

## Commentary

# Recently published papers: Pandemic flu, the latest ARDS trials, raising legs and other stories

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## Abstract

In this commentary, recent papers covering pandemic influenza, acute respiratory distress syndrome and cardiovascular issues are discussed.

### **Pandemic influenza: preparedness and novel therapy**

The burning question about pandemic flu is when, not if, it will strike. Given this general consensus and the proven benefits of planning for such emergencies, it was timely to read the results of an independent evaluation of preparedness in Europe [1]. As one might expect, the news is a classical mixture of good and bad with perhaps the most worrying deficit being an almost systematic absence of cooperation and communication between neighbouring states. This is exemplified by the fact that only three countries have undertaken simulation exercises, the results of which have yet to reach the public domain. We can only hope that the clear messages emerging from this study are acted upon by governments worldwide.

At the opposite end of the spectrum, an illuminating treatment hypothesis for some of the severest human cases of H5N1 avian influenza A has been proposed by a collaborative team from Sweden and Hong Kong [2]. Patients contracting this infection may develop haemophagocytic lymphohistiocytosis, which in turn causes multi-organ failure and death. These authors put forward a convincing argument to consider treating such patients with a combination of dexamethasone and the cytotoxic etoposide. They suggest, given the epidemiology of this disease, that the WHO should consider undertaking a clinical trial of this therapeutic approach. For a more detailed review of haemophagocytic lymphohistiocytosis see [3].

### **Acute respiratory distress syndrome (ARDS): ventilatory strategy, moderate dose corticosteroids and $\beta$ -agonists**

The difficulties of conducting randomised control trials in the intensive care unit (ICU) and more especially in ARDS patients cannot be underestimated. With this in mind, three recent trials merit consideration.

The Spanish group of ARDS investigators, ARIES, have published their randomised control trial comparing higher positive end-expiratory pressure (PEEP)/lower tidal volume ( $V_t$ ) ventilation with lower PEEP/higher  $V_t$  [4]. Their inclusion criteria were selected to include only patients who fulfilled standard ARDS criteria after 24 hours of undefined optimal mechanical ventilation, selecting a group of patients with the severest disease and an established high mortality. Their method of PEEP selection in the higher PEEP group was based on a single measurement of the lower inflection point of the inflation limb of the pressure volume curve, initial PEEP being set at 2 cmH<sub>2</sub>O above this level. PEEP was titrated dynamically on the basis of maintaining a level of oxygenation in both strategy groups. The trial was stopped early because of the detection of a dramatic mortality benefit in the higher PEEP/lower  $V_t$  group. There was also a statistically significant increase in ventilator-free days and a reduction in the number of organ failures after randomisation, almost exclusively cardiac. The authors' discussion is clear and concise and fully acknowledges the defects in study design. From a real-world perspective, they sensibly suggest that a decremental PEEP trial is perhaps the best current method of establishing this crucial parameter. In summary, this eloquent study adds further weight to the case for a higher PEEP (titrated to the individual patient)/lower  $V_t$  ventilatory strategy in patients with severe ARDS. The accompanying editorial adds further valuable insights [5].

In contrast, the ARDSnet trial investigating the safety and efficacy of moderate-dose corticosteroids in persistent ARDS [6] fails, in my opinion, to answer either question reliably despite the considerable efforts of the group. This important question rose to prominence after the small randomised control trial published by Meduri and colleagues [7]. The ARDSnet investigators were handicapped by numerous problems and managed to recruit only 180 patients from an eligible pool of 3,464 over a 6-year period. The protocol specified enrolment at any time point between days 7 and 28 of mechanical ventilation but a *post hoc* division into those entered between days 7 and 13 and those entered between days 14 and 28 was performed. The results demonstrated statistically significant improvements in the treatment group in lung mechanics (in the 14 days after enrolment), number of ventilator-free days, number of organ failures and number of ICU-free days (all at day 28). However, this failed to translate into a mortality benefit at 60 or 180 days. The subgroup analysis seemed to show an excess mortality in the treatment group, whose enrolment took place on day 14 or later. There were differences in the incidences of a variety of secondary endpoints between the two groups, thus rendering the safety issue equally difficult to address. In short, almost any interpretation can be placed on the results of this trial, and I therefore sadly reached the conclusion that it cannot inform clinical practice.

