
I think this paper is potentially one of the most important we've reviewed in the past year. Please carefully review it yourself – the following is just a brief summary, with some editorial comment.

The authors set out to prove a fundamental hypothesis – that a fluid bolus is beneficial for children with severe febrile illness with impaired perfusion. Shockingly, (no pun intended), they found the reverse. Fluid bolus therapy significantly increased mortality – with one excess death for every 30 children who received fluid bolus therapy. How can this be?

The study took place in 6 (non-ICU) centers in sub-Saharan Africa. Children up to age 12 were eligible upon presentation with a febrile illness and evidence of impaired perfusion (evidenced by severe tachycardia, weak radial pulse volume, cool extremities, or poor capillary refill), plus evidence of organ dysfunction (impaired consciousness or respiratory distress). The main study group was randomized to receive either 20mL/kg 5% albumin bolus, 20mL/kg saline bolus, or no bolus. Patients in the bolus therapy groups received additional boluses if perfusion did not improve. All patients received otherwise equivalent care including antibiotics and maintenance IV fluids at 2.5-4 mL/kg/hr.

The study was stopped when an interim analysis showed that mortality in the patients receiving bolus therapy was significantly increased. At that time, 3141 patients had been randomized to the main study stratum. The 48-hour mortality was 10.6%, 10.5% and 7.3% in the albumin bolus, saline bolus and control groups (p=0.003 for the comparison of any bolus vs control). The 4-week mortalities were 12.2%, 12% and 8.7% (p=0.004 for bolus vs control). Although study design did not allow precise classification of sepsis in these patients, it appears that most would have at least satisfied criteria for severe sepsis. Thirty-nine percent had serum lactate levels >5 mmol/L.

We used a standardized approach to critical appraisal. The study was found to have unusually high internal validity. It was well-powered, randomized and blinded. Patients were well-matched upon randomization, and were treated equally and with high adherence to study protocol. Follow-up exceeded 97%, and the statistical analysis was based on intention-to-treat. The effect size was large and precise, with a relative risk for death by 4 weeks of 1.45 (95%CI of 1.13 – 1.86). Additionally, the authors demonstrated that excess mortality with fluid resuscitation was consistent across all subgroups, including those based on age, hypotension, lactic acidosis, coma, and microbial pathogens (particularly malaria). This finding is remarkable not only in that it speaks to the validity of the association that these authors uncovered, but also because it shows that fluids were deleterious even in patients in whom we might think they would be most beneficial, e.g., those with hypotension, organ dysfunction and lactic acidosis.
We can only speculate why this might be. The authors propose that the vasoconstrictor response in shock may confer protection by reducing perfusion to nonvital tissues, and that rapid reversal by fluid bolus may induce a reperfusion injury. Rapid fluid shifts caused by bolus therapy might exacerbate capillary leak in the lungs or brain (although the study did not show an increase in pulmonary or cerebral edema in children that received bolus therapy). Recently, it's been recognized that intravenous resuscitation fluids might have direct deleterious immunomodulatory effects. If any of these explanations are valid in African children, there is no reason to believe that they could not also possibly contribute to the pathophysiology of resuscitated septic shock in adults.

The direct external generalizability of this study is poor in relation to the practice of adult critical care in the developed world. Yet few articles in regard to therapy or pathophysiology of sepsis, in any group of patients, approach the internal validity achieved by these authors. This study challenges such an entrenched and fundamental aspect of what we think we know about resuscitation, that it would not likely have even been considered ethical to perform in the US. Therefore, we should take advantage and consider the implications these findings might have on the practice of adult critical care.

Although this study will not have an immediate effect on sepsis resuscitation guidelines for adults, it will should raise questions in the minds of bedside clinicians, and cause investigators to take a step back. The current recommended practice of giving repeated fluid boluses to septic patients in order to achieve a goal central venous pressure is particularly vulnerable in this regard. In many institutions, this practice is now relentlessly driven by protocols that do not require any subsequent bedside evaluation by the physician.

In a wider context, this paper represents another stepping stone in the history of the evidence-based practice of Critical Care Medicine over the past 40 years – particularly in regards to the therapy of sepsis and associated multisystem organ failure. It is my observation that this history can be characterized by several generalizations: 1) initially promising therapies are ultimately proven to be disappointing; 2) less aggressive support measures are generally found to be superior to more aggressive strategies. [More on this topic in an upcoming editorial]

Robert A. Raschke MD, Critical Care Journal Club Editor


Numerous organizations use performance measures to monitor the quality of care. An appraisal of the evidence underlying such performance measures has never been reported. The authors’ objective was to estimate the effects of interventions recommended by performance measures and to determine the
quality of evidence from which those estimates derive, using the Joint Commission and the Centers for Medicare and Medicaid Services’ performance measures for community-acquired pneumonia (CAP) as examples.

The authors performed systematic reviews of the literature to identify evidence related to the performance measures for CAP which are listed below:

1. Pneumococcal vaccination
2. Smoking cessation counseling
3. Influenza vaccination
4. Blood cultures
5. Antibiotics within 6 hours
6. Guideline-compliant antibiotics

Metaanalyses were then performed to estimate the absolute and relative effects of the interventions recommended by the performance measures. The Grading Recommendations, Assessment, Development, and Evaluation system was used to determine the quality of evidence. Among these performance measures, only influenza vaccination was supported by high-quality evidence. One-step smoking cessation counseling was contradicted by moderate-quality evidence (smoking quit rate: RR, 1.05; 95% CI, 0.90–1.22).

The results suggest that the estimated effect usually favors the intervention that is recommended by the performance measure, but the evidence is frequently not high quality. This implies that there is uncertainty about the balance of desirable and undesirable effects of the intervention. Wilson and Schunemann believe that “…when such uncertainty exists, there should be other compelling factors that favor the intervention if it is going to be recommended by a performance measure”. We could not agree more.

The authors of the article did not have the opportunity of reading a recent article by Attridge et al. (reviewed in the May, 2011 Pulmonary Journal Club) which demonstrated an increased mortality when the ATS/IDSA antibiotic guidelines were followed (1,2). We could quibble about the beneficial effect of the other guidelines, but regardless, it would appear that their benefit is weak, and in the case of smoking cessation, potentially harmful.

The importance of this manuscript not only lies in the quality of the investigation but in the prestige of the authors. Wilson is the Deputy Editor — Pulmonary, Critical Care, and Sleep Medicine of UpToDate and Schunemann is the Chair of Medicine at McMaster University. He is also one of two chairs of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group and editor-in-chief of Health and Quality of Life Outcomes and co-convenor of the Applicability and Recommendations Methods Group of the Cochrane Collaboration. Criticism of a widely used guideline by such eminently qualified investigators should have some influence on the policy makers who implement these guidelines prior to doing the necessary investigation to ensure the guidelines’ evidence basis.
References
