MARCH 2011 CRITICAL CARE JOURNAL CLUB

I've made the executive decision this month to only fully review the three best papers from Journal club. These three were clearly a notch above the others, and provide plenty of food for thought. I include a brief discussion of "Bland-Altman" plots and the significance of the R-squared statistic in linear regression. These statistical issues were raised by the less-than-exemplary papers on Flo-trac cardiac output monitoring, and fluid resuscitation. I want to begin to review at least one or two biostatistic/clinical epidemiology issues at each Journal club. Bland-Altman plots seem a rather – well – "bland" topic. But actually, once Dr. Richard Gerkin explained them, they made perfect sense (see below).

The three best articles:

Swindell JS, et al. Shaping patient's decisions. Chest. 2011;139:424.

A very good discussion on the concept of autonomy, especially when the accompanying, somewhat contradictory editorial is also considered. Swindell's main points are that the ethical concept of autonomy is difficult to optimally apply in the ICU, and the physician's advice should be considered an ethically-valid addition in decision-making.True autonomy requires more from a patient than simply making a decision. The decision should be intentional - designed to carry out a specific plan, not simply based on intuition, impulse or habit. Autonomy should be founded on an understanding of the consequences of the plan, and its alternatives, and it should be free from undue influences (external and internal). These conditions are difficult, or even impossible for a patient to achieve in the ICU.

Studies show that patients generally *want* the physician to give them advice, and that this desire increases as they become sicker. It is also the physician's responsibility to consider other, possibly conflicting, ethical concerns. These might include issues of beneficence and social justice.

This paper was not meant to refute the primacy of patient autonomy, but to bring out it's limitations in the ICU setting. Intensivists should do their best to support sound decisions based on autonomy. But an appropriate degree of paternalism is likely to benefit many patients and their families. Personally, I feel it is the responsibility of the intensivist to offer the patient and family firm advice when they are struggling with decisions in the midst of critical illness. When properly accomplished, this can improve the soundness of the decision, and help take some of the emotional burden of the consequences off the patients/family's shoulders.

Waterer et al. Management of community-acquired pneumonia in adults. Am J Respir Crit Care Med. 2011;183:157.

A good update on CAP. Several key points:

Up to 50% of ICU admissions for CAP were initially admitted to the floor, and these patients suffer a higher mortality than those admitted directly to the unit. Therefore clinical scoring tools to predict mortality risk are theoretically beneficial if they could help clinicians identify high risk patients that don't obviously require ICU care. There are a number of different scoring systems being tested. The IDSA/ATS minor criteria (outlined below) seem to perform fairly well, but no scoring system to date has prospectively led to improved patient outcomes.

"IDSA/ATS minor criteria" for severity of CAP.

(3 or more criteria predict severe illness warranting ICU admission)

- Respiratory rate ≥30 breaths/min
- PaO_2/FiO_2 ratio ≤ 250
- Multilobar infiltrates
- Confusion/disorientation
- Uremia (BUN ≥ 20 mg/dL)

- Leukopenia (WBC count < 4000 cells/mm3
- Thrombocytopenia (platelet count < 100,000 cells/mm^3)
- Hypothermia (core temperature ≤ 36°C)
- Hypotension requiring aggressive fluid resuscitation

Research on biomarkers has progressed. The role of procalcitonin is further clarified. It cannot be relied upon to distinguish viral from bacterial pneumonia as once believed. Currently no biomarker has been shown to improve the predictive value of clinical scoring tools described above.

The authors present a series of references on the duration of antibiotic therapy for mild-moderate CAP that suggest that 5 days or less of antibiotics is adequate treatment in most cases. One study even showed that a single dose of antibiotics cured 70% of mild – moderate cases of CAP.

Evidence is accumulating however that two antibiotics are better than one in the treatment of *severe* CAP. Mortality is clearly associated with empirical choice of antibiotics that cover the offending organism – two antibiotics are more likely than one to achieve this coverage. In this regard, an increasing body of evidence suggests that macrolides are superior to fluoroquinolones and other agents as the second antibiotic. This may not be directly related to the sensitivity of infecting organisms to macrolides. Macrolides have other favorable qualities that might influence survival, including anti-inflammatory properties, and the ability to directly inhibit certain bacterial virulence factors.

