April 2012 Critical Care Journal Club

Present: Most all the fellows, Dr. Robbins, Singarajah, Bajo, Raschke and Gerkin

This month we looked at 7 articles, so the ground rules were to be concise and try to pick out just one or two take-home points from each article.

Hilton AK, Bellomo R. A critique of fluid bolus resuscitation in severe sepsis. Critical Care 2012;16:302-7.

A fascinating and provocative editorial that takes a strict evidence-based approach to appraisal of the use of IV fluid boluses for septic shock. The authors make a number of valid but seemingly heretical statements. We all give fluid boluses to patients with septic shock in the belief that their cardiac output is compromised and that fluid administration will restore tissue perfusion resulting in improved clinical outcomes. However the authors point out that none of the assumptions in this approach are proven. Furthermore, the adverse effects of liberal fluid resuscitation are clearly demonstrated by a large randomized controlled trial in patients with ARDS, and by the only RCT that looked at IV fluid bolus therapy in severe infections – the FEAST trial published in NEJM in 2011 – that showed fluid boluses *increased* the mortality of severely ill African children. The authors make the provocative statement that it is possible that the hypotensive state of septic shock might actually be a protective mechanism, and that artificially perturbing it should not be assumed to be beneficial without study. They suggest ongoing research comparing our standard approach to IVF bolus resuscitation with a more fluid conservative approach that employs earlier use of pressor agents to maintain blood pressure.

This paper is bravely written and should stand as a reminder to us of how little we really know, and how cautious we should be when standardizing care based on incomplete knowledge. I also hope this editorial might encourage our fellowship to consider performing the clinical trial that Hilton and Bellomo suggest.

Garcia MIM et al. Non-invasive assessment of fluid responsiveness by changes in partial end-tidal CO2 pressure during a passive leg-raising maneuver. Ann Intensive Care 2012;26:2-9.

This study showed that an increase of $\geq$5% in end-tidal CO2 triggered by a two-minute leg raising maneuver accurately predicted fluid-responsiveness (defined as a 15% increase in cardiac output in response to a 500mL colloid infusion), with a sensitivity of 91% and a specificity of 94%.

Taken in context with the previous editorial, this study provides additional background that might be useful in a clinical trial of fluid resuscitation in septic shock. It would be relatively easy, and non-invasive to assess fluid responsiveness by this technique, and the weight of evidence points strongly to

the assertion that dynamic measures of fluid responsiveness are superior to static measures such as the CVP. The problem pointed out by Bellomo is this – even if a patient is fluid responsive, we have not proven that an increase in cardiac output of uncertain duration outweighs the potential detriment of fluid overloading the patient.

Jakob SM et al. Dexmedetomidine vs. Midazolam or propofol for sedation during prolonged mechanical ventilation. JAMA 2012;307:1151-60.

This study reported the results of two multicenter randomized controlled trials comparing long-term sedation with dexmedetomidine to midazolam and to propofol respectively in a total of 998 adult ICU patients receiving mechanical ventilation. All three drugs provided good sedation. In the comparison between midazolam and dexmedetomidine, median length of mechanical ventilation was about 40 hours longer with midazolam p=0.03, but dexmedetomidine had more associated hemodynamic side effects of hypotension 21 vs. 12%, p=0.007 and bradycardia 14 vs. 5%, p<0.001. In both comparisons, patients receiving dexmedetomidine were somewhat more interactive while under sedation. All other comparisons between propofol and dexmedetomidine were equivalent.

We applied the User's Guide's to Critical Appraisal and uncovered one concern regarding the conduct of the study – there were 11,911 patients receiving mechanical ventilation, but only 1001 (5%) met inclusion and exclusion criteria of the study. The external generalizability of the findings is certainly eroded by excluding 95% of potential participants.

We didn't feel this study added much to what we already know. Increasing evidence suggests that prolonged use of benzodiazepine sedation in the ICU might contribute to ICU delirium and prolong mechanical ventilation. The near equivalence of dexmedetomidine and propofol in this study is not much of an argument for the added cost of dexmedetomidine.

Carlisle JB. The analysis of 169 randomised controlled trials to test data integrity. Anaesthesia 2012; doi: 10.1111/j.1365-2044.2012.07128

This fascinating article was brought to our attention by Steve Curry.
The author analyzed 169 randomized controlled trials published by a single author in the field of anesthesia over a 20-year period. He found many instances in which the distribution of data reported in the studies were statistically as unlikely as 10^{-33} power of having occurred naturally. It's hard to imagine how such results could have been anything but fabricated, although I am not aware whether the original researcher had a chance to reply to the implicit accusation.

I was trying to get my mind around the magnitude of the number 10^{33} and I noted that our entire solar system weighs about 2×10^{33} grams.

Albert RK. The role of ventilation-induced surfactant dysfunction and atelectasis in causing acute respiratory distress syndrome. Am J Respir Crit Care Med 2012;185:702-8.

The author puts forth a theory and supporting evidence regarding the etiology of ARDS. Essentially he posits that ARDS is an iatrogenic disease, largely caused by our practice of sedating patients and confining them to supine bedrest with inadequate PEEP. The resulting alveolar collapse causes surfactant dysfunction and atelectasis that underlie ARDS. I don't think any of us were completely sold on this theory, but I think we all recognize that less sedation, and adequate PEEP are important aspects of good practice. Although proning might one day be proven clinically preferable to supine bedrest, many practical concerns make it difficult and costly to consider as part of routine care. More evidence is required in this respect.

Streiner DL et al. Mine is bigger than yours: Measures of effect size in research. Chest 2012:141:595-598.

A single take-home point: be careful when authors report results such as a "10% reduction in mortality p=0.05". Although statistically significant, the clinical importance of relative risk reduction is not clear until you also consider the *absolute* risk reduction. If the mortality in the control group of this hypothetical study is only 1%, then a 10% reduction, down to 0.9% represents only a 0.1% absolute risk reduction – a very small effect size. Such a result can become statistically significant if the sample size of the study is large. Calculation of the number needed to treat (NNT = 1/absolute risk reduction) reveals that 1000 patients would have to be treated to prevent one death in this example.

Grasso S et al. ECMO criteria for influenze A associated ARDS: role of transpulmonary pressure. Intensive Care Medicine 2012;38:395-403.

Briefly, this study with only fourteen patients showed that half had significant bellows stiffness that contributed to high airway pressures during mechanical ventilation. This is potentially clinically important because measurement of esophageal pressures and calculation of transpulmonary pressures demonstrated that higher levels of PEEP could be tolerated in these patients without exceeding the upper physiological limit of transpulmonary pressure. Increased PEEP guided by this method allowed the patients to achieve acceptable oxygenation status and avoid ECMO.

We discussed the possibility of performing esophageal pressure measurements in our patients to help guide PEEP management. One comment in regard to ECMO. The potential benefit of ECMO in lung failure is not likely related to providing improved oxygenation parameters as these authors suggest. It is not uncommon to tolerate oxygen saturations in the mid 80s for prolonged periods while on ECMO. The potential benefit of ECMO lies in the reduction of ventilator associated lung injury that can be avoided when the ventilator need no longer be relied on to provide all oxygenation support.

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