Goal-Directed Resuscitation in Septic Shock: A Critical Analysis

Daniel J. Henning, MD, MPH[a,*], Nathan I. Shapiro, MD, MPH[b]

KEYWORDS

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

KEY POINTS

- The Early Goal-Directed Therapy versus Standard Care in 2001 suggested mortality could be reduced by using physiologic goals to guide patient care in septic shock.
- In 2014 and 2015, 3 multicenter, randomized trials did not demonstrate the superiority of goal-directed therapy over unstructured standard care.
- Sepsis mortality seems to be decreasing with early and meticulous care, including early identification, fluid resuscitation, antibiotics, and restoration of blood pressure.

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[1] 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.[2] A 1988 single-center, 88 patient study by Shoemaker and colleagues[2] 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[3] 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.[3]

This treatment approach continued until 1995 when Gattinoni and colleagues[4] 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[5] 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.[6] Interestingly, when stratified by interventions

Disclosure Statement: Dr N.I. Shapiro has received research funding from Thermo-Fischer and Cheetah Medical, and has been a consultant on an advisory board for Cheetah-Medical.

[a] Division of Emergency Medicine, Harborview Medical Center, University of Washington School of Medicine, 325 9th Avenue, Box 359702, Seattle, WA 98104, USA; [b] Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, One Deaconess Road, W-CC2, Boston, MA 02215, USA
* Corresponding author.
E-mail address: henning2@uw.edu

Clin Chest Med 37 (2016) 231–239
http://dx.doi.org/10.1016/j.ccm.2016.01.016

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[7] 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,[1] 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[8–13] and quality assurance initiatives such as the Surviving Sepsis Campaign's guidelines[14] 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.[15–17] 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; $P = .52$).[16] 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; $P = .90$).[15] 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%; $P = .90$).[15,17] 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.[18]

The ProCESS, Australasian Resuscitation in Sepsis Evaluation (ARISE), and ProMISe triad 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.[19,20]

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,[21,22] because septic shock is categorized as a time-critical disease.[23] 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.[24–26] Owing to the high frequency of sepsis as the cause for shock,[27] 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