The authors reviewed research on clinical care processes being implemented in an attempt to improve outcomes. In some instances, efforts to improve outcomes by altering intermediate process variables are based on flawed logic. For instance, efforts to speed up the time it takes to administer the first dose of antibiotics have shown no benefit, and resulted in serious negative effects including over diagnosis of CAP, overuse of antibiotics, and increased antibiotic toxicity including *C. difficile* colitis. The authors point out that there may be valid reasons to delay antibiotic therapy in patients with multiple comorbidities, as physicians struggle to sort out a proper diagnosis. Comorbidities, such as CHF and COPD, that may confuse the diagnosis of CAP, are independently associated with mortality, and therefore confound our understanding of the relationship between antibiotic timing and survival. True clinical outcomes, such as severity-adjusted mortality, should remain the primary standard by which good care is measured.

Finally, the authors review the long term consequences of CAP. Studies show that survivors of CAP suffer a doubling of subsequent mortality for as long as two years post discharge. This might be due to an increase in cardiovascular deaths. It's possible that the inflammatory response to CAP leads to long-lasting changes in coronary plaque that increase the chances of plaque rupture. Further studies in this area are needed.

Volpicelli G. Sonographic diagnosis of pneumothorax. Intensive Care Medicine. 2011;37:224.

Another excellent paper with a manageable number of take-home points.

Studies suggest that the sensitivity of the ultrasound for detecting pneumothorax is actually *better than* an anterior-posterior chest x-ray, and rivals CT scanning.

Specificity is not as good, unless the "lung point" sign is found. This has a specificity of 100%.

Clinicians need to **read this paper** and the accompanying illustrations to better understand how to perform a good ultrasound examination for pneumothorax. I won't try to bypass that necessity, but will mention the four cardinal elements of the exam.

1) Sliding lung. Horizontal movement of lung underlying pleura with respiration. The presence of sliding lung rules strongly against pneumothorax at the anatomical area being examined.

2) B lines. Artifactual vertical bright lines that radiate distally from the pleural surface - B-lines rule strongly against pneumothorax at the anatomical site under exam.

3) Lung pulse. Vertical movement of lung seen when respiration is interrupted. As with the first three findings, it's presence rules pneumothorax out. All three of the above tests are highly *sensitive*.

4) Lung point. Determination of lung point involves ultrasound exam for sliding lung at multiple points across the chest. The lung point is the anatomical site at which sliding lung is found, when it was absent at less dependent sites. The lung point correlates with the least dependent portion of the lung that is not collapsed and still in direct contact with the parietal pleura. Unlike the above findings, lung point is highly *specific* for pneumothorax (strongly rules it in).

The clinical utility of bedside ultrasound is clearly dependent on the experience of the operator. I recommend that our fellows do an ultrasound examination of the lungs, anytime they have the ultrasound in a patient's room for any reason. It is particularly important to practice ultrasound exam of the lungs in all patients with known pneumothorax, if time allows. Becoming comfortable with these findings in controlled situations will enhance the utility of ultrasound in emergencies.

As an aside, I want to plug again for all intensivist groups to be equipped with a good portable ultrasound machine, with cardiac and vascular probes. Our group has accumulated an increasingly positive experience with the use of our ultrasound machine to place central venous and arterial lines, to guide thoracentesis and paracentesis, and to determine the cause of PEA arrest in codes. This article provides a further use –

ultrasound should improve the sensitivity of early detection of spontaneous, ventilator-associated or post-procedural pneumothorax.

Biostatistics comments:

