Critical Review Form
Therapy

Mouncey PR, Osborn TM, Power GS, et al; ProMISe Trial Investigators. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015 Apr 2;372(14):1301-11.

Objectives: **To test "the hypothesis that the 6-hour EGDT resuscitation protocol is superior, in terms of clinical and cost-effectiveness measures, to usual care in patients presenting with early septic shock to National Health Service (NHS) emergency departments in England." (p. 1302)**

Methods: **This prospective, randomized, open-label trial was conducted between February 16, 2011 and July 24, 2014 at 56 sites in the United Kingdom. Adult patients aged 18 years or older were eligible if they had a suspected or confirmed infection, two or more criteria of the systemic inflammatory response syndrome, and either refractory hypotention (systolic blood pressure < 90 mmHg or mean arterial pressure < 65 mmHg after fluid challenge) or a blood lactate level of 4.0 mmol/L or more.**

Patients were randomized to receive either early goal-directed therapy (EGDT) or usual care for 6 hours. Patients in the usual care group were treated according to the discretion of the clinical team. Patients in the EGDT group underwent arterial and central venous catheter placement with continuous ScvO2 monitoring. The EGDT algorithm was followed for the first 6 hours of care.

The primary outcome was death from any cause within 90 days. Secondary outcomes included all-cause mortality at 28 days, at time of discharge, and at one year; Sequential Organ Failure Assessment (SOFA) score at 6 hours and 72 hours; emergency department length of stay, ICU length of stay, and hospital length of stay; duration of mechanical ventilation, duration of vasopressor therapy, duration of renal-replacement therapy; quality of life as measured by the European Quality of Life-5 Dimensions [EQ-5D] questionnaire at 90 days and one year; and cost at 90 days and one year.

A total of 1260 patients were enrolled. After the exclusion of 9 subjects there were 1251 in the initial analysis (625 in the EGDT group and 626 in the usual care group). Eight subjects withdrew before 90 days, leaving 1243 subjects in the analysis of outcomes (623 patients and 620 patients in the usual care group). respectively. Refractory hypotension was present in 54.1% of patients in the EGDT group and 55.6% in the usual care group, while an elevated lactate was found in 65.4% of

patients in the EGDT group and 63.7% in the usual care group. The mean initial ScvO2 value measured in the EGDT group was 70%.

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 assigned in a 1:1 ratio by means of 24-hour telephone randomization to receive either EGDT or usual care. Study-group assignment was performed by means of randomized permuted blocks, with variable block lengths of 4, 6, and 8, and stratified according to site." (p. 1302-1303)
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. The use of a centralized telephone system should prevent subversion of the randomization scheme, allowing proper allocation concealment
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "All analyses were performed according to the intention-to-treat principle." (p. 1303)
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, criteria for sepsis, initial blood lactate, amount of IV fluids administered prior to randomization, initial vital signs, APACHE II score, SOFA score, and site of infection.
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. " Blinding to study-group assignment was not possible." (p. 1303) 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. As above. It is possible that significant performance bias on the part of the clinicians would affect the outcomes.
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?	Mostly yes. Of patients in the EGDT group who were randomized, 3 requested removal of data and 2 were ineligible; 2 withdrew before 90 days; and an additional 17 had incomplete 90-day EQ-5D information. Of patients in the usual care group who were randomized, 1 requested removal of data and 3 were ineligible; 6 withdrew before 90 days; and an additional 22 had incomplete 90-day EQ-5D information.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• For the primary outcome of all-cause mortality at 90 days, results were similar between the EGDT and usual care group (29.5% vs. 29.2%, p = 0.90; RR = 1.01, 95% CI 0.85-1.20). • There was no difference between the EGDT and usual care groups with regards to 28-day mortality (RR 1.01, 95% CI 0.83-1.23) or death prior to hospital discharge (RR 1.04, 95% CI 0.86-1.23). • SOFA scores at 6 hours were higher in the EGDT group compared to the usual care group (6.4±3.8 vs. 5.6±3.8, p < 0.001); at 72 hours there was a small, statistically insignificant difference (4.0±3.8 vs. 3.7±3.6, p = 0.056). • There was no difference between the groups with respect to need for advanced cardiovascular support, advanced respiratory support, or renal support up to 28 days. • The median LOS in the ED and hospital were similar between the groups. The median LOS in the ICU was higher in the EGDT group compared to the usual care group (2.6 days vs. 2.2 days, p = 0.005).

		• Quality of life, based on EQ-5D scores at 90 days, was similar between the EGDT and usual care groups, as were costs at 90 days.
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?	No. This was multi-center study performed in the UK. This was a very heterogeneous study conducted in a mix of tertiary care, community, and rural hospitals. While some of the patients in this study were likely similar to ours (patients with severe sepsis or septic shock cared for in large tertiary care hospitals), the overall cohort is much more diverse, allowing the results to be generalized to a broader group of institutions.
2.	Were all clinically important outcomes considered?	Yes. The authors considered mortality at varying times points, healthcare utilization, LOS in the ED/ICU/hospital, quality of life at 90 days, and healthcare costs.
3.	Are the likely treatment benefits worth the potential harm and costs?	No. This rigorously performed multicenter study demonstrated no benefit to protocol-base early goal-directed therapy in patients with severe sepsis or septic shock. The usual care group had shorter ICU length of stay, with no difference in mortality, quality of life, or cost.

Limitations:

1. **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.**

2. **Patients were enrolled after being in the ED a median of over 2.5 hours, during which time they received a median of ~2 L of fluid as well as other interventions. This could potentially wash out any benefit to EGDT. This likely explains the significantly higher initial ScvO2 measurements in the EGDT group compared to those seen in the study by Rivers et al.**

3. **The study was performed in a variety of clinical settings in the UK, potentially making it difficult to apply the results to a single large, academic center (external validity). This does, however, make the results more generalizable.**

Bottom Line:

This large, multicenter trial conducted at 56 hospitals in the UK compared early goal-directed therapy with usual care for the management of severe sepsis and septic shock. The results demonstrated no benefit to EGDT, despite a higher median length of stay in the ICU for this group. These results suggest that monitoring of ScvO2 and blood transfusion to preset goals do not improve outcomes. It is likely that more aggressive management of sepsis with larger volumes of fluids and earlier administration of antibiotics explain the difference in outcomes in this study compared to the original study by Rivers et al.