Critical Review Form
Therapy

ProCESS Investigators, Yealy DM, Kellum JA, Huang DT, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014 May 1;370(18):1683-93.

Objectives: **To determine "whether protocol- based resuscitation was superior to usual care and whether a protocol with central hemodynamic monitoring to guide the use of fluids, vasopressors, blood transfusions, and dobutamine was superior to a simpler protocol that did not include these elements." (p. 1684)**

Methods: **This multicenter open label randomized controlled trial was conducted between March 2008 and May 2013 at 31 academic hospitals in the United States. Adult patients, aged 18 years or older, in whom sepsis was suspected in the emergency department, were recruited. Eligibility required two or more criteria for systemic inflammatory response syndrome, and refractory hypotension or a serum lactate level of 4 mmol per liter or higher. Refractory hypotension was defined as a systolic blood pressure less than 90 mmHg or the need for a vasopressor to maintain a systolic blood pressure greater than 90 mmHg after a fluid challenge.**

Patients were randomly assigned in a 1:1:1 ratio, to either early goal directed therapy (EGDT), standard therapy, or usual care.

- **Patients in the EGDT group underwent central venous placement with central venous pressure and ScvO2 measurement, and were treated according to a protocol similar to that used by Rivers et al.**
- **Patients in the standard therapy group were treated with the use of a six-hour resuscitation instruction set that did not require central venous access, but involving administration of fluids and vasoactive agents to reach goals for systolic blood pressure and shop index, as assessed clinically every hour. Patients in this group received blood transfusion only if the hemoglobin was less than 7.5 g/dL.**
- **Patients in the usual care group were treated at the discretion of the bedside providers with no prompting provided.**

The primary outcome was in-hospital death from any cause at 60 days. Secondary outcomes included death from any cause at 90 days, cumulative mortality at 90 days and one year, the duration of vasopressor requirement, the duration of mechanical ventilation requirement, and the duration of dialysis during the acute hospitalization. Additional outcomes included length of hospital stay, length of intensive care unit (ICU) stay, and hospital discharge disposition.

A total of 1351 patients were enrolled, care of whom withdrew from the study leading a final cohort of 1341 patients in the final analysis. Of these 439 were randomized to EGDT, 446 to standard care, and 456 to usual care. At 6 hours, incomplete protocol adherence was noted in 11.9% of patients in the EGDT group and 4.4% of patients in the standard therapy group. Thirty patients (6.8%) in the EGDT group did not undergo central venous catheter placement. A central venous catheter was placed in 56.5% of patients in the standard therapy group and 57.9% of patients in the usual care. Only 4% of patients in the standard therapy group and 3.5% in the usual care group underwent serial monitoring of ScvO2, compared to 93.6% 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. "Randomization was performed with the use of a centralized Web-based program in variable block sizes of 3, 6, or 9, with stratification according to site and race." (p. 1685)
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 web-based program should prevent subversion of the randomization scheme, allowing proper allocation concealment.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "We analyzed all data according to the intention-to-treat principle." (p. 1686)
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, source of infection, APACHE II score, presence of refractory hypotension, hyperlactatemia, initial systolic blood pressure, and initial serum lactate.
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.
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. For most of the outcomes, including the primary outcome (in-hospital death by 60 days), data was available for all patients. There were a handful of patients without data on 90-day mortality (34 in the EGDT group, 31 in the standard therapy group, and 44 in the usual care group).
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• The primary outcome, in-hospital death by 60 days, there was no significant difference between the three groups (21.0% in the EGDT group, 18.2% in the standard therapy group, and 18.9% in the usual care group; p = 0.83). • The 60-day in-hospital mortality for the combined protocol-based groups did not differ significantly from that of the usual care group (relative risk 1.04; 95% confidence interval 0.82 to 1.31). • There was no significant difference between the three groups with regards to death by 90 days (31.9% in the EGDT group, 30.8% in the standard therapy group, and 33.7% in the usual care group; p = 0.66). • There was no significant difference between the three groups with regards to the duration of vasopressor use, mechanical ventilation, or dialysis. • Patients in the EGDT group were slightly more likely to require ICU admission (91.3% compared to 85.4% in the standard therapy group and 86.2% in the usual care group; p = 0.01). All patients admitted to the ICU the direction of ICU stay was similar between the three groups, as well as overall

		hospital length of stay. • Discharge status and location at 60 days was also similar between the three 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 sepsis or septic shock strictly defined by previously accepted requirements, cared for in large US academic emergency departments. The primary difference noted was in the implementation of care in the two protocol-based groups. For these two groups a dedicated team, not involved in the clinical care of other patients, was assigned to the care of these patients and received timed prompts by a bedside nurse. Septic patients in our emergency department are cared for by clinicians and nurses involved in the care of several other potentially ill patients and do not receive timed prompts.
2.	Were all clinically important outcomes considered?	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 care in patients with severe sepsis or septic shock, despite the use of a dedicated team and timed prompts to assist in the care of these two groups. The usual care group was less likely to undergo central venous catheter placement or have ScvO2 monitored and less likely to require ICU admission. Despite these differences there was no improvement in mortality.

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 study coordinator provided time prompts to clinicians involved in the care of patients in the EGDT and standard therapy groups. This does not reflect real**

world care of septic patients in the emergency department and could bias the results in favor of these two groups.

3. **Patients were enrolled after being in the ED a median of over 3 hours, during which time is likely that they received a significant amount 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.**

Bottom Line:

This large, multicenter trial conducted at 31 academic hospitals in the US compared early goal-directed therapy to a standard protocolized therapy and usual care for the management of severe sepsis and septic shock. The results demonstrated no benefit in either of the protocolized care groups, despite increased use of central venous lines and increased ICU admission rates. 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.