



Article Appraisal

Article: The ProCESS Investigators. A Randomized Trial of Protocol-Based Care for Early Septic Shock. N Engl J Med. 2014 Mar 18. [Epub ahead of print]. DOI: 10.1056/NEJMoa1401602

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Resident Reviewer Name(s) and Residency Affiliation: Dr. Nicolle Holm, PGY2, RCPS-EM Residency Program

Faculty Methodology/Biostatistics Resource Person: Dr. Riyad Abu-Laban

Background and Study Objective(s)	In 2001, Rivers et al. found mortality benefit from instituting a 6-hour early goal directed therapy (EGDT) sepsis protocol based in a single urban ED. Many studies since have questioned this, and more specifically questioned whether all elements of EGDT are necessary. The objective of this study was to determine whether or not protocol based resuscitation superior to usual care, and whether or not a protocol with CVC monitoring to guide resuscitation is superior to a simpler protocol
Study Design	This was a multi-center trial carried out at 31 academic/tertiary centers comparing resuscitation strategies in 1341 patients. Inclusion criteria were: 18 years of age, ≥ 2 SIRS criteria and refractory hypotension or lactate ≥ 4 . Patients were randomized by a 1:1:1 ratio to EGDT, protocol based care (clinical judgment with guidelines) or a usual care group. The primary outcome was in hospital mortality at 60 days.
Results	Patients were well matched and protocol adherence was good. EGDT patients received more central lines, dobutamine infusions and transfusions but in the end, there were no significant differences between groups for any of the outcomes, including mortality.
Validity of Results	Clinical coordinator/investigators were unaware of results until data was locked. However it was noted that a Hawthorne effect could be at play, given the fact physicians were aware that data was being collected. It was also noted that the authors reduced sample size when mortality was lower than anticipated, there was discussion at Journal Club over the fact that this actually decreased the ability of the study to find the relative improvement that was deemed clinically significant (despite the author's mathematically correct, but misleading assurances that with a smaller sample size the power was unchanged for the same absolute improvement). It was also noted that the trial faced challenges with enrollment, thus undoubtedly encouraging the investigators to justify early termination.
Generalizability of Results	The results were felt to be generalizable to tertiary care center where resources are available like they were at these centers. However it was noted that "usual care" is not necessarily the same in this study as in non teaching centres. Moreover, even at Canadian academic centres care likely differs, as illustrated by the 44% rate of vasopressor use in the usual care group. It was noted that the study patients were less sick than in the original Rivers study. An important take home, though, was felt to be that usual care had EP directing care, while other groups had entire sepsis team, and no difference was found!
The Bottom Line	This trial re-affirms that early recognition of sepsis, early administration of antibiotics, early adequate volume resuscitation and clinical assessment of circulation by an attentive physician (even without an entire team) are all essential to reduction in mortality associated with sepsis. Protocolized therapies mandating central venous monitoring and ScvO2 are not necessary in all patients, although they may still be valuable in selected groups.