

September 2015 Phoenix Critical Care Journal Club: Goal-Directed Therapy and DNR

Three articles were selected for this month's journal club. Two dealt with early goal-directed therapy for sepsis and came to essentially opposite conclusions. The third dealt with do not resuscitate (DNR) orders. Both topics are important to critical care physicians and have led to the development of guidelines.

Rhodes A, Phillips G, Beale R, et al. The Surviving Sepsis Campaign bundles and outcome: results from the International Multicentre Prevalence Study on Sepsis (the IMPReSS study). *Intensive Care Med.* 2015;41(9):1620-8. [\[CrossRef\]](#) [\[PubMed\]](#)

This was a prospective, observational, quality improvement study of compliance with the surviving sepsis campaign 3 and 6 hour bundles in patients with either severe sepsis or septic shock. The 3 hour bundle consists of measurement of lactate, obtaining blood cultures, administering broad spectrum antibiotics and administration of 30 mL/kg crystalloid for hypotension. The 6 hour bundle is composed of repeating the lactate, vasopressors for hypotension, measuring central venous pressure, and measuring central venous oxygen saturation. A total of 1794 patients from 62 countries were enrolled in the study with either severe sepsis or septic shock. Compliance with the bundle metrics was not high. Overall compliance with all the 3-h and 6-h bundle metrics was 19 % and 36% respectively. Compliance with the 3-h and 6-h bundles was associated with lower hospital mortality than non-compliance ($p < 0.001$, both comparisons). Patients whose care included compliance with all of these metrics had a 40 % reduction in the odds of dying in hospital with the 3-h bundle and 36 % for the 6-h bundle.

The only therapeutic guidelines in the bundles are to administer antibiotics and to support the blood pressure first with fluids and then vasopressors if fluids do not correct the hypotension. Unless one rejects the germ theory, the only real therapeutic option is whether to administer fluids and/or vasopressors, or essentially early goal-directed therapy.

Angus DC, Barnato AE, Bell D, et al. A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISE Investigators. *Intensive Care Med.* 2015;41(9):1549-60. [\[CrossRef\]](#) [\[PubMed\]](#)

This was a meta analysis of the five randomized clinical studies of early goal-directed therapy for sepsis ($n = 4735$ patients). There was no effect on the primary mortality outcome ($P = 0.9$). The authors conclude that early goal-directed therapy is not superior to usual care for patients with septic shock but is associated with increased utilization of ICU resources.

In the context of the first study by Rhodes et al., one wonders how can this be? The first study found a statistically significant mortality benefit while the later study did not. This points out to a common problem evaluating medical literature-different study techniques

measuring slightly different variables coming to different results. The first study was an observational study, while the later used randomized studies. The first study was by a group who promoted sepsis guidelines and has been accused of significant conflicts of interest over the use of activated protein C (1). Furthermore, the authors repeatedly overstated the evidence basis and benefits of the bundles. This weakens the authors' argument and makes one question whether there is confirmation bias or the tendency to interpret new evidence as confirmation of one's existing beliefs or theories. Of note is that the first author of the later article, Derek Angus, is a former member of the surviving sepsis campaign.

In our own groups we have differing opinions over early goal-directed therapy. However, regardless of our opinions, the evidence is conflicting and it is hard to fault usual care instead of goal-directed therapy in sepsis. In other words, early goal-directed therapy does not meet the evidence basis for a guideline at this time.

Fendler TJ, Spertus JA, Kennedy KF, et al. Alignment of do-not-resuscitate status with patients' likelihood of favorable neurological survival after in-hospital cardiac arrest. JAMA. 2015;314(12):1264-71. [\[CrossRef\]](#) [\[PubMed\]](#)

This was a prospective observational study to assess whether patients' or families' decisions for do-not-resuscitate (DNR) orders after a successful resuscitation from in-hospital cardiac arrest are aligned with the patient's expected prognosis. The authors identified 26,327 patients with return of spontaneous circulation after in-hospital cardiac arrest between. Each patient's likelihood of favorable neurological survival (i.e., without severe neurological disability) was calculated. DNR orders after in-hospital cardiac arrest were generally aligned with patients' likelihood of favorable neurological survival. Overall, 5944 (22.6%) patients had DNR orders within 12 hours. This group was older and had higher rates of comorbidities (all $P < 0.05$) than patients without DNR orders. The actual rate of favorable neurological survival was higher for patients without DNR orders than it was for those with DNR orders. This pattern of lower survival among patients with DNR orders was seen in every decile of expected prognosis. However, only one-third of patients with the worst prognosis had DNR orders.

The authors recommend that after patients survive an in-hospital cardiac arrest, discussions should occur about prognosis and preferences for future resuscitative efforts. We all agree but with the caveat that patients and their families do not necessarily follow, or should they be expected to follow, prediction equations for neurological survival. For many DNR is an emotional decision. Furthermore, if the prognosis is quite grim, the physician might not seek a DNR order reasoning the patient is unlikely to survive. There may also be personal or religious conflicts or a lack of confidence in the physician's recommendation for or against a DNR order.

Like the first article on early goal-directed therapy, the authors overstate their case using the phrase "get with the guidelines". The lack of total alliance with the expected neurological outcome is expected given the emotional and stressful situation and the uncertainty that occurs with a prediction equation or scale. Failure to recognize the

many instances where there should be lack of agreement between DNR and expected outcome only reinforces those skeptical of hospitals and physicians motivation. Furthermore, it strengthens the perception that the medical community might be "pulling the plug on grandma" further eroding confidence in the physician.

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Reference

1. Eichacker PQ, Natanson C, Danner RL. Surviving sepsis--practice guidelines, marketing campaigns, and Eli Lilly. N Engl J Med. 2006;355(16):1640-2. [\[CrossRef\]](#)
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