

## Commentary

# Recently published papers: A number of treatment controversies

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### Abstract

In the present commentary I review some current therapeutic debates. Is noninvasive ventilation going to become the gold standard for acute hypercapnic respiratory failure, and if we have to intubate and ventilate then what is the gold standard for sedation? Old therapies are challenged (e.g. diuretics may worsen outcome) and new ones suggested (e.g. some critically ill patients may benefit from regular erythropoietin). In addition, we must of course mention steroids and sepsis.

**Keywords** respiratory failure, sedation, sepsis, ventilation

### Growing evidence to support non-invasive ventilation

In a report [1] and accompanying editorial [2], the December issue of *Intensive Care Medicine* casts further light on the topical issue of noninvasive positive pressure ventilation (NIPPV) in the critically ill. Dr Elliot's editorial [2] eloquently reviews the evidence for use of NIPPV in ventilatory failure resulting from acute exacerbations of chronic obstructive pulmonary disease (COPD). He highlights the substantial body of evidence demonstrating the advantages of NIPPV in this group of patients, namely a reduction in the need for endotracheal intubation and associated complications (infectious complications in particular), a reduction in both intensive care and hospital duration of stay and consequently health care costs, and even a significantly improved survival rate in one large study [3].

The majority of studies thus far have targeted patients with mild to moderate acute exacerbations of COPD who do not require immediate endotracheal intubation and mechanical ventilation, which most would deem to be the gold standard for management of acute severe respiratory failure. Some have even suggested that in the more severely ill the implementation of NIPPV may deleteriously delay intubation and ventilation, leading to a poorer outcome [4]. In contrast Conti and coworkers [1] targeted a sick group of patients, as evidenced by their mean pH of 7.2 and failure of standard

medical therapy following initial improvement on the emergency ward. Having met predetermined criteria for mechanical ventilation, patients were randomized to either NIPPV ( $n = 23$ ) or conventional intubation and ventilation ( $n = 26$ ). Strikingly patients were followed up for a total of 1 year.

In contrast to previous investigators, Conti and coworkers failed to show a benefit from NIPPV in terms of duration of mechanical ventilation, duration of hospital or intensive care unit (ICU) stay, and hospital mortality. Importantly, however, no harm was demonstrated either. Over half of the NIPPV group required conversion to conventional ventilation – a much higher percentage than in other studies – but none of these were emergent. Unsurprisingly, patients in this subgroup were sicker than those who did not require conversion.

The NIPPV group did show a trend toward a lower incidence of septic sequelae, in particular a lower rate of ventilator-associated pneumonia, this being consistent with previous work. Most interesting, though, is that 12-month follow up revealed the NIPPV group to have a statistically significant decrease in hospital readmission and need for oxygen supplementation at home as compared with the intubated group. There was even a trend toward improved survival, probably as a result of fewer septic complications.

So what can we conclude? First, the sickest patients are most likely to need conventional intubation and ventilation. Second, however, if these sick patients manage to avoid this then they have improved long-term outcome. Third, a trial of NIPPV appears to do no harm. Consequently, if I turn up at your hospital with an acute exacerbation, please strap the mask on!

To continue the COPD theme, let us turn to a recent article in *Intensive Care Monitor* [5], in which a paper from *Chest* [6] is reviewed. The authors of this paper conducted a retrospective case-controlled study comparing negative pressure iron lung ventilation with face mask NIPPV in patients with acute exacerbations of COPD. The results showed a decrease in mechanical ventilator days and ICU duration of stay in the negative pressure ventilation group as compared with the NIPPV group. Unfortunately, as well as being a retrospective study with the two treatment modalities occurring on separate sites, there was no standardization for either weaning of mechanical ventilation or ICU discharge. So, to quote *Intensive Care Monitor*, 'don't buy an iron lung yet'.

### No consensus on how to sedate

Sedation is an integral part of good critical care but a neglected one, particularly by doctors. Which agent(s) should be used, and how much and how often? These are important questions but they are not easily answered. Anxiolysis, analgesia, amnesia and sedation are just a few of the elements to be considered. It is now widely accepted that unbridled sedation, given with best of intentions, is harmful in terms of ventilator and ICU days and consequently outcome, and that a sedation protocol including daily cessation of sedative agents is of benefit. However, is any one agent or group of agents superior to the others? A systematic review of the literature addressing this very question was recently published in *Critical Care Medicine* [7].

