Critical Review Form
Therapy

ARISE Investigators; ANZICS Clinical Trials Group, Peake SL, Delaney A, Bailey M, et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014 Oct 16;371(16):1496-506.

Objectives: **"to test the hypothesis that EGDT, as compared with usual care, would decrease 90-day all-cause mortality among patients presenting to the emergency department with early septic shock in diverse health care settings." (p. 1497)**

Methods: **This prospective, randomized, open-label trial was conducted between October 5, 2008 and April 23, 2014 in 51 hospitals in a variety of settings in 5 countries (Australia, New Zealand, Finland, Hong Kong, and Ireland). 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, with the caveat that ScvO2 measurement was not permitted. Patients in the EGDT group were treated by a separate study team, and all these patients 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 survival time up to 90 days, ICU mortality, 28-day mortality, 60-day in-hospital mortality, emergency department length of stay, ICU length of stay, hospital length of stay, duration of mechanical ventilation, duration of vasopressor therapy, duration of renal-replacement therapy, and destination at the time of discharge.

A total of 1600 patients were enrolled, 796 in the EGDT group and 804 in the usual care group. Nine subjects dropped, leaving 793 patients and 798 patients in the two groups, respectively. Refractory hypotension was present in 70% of patients in the EGDT group and 69.8% in the usual care group, while an elevated lactate was found in 46.0% of patients in the EGDT group and 46.5% in the usual care 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?	"Randomization was stratified according to study center with the use of a permuted-block method and was performed by means of a centralized telephone interactive voice-response system that was accessible 24 hours a day." (p. 1498)
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?	"All analyses were conducted according to the intention-to-treat principle." (p. 1498)
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, usual residence, APACHE II score, need for mechanical ventilation, need for vasopressor therapy, volume of fluids administered, and time to antibiotic administration
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?	"Because of the nature of the intervention, all patients and clinicians involved in their care were aware of study-group assignments." (p. 1498) 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. "By day 90, 1 patient in the usual-care group had revoked consent, and 2 patients (1 in each group) were lost to follow-up, leaving a final cohort of 1588 patients for whom the primary outcome was available: 792 (99.5%) in the EGDT group and 796 (99.0%) in the usual-care group." (p. 1499)
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• A higher proportion of patients in the EGDT group were admitted to the ICU compared to the usual care group (87.0% vs. 76.9%, $p < 0.001$). • A much higher proportion of patients in the EGDT group underwent central venous catheter placement in the first 6 hours compared to the usual care group (90.0% vs. 61.9%; $p < 0.002^{\dagger}$) • The volume of fluids administered in the first 6 hours following randomization was slightly higher in the EGDT group compared to the usual care group (1964 mL vs. 1713 mL, $p < 0.001$). • More patients in the EGDT group received a vasoproessor infusion, red blood cell transfusion, or dobutamine infusion compared to the usual care group. • For the primary outcome, all-cause mortality at 90 days, results were similar between the EGDT and usual care groups (18.6% vs. 18.8%, $p = 0.90$; RR 0.98, 95% CI 0.80-1.21). There was no difference in survival time. • The median length of stay was shorter in the EGDT group compared to the usual care group (1.4 hours vs. 2.0 hours, $p < 0.001$). † Calculated using http://vassarstats.net/propdiff_ind.html
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 an international study and none of the centers were in the US. This was also 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. Yet. The authors considered mortality, organ failure, length of stay, and discharge status. They do not consider costs, patient satisfaction, or quality of life.
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. Patients in the EGDT group were more likely to receive vasopressors, blood transfusion, and dobutamine infusion, with no difference in mortality or survival time.

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. **A separate study team not involved in the clinical care of other patients treated patients in the EGDT group. This does not reflect real world care of septic patients in the emergency department and could bias the results in favor of this group.**

3. **Patients were enrolled after being in the ED a median just under 3 hours, during which time they received a median of ~2.5 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.**

4. **The study was performed in a variety of clinical settings in several different countries, 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, international trial 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 increased use of central venous catheters, vasopressors, and blood transfusions 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.