Critical Review Form

Therapy

Early Goal Directed Therapy in Severe Sepsis and Septic Shock, *NEJM* 2001; 345: 1368-1377

Objective: To examine "whether early goal-directed therapy before admission to the ICU effectively reduces the incidence of multi-organ dysfunction, mortality, and the use of health care resources among patients with severe sepsis or septic shock." (p. 1369)
Methods: Open, randomized, partially blinded trial" (p. 1376). See CONSORT diagram (Figure 1, p. 1369) for an overview of patient enrollment and hemodynamic support. Eligible if > 18 years old presenting between March 1997 and March 2000 to Henry Ford Hospital (Detroit, MI) without bleeding risk, complicated sepsis (such as concurrent acute coronary syndrome or cardiogenic shock), atypical immune system (HIV or cancer), or contra-indications to invasive procedures. Eligible subjects also had to possess a systolic blood pressure < 90 mm Hg (after a 20-30 cc/kg bolus over 30-minutes) OR lactate > 4mmol/L AND two out of five of the following: 36°C > T > 38°C, heart rate > 90, respiratory rate > 20, partial pressure of carbon dioxide < 32 mm Hg, 4 > WBC > 12 OR >10% Bands. "The study was conducted during the routine treatment of other patients in the ED" (p. 1370) in a setting nearly identical to TCC at BJH. Patients were followed up to 60-days or death. Primary outcome was in-hospital mortality. Secondary outcomes included resuscitation endpoints, organ dysfunction, severity scores (APACHE II, SAPS II, MODS – see the original article for references if you are not familiar with these scoring systems), coagulation related variables, administered treatments, and the consumption of healthcare resources.

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.** After clinicians assessed patients for eligibility, consent was obtained and then assigned to EGDT or standard therapy (ST).
2.	Was randomization concealed (blinded)?	**Yes.** 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 part of the study investigators" (p. 1370)

3.	Were patients analyzed in the groups to which they were randomized?	All 263 were included in the intention-to-treat analysis (p. 1371).
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Some differences noted between groups, but most would *favor* ST group! (Table 1, p. 1372)

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?	This is not clearly stated, but probably yes – unless ST group received sham CVP lines, arterial line, and fluids).
2.	Were clinicians aware of group allocation?	Not during the initial assessment, but they were during ED treatment. ICU clinicians blinded to group assignment.
3.	Were outcome assessors aware of group allocation?	"Critical care clinicians assumed the care of all the patients; these physicians were unaware of the patients' study-group assignments." (p. 1370)
4.	Was follow-up complete?	27 patients did not complete the initial six-hour study period (14 in ST group, 13 EGD group) for a variety of reasons (p. 1371). There was no significant differences between the patients who completed the initial six-hour study period and those who did not in any of the baseline characteristics." (p. 1372-1373) Additionally, "similar results were obtained after data from the 27 patients who did not complete the initial six-hour study period were excluded from analysis."
II.	**What are the results (answer the questions posed below)?**	

1.	How large was the treatment effect?	1) In-hospital mortality EGD 30.5% versus ST 46.5% (ARR = 16%, NNT = 6 patients, p = 0.009). These findings are consistent among those subjects with severe sepsis, septic shock, and sepsis syndrome (Table 3, p. 1374). 2) Secondary outcomes showed statistically significant differences in favor of EGD at 6-hours for CVP, MAP, CVO_2, lactate, and APACHE-II score (Table 2, p. 1373).

2.	How precise was the estimate of the treatment effect? *In other words, what are the confidence intervals?*	In-hospital mortality relative risk (RR) = 0.58 (95% CI 0.38-0.87). 60-day mortality RR = 0.67 (95% CI 0.46-0.96). No other Confidence Intervals are reported.
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. Similar patients in a similar busy, urban teaching ED.
2.	Were all clinically important outcomes considered?	The mortality benefit is most important in this first ED-initiated EGDT study, but subsequent studies might also assess Quality of Life indicators.
3.	Are the likely treatment benefits worth the potential harm and costs?	No differences between groups were noted on resource consumption or hospital length of stay (LOS, 13.0 versus 13.2 days), but among those surviving to hospital discharge ST group had significantly longer LOS (18.4 days versus 14.6 days, p = 0.04).

Limitations - Not many. Well-designed, impeccably conducted project on a high-cost, high-prevalence issue certain to only increase in frequency.

1) Not double-blinded. Could have theoretically utilized sham lines and interventions, but that would have likely violated the ethical principle of beneficence.
2) No perspective on ED-intervention related co-morbidities (pneumothorax, line misplacement, bleeding).
3) No perspective on "the rest of the ED". How long was care delayed for other patients? How did that delay impact time-dependent conditions like ST-elevation myocardial infarction and ischemic cerebrovascular accident?

Bottom Line

Among hypotensive (systolic blood pressure < 90 mm Hg after initial volume resuscitation) or hypoperfused (Lactate > 4 mmol/L) adult patients with systemic inflammatory response syndrome, early goal-directed therapy with crystalloid and packed red blood cells as needed to maintain CVP ≥ 8-12 mm Hg, MAP ≥ 65, urine output > 0.5 cc/kg/hr and $SVO_2 \geq 70\%$, the ARR of mortality during hospitalization is 16% (6 patients would need to be treated with EGDT to prevent one death) when compared with standard therapy. This contradicts earlier research conducted in ICU's which may be too late in the "golden hour" of sepsis management pointing towards a definite role for EM in improving detrimental sepsis outcomes. Further research should analyze this study's reproducibility (external validity) at academic and non-academic facilities as well as the impact of this highly intensive therapy on "the rest of the ED".