A total of 15 randomized controlled trials that compared agents given to predominantly medical ICU patients undergoing mechanical ventilation fulfilled the authors' criteria [7]. A wide variety of outcome measures were employed, including costing, quality of sedation, haemodynamic stability and time to extubation, among others. Unsurprisingly, the studies showed wide clinical heterogeneity and this precluded formal statistical analysis. Although the authors were able to draw some definitive conclusions (e.g. recovery from sedation is faster with propofol than with midazolam), the lasting impression from the review is the lack of consensus on which, if any, agent is best and the wide variability on what is considered to be a good measure of best sedation. It is probably a case of not what you use but how you use it that really matters.

### Diuretics in acute renal failure and the benefits of erythropoietin

For those who have never administered a large dose of diuretic in a desperate attempt to pretend that a patient has

not developed acute renal failure (ARF), please feel free to cast the first stone. In a paper published in November [8], it was concluded that diuretics in critically ill patients with ARF was associated with increased risk for death and nonrecovery of renal function. It is true to say that there is scant evidence to support any beneficial effect of diuretics on outcome from ARF, but until now there was little to suggest a possible harmful result other than in some specific scenarios such as in radiocontrast nephropathy. However, a word concerning the methodology of this study is warranted. It is a prospective cohort study employing a maelstrom of statistics that leave me feeling quite inadequate; 'multivariable logistic regression ... using backward variable selection, with variable exit criteria', and 'residual confounding and selection effects were addressed using propensity scores' is a small sample. I do not and could not dispute the mathematical correctness of this but it does sound familiar. Connors and coworkers in 1996 [9] associated the pulmonary artery catheter with increased mortality using similar methodology; the dispute resulting from that assertion reverberates to this day. As with the pulmonary artery catheter story, it is possible that the intervention group (in this case receiving diuretics) is intrinsically the sicker and that this is not adequately adjusted for; this the authors acknowledged. In the study the diuretic group were older, with an increased incidence of cardiovascular and respiratory failure, although there was no statistically significant difference in mean Acute Physiology and Chronic Health Evaluation III scores between the two groups.

If this observation is real, then direct diuretic renal toxicity is one possible explanation. A more intriguing suggestion is the possibility of diuretic responsiveness imbuing a false sense of security, resulting in delayed renal replacement therapy. However, in the study reported by Mehta and coworkers [8] it was the diuretic nonresponders who largely bore the burden of increased risk. With this in mind, the report suggests that this phenomenon may be used to risk stratify patients in early ARF (i.e. diuretic nonresponders should receive renal replacement therapy sooner rather than later). A large randomized trial is needed to investigate this further. As things stand at the moment at best, we can state that an association between diuretic use in ARF and poor outcome has been shown but no causality proven.

To transfuse or not to transfuse is often a debatable issue. Following some very significant publications over the past few years [10], it appears good practice to avoid unnecessary allogenic red blood cell (RBC) transfusion. The critically ill are at high risk for receiving RBC transfusion [11], and this is partly due to bone marrow impairment and inappropriately low plasma erythropoietin levels. The results of a large, multicentre, randomized, placebo-controlled trial [12] were published by the EPO Critical Care Trials Group. They randomized a heterogeneous group of critically ill

patients to either receive recombinant human erythropoietin or placebo, and compared need for RBC transfusion and cumulative mortality during the first 28 days. The treatment group contained a significantly increased number of transfusion-independent patients, as well as a reduction in cumulative number of RBC units transfused when compared with placebo patients (a reduction of 19%). In parallel with this, the treatment limb demonstrated a significantly greater increase in mean haemoglobin level from baseline. No differences in 28-day mortality or adverse events were detected. Ventilator days, and ICU and hospital duration of stay did not differ between the groups.

Although no outcome benefit was demonstrated in this trial and the authors admitted that in their study the cost of recombinant human erythropoietin per patient was far in excess of the money saved by, on average, avoiding one RBC unit transfusion per patient, targeting high risk patients (i.e. probable long-stay patients) may magnify clinical benefits that are not discernable in the study. Further trials are sure to follow.

### To finish

Two further interesting reviews presented in the latest edition of *Intensive Care Monitor* are worthy of mention [13,14]. The precise role of steroid therapy in septic shock remains elusive but much debated. A report published in *JAMA* this year [15] claimed to show improved survival among patients receiving low-dose steroid therapy who had relative adrenal insufficiency diagnosed by a short corticotrophin test. Although this study is not methodologically watertight, as discussed in an accompanying editorial, it nonetheless provides further evidence for steroid use; however, a question remains as to whether steroid usage may be harmful in patients without adrenal insufficiency.

Finally, which is best in ARF – intermittent or continuous renal replacement therapy? A meta-analysis reported in *Intensive Care Medicine* [16] concluded that, once the severity of illness has been adjusted for, continuous renal replacement therapy results in reduced mortality as compared with intermittent. Of course, we await a large randomized trial to confirm this.

### Competing interests

None declared.

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