EVMS Emergency Medicine Journal Club
Therapy Worksheet

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CITATION: Mouncey et al., Trial of Early, Goal-Directed Resuscitation for Septic Shock. N Engl J Med 2015;372:13011-11. ProMISe trial.

A. What is being studied? (Answer below)	**Comments**
1. Study Objective	1. To compare 6 hours EGDT vs usual care for pt w/ early septic shock to the ER in National Health Service Hospitals in England. 2. To provide additional data comparing EGDT vs usual care and allow meta analysis of three major modern trials comparing EGDT vs usual care.
2. Study Design	Multi center, prospective*, open label randomized trial in 56 ER's in England that did not routinely use EGDT. Total of 1260 subjects enrolled, 1251 in initial analysis and 1243 in final outcome analysis *Data obtained prospectively in EGDT and retrospectively in usual care
3. Inclusion Criteria	1. Adults; 18 years or older 2. Within 6 hours of presentation 3. Known or presumed infection 4. 2 or more SIRS criteria 5. Refractory hypotension (SBP < 90 or MAP < 65) despite at east 1 L IVF within 60 minutes or hyperlactatemia (greater than or equal to 4)
4. Exclusion Criteria	Did not explicitly state
5. Interventions Compared	Either EGDT vs. Usual care EGDT: resuscitation protocol for 6 hours

	(see handout), central venous catheter placed Usual care: per treating clinician All pts. received antimicrobials prior to randomization.
6. Outcomes Evaluated	Primary: all cause mortality at 90 days Secondary: 1. Sequential organ failure assessment (SOFA) at 6 and 72 hours 2. Receipt of advanced support and number of days free from such support in the first 28 days (cardiovascular, advanced respiratory, or renal) 3. LOS (ED, ICU, hospital) 4. Duration of survival 5. All cause mortality at 28 days, hospital discharge, and 1 year 6. Health related quality of life 7. Resource use 8. Costs at 90 days and 1 year Adverse events measured up to 30 days
B. Are the results of the study valid? Answer questions below	
1. Were patients randomized?	Yes, 1:1 ratio by means of 24 hour telephone randomization, permuted blocks w/ variable block lengths, stratified according to sit
2. Was randomization concealed (Blinded)	Yes. The randomization scheme was blinded by the use of a centralized phone system insuring proper allocation concealment.
3. Were patients analyzed in the groups to which they were randomized?	All analyses were conducted according to intention-to-treat principle.
4. Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes except for age; pt.'s receiving usual care was slightly younger than pt.'s receiving EGDT. Looking at figure 1 I am not sure this is clinically significant. Gender, sepsis criteria, Apache II, VS, SOFA score and infection sites all similar

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. Study states blinding was not possible, don't think it was possible to blind pt.'s given the consents needed for the procedures/transfusions related to EGDT. Measures were non-subjective and patients were sick so likelihood of performance bias from patient is low.
2. Were clinicians aware of group allocation?	Yes. In this case performance bias may be more relevant
3. Were outcome assessors aware of group allocation?	Unclear. No mention if outcome assessors were aware of group allocation. Objective outcome measures protect somewhat from assessor bias.
4. Was follow-up complete?	Complete follow up was 81% in both groups Primary analysis was completed in 623/625 in EGDT and 620/626 in usual care
D. What were the results?	
1. How large was the treatment effect? (difference between treatment and control group).	Primary outcome: all cause mortality at 90 days EGDT 29.5% vs. usual care 29.2 (not significantly different) p = 0.90; RR = 1.01, (95% CI 0.85-1.20). Secondary: **1.** Sequential organ failure assessment **(SOFA) at 6 hours= EGDT 6.4, UC 5.6 (p < .001) (baseline SOFA score not significantly different) SOFA score takes into consideration BP and pressors this may artificially increase SOFA score.** 72 hours: NSD 4.0 vs. 3.7 p=0.056 2. Receipt of advanced support and number of days free from such support in the first 28 days **Cardiovascular: EGDT 37% UC 30.9% (p =.026)** Advanced respiratory: NSD

	Renal: NSD Days free: NSD in any category 3. Median LOS In the ED: NSD **ICU: EGDT 2.6 UC 2.2 (p = .005)** Hospital: NSD 4. Duration of survival NSD 5. All cause mortality at 28 days: EGDT 24.8 UC 24.5 NSD Hospital discharge: EGDT 25.6 UC 24.6 NSD RR 1.01, (95% CI 0.83-1.23) or death prior to hospital discharge RR 1.04, (95% CI 0.86-1.23). 1 year: 6. Health related quality of life NSD 7. Resource use 8. Costs at 90 days: EGDT $17647 UC $16239 p = .26) 1 year: Adverse events EGDT 4.8% UC 4.2% (p = .58)
2. How precise was the estimated treatment effect at a 95% confidence interval?	No treatment effect ARR 1.01 (.85-1.2) P value .90
D. How can I apply the results to patient care	
IV. Were the study patients similar to my patients?	Maybe. UK study so patient characteristics may be different. Similar to our community settings as opposed to our tertiary care hospital.
1. Were all clinically important outcomes considered?	Yes.
2. Are the likely treatment benefits worth the potential harms and costs?	No, EGDT has more interventions, uses more cardiovascular support, has a longer ICU LOS, trends toward being more expensive, trends to having more adverse

	events and has not shown a mortality or quality of life benefit

Limitations:
Lower than expected mortality; questions applicability to high mortality settings
Open label trial may bias clinicians in their management of the groups they favored.
Majority of patients received fluid resuscitation prior to enrollment in the study. This intervention may negate other favorable effects of EGDT. Patients were likely less ill when enrolled as compared to Rivers data.

Clinical Bottom Line:
EGDT appears to have no benefit over modern usual care for early sepsis care in the emergency department. Early recognition, aggressive fluid resuscitation and antibiotics may be interventions of greatest impact.