clearance and $S_{\overline{CV}O_2}$ groups (17% vs 23%) was similar to the triad of validation trials, all of which were much lower than the original EGDT trial.

The ProCESS, ARISE, and ProMISE trials showed similar rates of $S_{\overline{CV}O_2}$-directed interventions in the EGDT groups (see Figs. 3 and 4) as the Jones trial, reaffirming that few patients met the $S_{\overline{CV}O_2}$ criteria that were more common in the Rivers trial. Furthermore, in comparison with patients in the EGDT groups, those treated by standard care used significantly less packed red blood cells and dobutamine, and had very low numbers of $S_{\overline{CV}O_2}$ catheters placed. These studies demonstrate significantly greater resource use in the EGDT groups, triggered by $S_{\overline{CV}O_2}$ monitoring. Last, the near absence of $S_{\overline{CV}O_2}$ catheter placement suggests that very few clinicians are using this measure, without any detriment to patients (see Fig. 2).

Although the Jones trial offered lactate clearance as an alternative resuscitation endpoint to $S_{\overline{CV}O_2}$ monitoring, the true role of lactate measurements as a resuscitation goal remains incompletely defined. In the context of the subsequent triad of trials, it is plausible that the equivalence of $S_{\overline{CV}O_2}$ monitoring and lactate clearance in the Jones trial is potentially a result of neither intervention having a significant effect on outcomes, as opposed to equivalence between the measurements in guiding therapy. There is reasonable observational evidence that lactate concentration and clearance patterns are useful in prognostication. Persistently abnormal values of lactate should, however, at least trigger a clinical reassessment of the resuscitation.

![Fig. 4. Rates of dobutamine administration between EGDT and standard care groups. ARISE, Australasian Resuscitation in Sepsis Evaluation; EGDT, early goal-directed therapy; ProCESS, Protocol-Based Care for Early Septic Shock; ProMISE, Protocolised Management in Sepsis.](image-url)
Moving Forward

Since the time that Rivers’ protocol was published, studies support a declining mortality rate for severe sepsis and septic shock. We cannot truly identify why this mortality reduction has occurred; however, it is reasonable to postulate that there has been an increase in early recognition and timely intervention over this time period. This potential emphasis on the early aspects of care, inspired in a large part by the Rivers study, has created a number of quality assurance initiatives such as the Surviving Sepsis Campaign that have reinforced the concept of early, meticulous care in septic shock. The EGDT protocol encouraged physicians to be diligent in their surveillance of septic patients, aggressive in the early resuscitation of these patients, and to reassess the effect of their interventions. However, although trials demonstrate that the EGDT protocol did not confer a mortality benefit when compared with standard clinical care, the level of standard clinical care may be considered to be “high quality.” It is also important to note that EGDT did not show harm; thus, it is still a reasonable treatment strategy.

It is likely that new approaches to septic shock will be developed. Questions remain regarding multiple aspects of care including methods for early identification, the amount of fluids that should be given, methods to monitor fluid responsiveness, and how to monitor tissue perfusion. The research that is available currently does not provide distinct solutions that can be applied broadly to improve these aspects of care. However, the introduction of novel biomarkers, dynamic monitoring of fluid responsiveness, and novel techniques for monitoring changes in tissue perfusion during resuscitation may provide the next steps forward in sepsis care. Until then, the concepts of early and meticulous care demonstrated in ProCESS, ARISE, and ProMiSe trials provide us with the most current standard of clinical care for the treatment of severe sepsis and septic shock.

REFERENCES