EVMS Emergency Medicine Journal Club
Therapy Worksheet

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Date: **8/31/15**

CITATION: Yealy DM, Kellum JA, Huang DT, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med 2014;370:1683-1693

A. What is being studied? (Answer below)	**Comments**
1. Study Objective	Is early goal-directed therapy (EGDT) or other protocol-driven therapy superior to usual care in the treatment of septic shock?
2. Study Design	Multi-center open label randomized controlled trial. Included 31 Academic Emergency Departments in the US. Included a random, block assignment, (1:1:1), of septic shock patients to either a 1) EGDT cohort, 2) protocol-based standard therapy cohort, or 3) usual care cohort for comparison.
3. Inclusion Criteria	Adults 18 years or older who had at least 2 SIRS criteria, and who had either refractory hypotension or a lactate > 4mmol/L
4. Exclusion Criteria	Patients with acute CVA, ACS, pulmonary edema, major arrhythmia, status asthmaticus, active GI hemorrhage, seizure, drug overdose, burn, trauma, need for immediate surgery, CD4 <50, an advanced directive that would restrict the protocol, contraindication to CVC, likelihood of refusing blood transfusion, a physician who believed resuscitation to be futile, pregnancy, involvement in another investigational trial, or transfer from another hospital
5. Interventions Compared	1. EGDT – Original Rivers bundle, which included placement of a Central Venous Catheter (CVC) to monitor pressure and Scvo2 and to give IVFs, vasopressors,

	Dobutamine, or PRBCs. The amount and timing of IVF was specified. 2. Protocol-based standard therapy- (a set of 6 hour resuscitation guidelines, but less aggressive than the Rivers bundle) adequate peripheral venous access, IVF and vasopressor administration to achieve adequate systolic blood pressure, fluid status and hypoperfusion was assessed at least each hour, blood transfusion provided if Hgb was < 7.5g/dL, 3. Usual Care – Bedside physicians directed all aspects of care without any protocol or prompting
6. Outcomes Evaluated	1. Primary Outcome – rate of 60 day all cause mortality 2. Secondary Measures include- mortality at 90 days, mortality at 90 days to one year, need for organ support (i.e. cardiovascular failure, respiratory failure, acute renal failure), duration of hospital stay, duration of ICU stay, and hospital disposition
B. Are the results of the study valid? Answer questions below	
1. Were patients randomized?	Yes. Used a web based program with variable block sizes of 3, 6 or 9
2. Was randomization concealed (Blinded)	Yes, the randomization was properly blinded so allocation concealment was achieved regarding assignment of groups.
3. Were patients analyzed in the groups to which they were randomized?	Yes. All groups were analyzed using the "intention-to-treat" analysis.
4. Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Age, gender, Apache score, lactate levels, blood pressure were all evenly matched between groups.
C. Did experimental and control groups retain a similar prognosis after the study started (answer the questions below)?	

1. Were patients aware of group allocation?	Yes. As an open label, patients would be aware of interventions. Hard to say if this would predispose to bias in that this was a sick patient population and parameters that were assessed were not subjective on the part of the patient response.
2. Were clinicians aware of group allocation?	Yes. This could present a problem regarding performance bias on the part of the physicians.
3. Were outcome assessors aware of group allocation?	Uncertain. There is no specific mention of who the outcome assessors were. The fact that outcomes being assessed were fairly objective may protect from bias here as well.
4. Was follow-up complete?	Yes. In hospital death by 60 days was primary f/u and did not differ between the groups. A small percentage of patients that was equally distributed between the groups was lost to 90 day f/u
D. What were the results?	
1. How large was the treatment effect? (difference between treatment and control group).	1) Primary Outcome: In hospital death at 60 Days no sig. difference. EGDT Group – 21.0% 60 day mortality Protocol based standard therapy – 18.2% Usual Care – 18.9% p=0.83 There was no statistically significant difference in mortality between the three groups at 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). 2) The only secondary outcomes that were statistically significant were an increase in ARF in the Protocol-based standard therapy group as compared to usual care 6.0% v. 2.8%, p=0.04 and an increase in the ICU stay in the EGDT group compared to the usual care group 91.3% v. 86.2%, p=0.01
2. How precise was the estimated treatment effect at a 95% confidence interval?	The Relative Risk of any protocol-based treatment compared to usual care was

	1.04% with a 95% CI of 0.82-1.31; p=0.83
D. How can I apply the results to patient care	
IV. Were the study patients similar to my patients?	Yes. SNGH is an academic ED in the US. It is likely that the patients in this study would be similar enough that this study would be relevant to my patients.
1. Were all clinically important outcomes considered?	Yes. Death, length of stay, organ failure, time to discharge all included. Did not do a cost analysis or a quality of life assessment. I find this study applicable. Serial lactate levels could also have been trended as a secondary measure as it is a good surrogate for improvement.
2. Are the likely treatment benefits worth the potential harms and costs?	No. EGDT is definitely not worth instituting, as there is not a proven benefit and potential harms of placement of a catheter. Using CVCs on every patient could introduce harm and is often unnecessary. The same can be said for inotropes and vasopressors. All of these are also costly. Allowing for the clinical judgement of the physician provides similar efficacy, and without introducing potential costs and harm that can be uncured by unnecessary treatments.

Limitations:

1. It cannot be known how well physicians adhered to protocols that were in the protocol-based groups. Also, being open label predisposes to performance bias.
2. There was a dedicated team to assist in the management of patients in two groups which is not typical of usual practice in most ED's
3. Power was limited to address whether or not certain treatments would prove more effective within certain subgroups; a greater sample size would have been required

4. The majority of patients prior to enrollment (3 hrs.) received aggressive fluid resuscitation, which may have reduced benefits of EGDT as it is not that "early" any longer in the resuscitation.
5. Results clearly applicable to academic institutions. Unclear if same effects would apply to community setting.

Clinical Bottom Line: Large multi-centered academic trial. Appears to demonstrate no benefit to EGDT or protocol driven treatment in patients after 3 hours of "usual care". Early fluid resuscitation and antibiotics may be identified as highest yield interventions in this patient population. So, if patients are identified as having sepsis early, given IVF and antibiotics early, then the pathway chosen, albeit EGDT, protocol-driven, or usual care doesn't matter so much as to mortality or survival.