Critical Review Form
Therapy

Rivers E, Nguyen B, Havstad S, et al; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001 Nov 8;345(19):1368-77.

Objectives: **To determine "whether early goal-directed therapy before admission to the intensive care unit effectively reduces the incidence of multiorgan dysfunction, mortality, and the use of health care resources among patients with severe sepsis or septic shock." (p. 1369)**

Methods: **this prospective randomized study was conducted at Henry Ford Hospital, a large urban academic center, between March 1997 and March 2000. Adult patients presenting to the emergency department with two criteria for the systemic inflammatory response syndrome and either a systolic blood pressure of 90 mmHg or less after a fluid challenge, or blood lactate of 4 mmol per liter or more were eligible for inclusion. Patients were randomized to either early goal directed therapy (EGDT) or standard therapy.**

All patients in both groups underwent arterial in central venous catheterization. Patients in the standard therapy group treated at the discretion of the treating physicians according to a protocol that aimed at maintaining central venous pressure (CVP) between 8 and 12 mmHg, mean arterial pressure (MAP) ≥ 65 mmHg, and urine output ≥ 0.5 mL/kg/hr. These patients were admitted for inpatient care as soon as possible.

Patients in the EGDT group were treated according to protocol for at least six hours in the emergency department prior to admission. This protocol consisted of a 500 mL bolus of fluid every 30 minutes to achieve a CVP of 8 to 12 mmHg. Vasopressors were given to maintain a MAP of at least 65 mmHg, when necessary. Vasodilators were given to maintain a MAP of less than 90 mmHg, when necessary. All patients underwent continuous central venous oxygen saturation (ScvO2) monitoring. If the ScvO2 was less than 70%, packed red blood cells were transfused to maintain a hematocrit of at least 30%; if the ScvO2 was still less than 70% dobutamine was infused at 2.5 µg per kilogram of body weight and titrated until the oxygen saturation was 70% or higher.

The primary outcome was in-hospital mortality. Secondary outcomes included organ dysfunction scores (APACHE II, SAPS II, and MODS), treatments administered, and the consumption of healthcare resources (duration of vasopressor therapy and mechanical ventilation and hospital length of stay). A total of 263 patients were

randomized, open 236 completed the initial six-hour study period. There were 133 subjects in the standard therapy group and 130 subjects in the EGDT group.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. "Patients were randomly assigned either to early goal-directed therapy or to standard (control) therapy in computer-generated blocks of two to eight. The study-group assignments were placed in sealed, opaque, randomly assorted envelopes, which were opened by a hospital staff member who was not one of the study investigators." (p. 1370)
2.	Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	Yes. Based on the protocol above, it is unlikely that randomization could have been subverted, allowing proper allocation concealment.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. Although 27 patients randomized did not complete the initial 6-hour study period, All 263 were included in the intention-to-treat analyses" (p. 1371) and all patients were analyzed by group allocation rather than treatment received.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, gender, initial vital signs, baseline laboratory values, medical comorbidities, degree of sepsis, and diagnosis.
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	Yes. This was an open label trial and all patients were aware of group allocation. However, it is unlikely that significant performance bias on the part of the patients would affect the outcomes.

2.	Were clinicians aware of group allocation?	Yes. This was an open label trial and all clinicians aware of group allocation. It is possible that significant performance bias on the part of the clinicians would affect the outcomes. However, critical care physicians who assumed care of the patients following admission were unaware of group assignment.
3.	Were outcome assessors aware of group allocation?	Uncertain. The authors do not specifically mention blinding of outcome assessors, and do not specify the manner in which outcomes were assessed. However all of the outcomes of the study were objective and it is unlikely that observer bias would have affected interpretation of these outcomes.
4.	Was follow-up complete?	Yes. Follow-up data was reportedly available for all enrolled patients.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• 60-day mortality was significantly lower in the EGDT group than in the standard therapy group (44.3% versus 56.9%; relative risk [RR] 0.67, 95% CI 0.46-0.96, NNT = 8). • 28-day mortality was significantly lower in the EGDT group than in the standard therapy group (33.3% versus 49.2%; relative risk [RR] 0.58, 95% CI 0.39-0.87). • Patients assigned to the EGDT group received significantly more fluid in the first six hours than those in the standard therapy group (4981 mL versus 3499 mL, $p < 0.001$), and were more likely to receive red blood cell transfusion and inotropic support. • The mean duration of vasopressor therapy, the mean duration of mechanical ventilation, and the mean length of stay were similar between the two groups.
2.	How precise was the estimate of the treatment effect?	See above.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Yes. These were patients with severe septic or septic shock cared for in a busy, urban, academic ED that is similar in many respects to ours.
2.	Were all clinically important	Yes. The authors considered the most important

	outcomes considered?	outcomes, including mortality, length of stay, and healthcare utilization. They did not assess cost, patient/family satisfaction, quality of life, or disposition location.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. Based on this study alone, EGDT does appear to reduce mortality. Unfortunately, it is difficult to tease out which components of the protocol actually resulted in the reduced mortality. Patients in the EGDT received significantly more fluid in the first 6 hours of care, and this additional fluid administration may have been a large cause of the reduced mortality observed. Subsequent studies (ProCESS, ARISE, PROMISE) have shown no benefit to EGDT compared to what is now considered usual care, which includes aggressive hydration up-front, early antibiotic administration, and serial plasma lactate measurements to monitor the response to resuscitation.

Limitations:

1. **The intervention being assessed was a bundle, including many separate interventions (ScvO2 monitoring, CVP monitoring, aggressive blood transfusion, and the use of inotropic infusions). It is unclear which component(s) led to the observed reduction in mortality.**

2. **The study was not blinded, and there is a very real risk of performance bias as a result.**

3. **Patients in the EGDT received significant more IV fluids in the 6-hour treatment window, which potentially could have resulted in the observed reduction in mortality.**

4. **The protocol required central venous access and arterial cannulation in all patients in both study arms. This is contrary to standard practice in many institutions, where central venous and arterial access is reserved for patients requiring vasopressors.**

5. **The study evaluated a treatment protocol with multiple components. It is difficult to ascertain the actual benefit of each individual component.**

Bottom Line:

This large, randomized trial conducted at a large academic institution in the US demonstrated a significant reduction in mortality with the use of early-goal directed therapy in severe sepsis and septic shock. The use of a treatment protocol as the

intervention makes it difficult to ascertain which individual components contributed to the efficacy of the protocol. Patients in the EGDT group received nearly 1.5 more liters of fluid in the first six hours than the usual care group, which may have had a significant impact on the reduction in mortality. More recent studies have shown no benefit to EGDT in these patients, likely due to the more aggressive management utilized in sepsis currently.