Bland-Altman plots

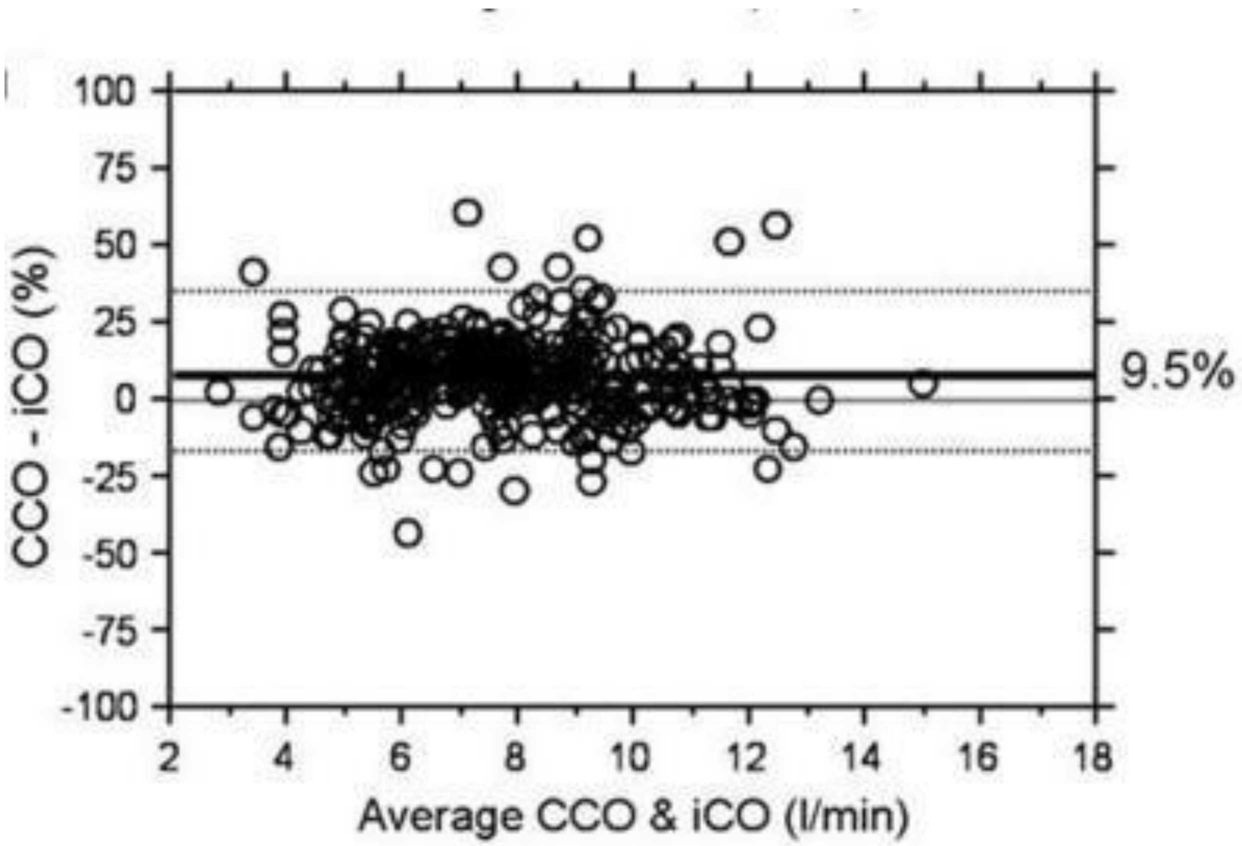
From: Backer DD et al. Arterial pressure-based cardiac output monitoring: a multicenter validation of the third-generation software in septic patients. Intensive Care Med 2011;37:233.

The **Bland – Altman plot** allows comparison of two simultaneous measurements of the same parameter by two methods. Ideally, one method should be the gold standard.

In the plot below, iCO refers injectate cardiac output, determined by thermodilution with a Swan Ganz catheter – the gold standard. CCO refers to continuous cardiac output measured simultaneously by the Swan (without injectate). The idea here is to see how accurately and precisely the CCO measures the cardiac output, compared to the gold standard iCO. Note on the plot, the X-axis is the mean of each of the paired measurements, and the Y-axis is the difference. The result is a graphical display that illustrates accuracy and precision of the CCO measurement.

Overall (mean) accuracy is shown by the solid horizontal line, which illustrates the mean difference. In this case, CCO overestimates iCO cardiac output by 9.5%. This parameter is sometimes called "bias" – in this case the CCO has a 9.5% bias to overestimate iCO.

Precision is illustrated by the spread of the points and their relationship to the two dotted horizontal lines, which represent the 95% confidence intervals of the differences. This facet of the plot shows that in individual data points, the precision of the CCO is pretty poor – commonly off by as much as 30% too high or 20% too low. This doesn't seem too reassuring in light of our recent switch from iCO to CCO Swan Ganz catheters!

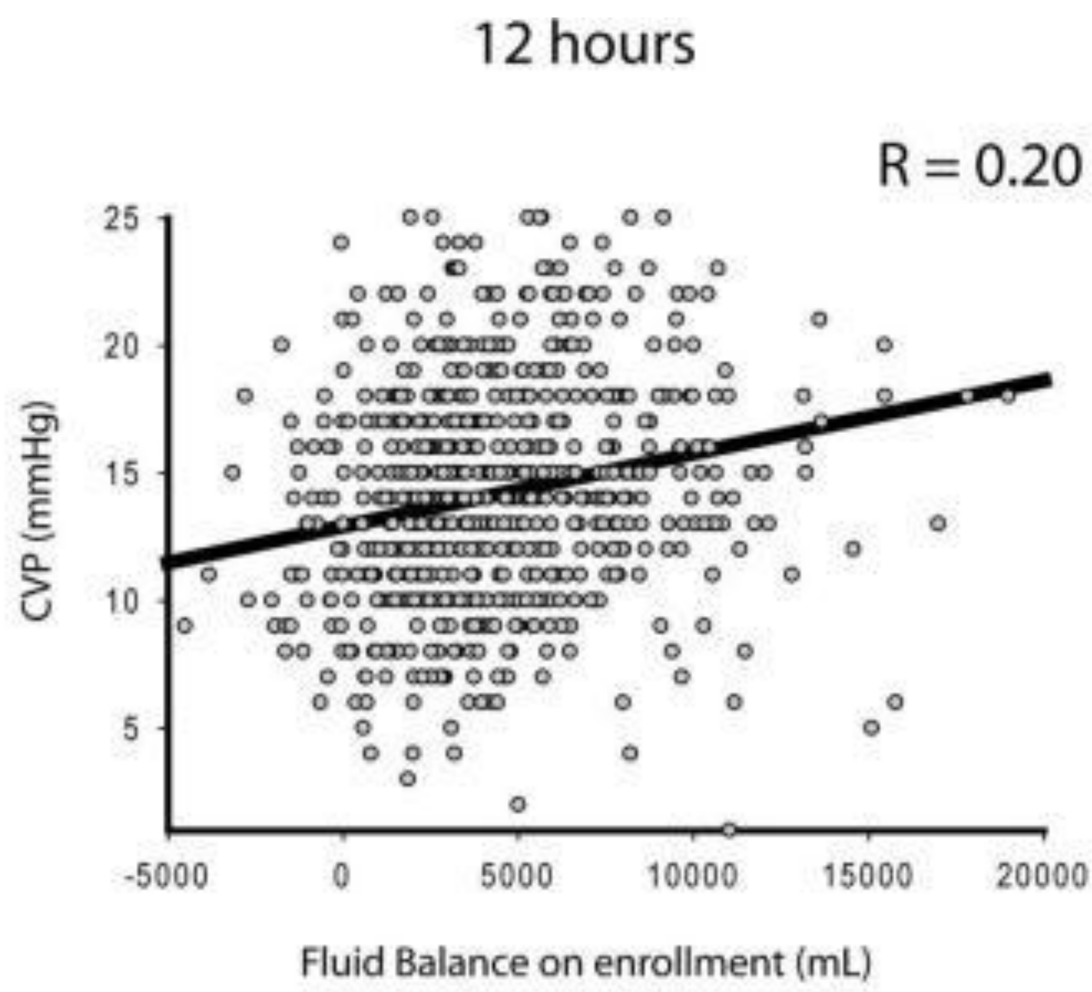


Interpretation of the R^2 statistic in linear regression

from: Boyd JH, et al. Fluid resuscitation in septic shock: A positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med 2011;39:259.

This graph from the paper shows the relationship between CVP and fluid resuscitation in septic shock. The authors state that this relationship is statistically significant - and indeed, the p value is < 0.05. However, to a non-statistician, it looks like they fired a shotgun at a piece of paper to generate the plot. How can this relationship be *clinically* significant?

In linear regression, the R^2 value is often as important as the p value in interpretation of significance. R^2 – in this case: $(0.20)^2 = 0.04$ – gives the percent variation of the *dependent* variable that is explained by changes in the independent variable(s). Thus, this study shows that only 4% of the variability in CVP is accounted for by how much fluid resuscitation the patient received. Even though the relationship is statically significant, it is clearly of no clinical value to try to use such a weak predictor as CVP to guide fluid management. The authors of this paper were incorrect in their conclusions on this point.



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