The third trial of interest is a phase II randomised control trial, of continuous intravenous (i.v.) salbutamol in ARDS [8]. The rationale is that  $\beta$ -agonists increase the rate of alveolar fluid clearance and therefore might accelerate disease resolution. The authors chose extravascular lung water measurements as their primary endpoint, with a standard list of secondary endpoints including 28-day mortality. It is noteworthy that the dose of i.v. salbutamol used was 15  $\mu\text{g}/\text{kg}$  per hour, which equates to the top end of the recommended dosage range of 3 to 20  $\mu\text{g}/\text{min}$ . The treatment group had statistically significantly lower lung water from day 3 to day 7, with a mean decrease of 27%. Of perhaps greater significance was the finding that plateau airway pressures were significantly lower in the treatment group at day 7. There were no significant differences in any of the other secondary outcomes although, notably, the mortality rates in both groups were high (58% and 66%, respectively) reflecting the severity of illness in the study population. Surprisingly, and in contrast to recent reviews of i.v. salbutamol in acute severe asthma [9], no safety or tolerability issues were identified. The conclusion that a phase III trial is merited on this evidence seems justified. Before this, however, several issues arise including inhaled versus i.v. administration, the use of long-acting or short-acting  $\beta$ -agonists, and the adjunctive use of inhaled and/or systemic corticosteroids.

### Corticosteroids and weaning from mechanical ventilation

Continuing with the corticosteroid and respiratory theme, although not in ARDS patients, a Taiwanese study has

investigated the association between adrenal insufficiency and weaning from mechanical ventilation [10]. They screened all patients ventilated for more than 72 hours and enrolled 93 of the 472 patients identified. The authors found a high incidence of adrenal insufficiency (70 of 90; 78%). Those identified were randomised to receive either stress dose exogenous replacement (50 mg i.v. hydrocortisone, every 6 hours) or placebo (saline). The patients with normal adrenal function and those given exogenous replacement were comparable in their durations of mechanical ventilation and lengths of stay both in the ICU and in hospital. Those in the placebo group took on average 3 days longer to wean, which was reflected in their longer ICU and hospital stays. This study is arguably most notable for providing the impetus to monitor adrenal function in all critically ill patients, who require complex organ support for more than few days. Stress dose replacement should also be continued until the patient has been weaned from all circulatory and respiratory support.

### Cardiovascular issues

A further report from the Sepsis Occurrence in Acutely Ill Patients (SOAP) group reports a worse outcome in patients with shock associated with the use of dopamine and adrenaline (epinephrine) but not dobutamine or noradrenaline (norepinephrine) [11]. The statistical analysis identified only dopamine as an independent risk factor for 30-day mortality, conferring a 20% increase in risk. As with mechanical ventilation, despite administering vasoactive drugs to support the circulation of shocked patients for several decades, we still have insufficient clinical data to support an optimal therapeutic strategy. This study adds to the concerns of many practitioners about the use of dopamine, and perhaps it will create further impetus for well-designed outcome trials of differing cocktails of drugs.

The issue of the optimal method of assessing the adequacy of cardiac preload or, perhaps more precisely, volume responsiveness remains a daily challenge. Monnet and colleagues have published a study assessing the utility of the simple bedside manoeuvre of passive leg raising (PLR) [12]. They performed this manoeuvre before a dynamic fluid challenge and used oesophageal Doppler measurements of descending aortic flow as their estimate of stroke volume (SV). They found that a minimum of 10% increase in SV with PLR predicted a 15% or more increase in SV after an infusion of 500 ml of saline over 10 minutes. The calculated sensitivity was 97% and specificity 94%. The obvious attraction of this technique is its simplicity and ease of repeatability. It will be interesting to see whether it becomes a widely adopted practice.

Advances in practice lead, perhaps inevitably, to unforeseen complications. Radiofrequency ablation around the pulmonary vein is rapidly becoming the treatment modality of choice for patients with both paroxysmal and chronic atrial fibrillation [13]. A brief report by Cummings and colleagues describes nine cases of fatal atrial-oesophageal fistulae

presenting 10 to 16 days after catheter ablation [14]. The authors stress the wide-ranging presentation of these cases and the fact that ante-mortem diagnosis was achieved only in the minority. Three patients did undergo attempted surgical repair. The authors rightly counsel that this diagnosis be considered in any patient presenting with fever, malaise, leukocytosis, dysphagia, upper gastrointestinal haemorrhage or neurological symptoms after catheter ablation.

## Conclusion

Recent studies suggest:

- Checking on your local level of preparedness for pandemic flu and talking to your neighbours about it.
- Refining your ARDS ventilatory strategy towards ARIES while taking a pragmatic decision regarding moderate dose corticosteroids in persistent disease.
- Considering hypoadrenalism in all ICU patients requiring more than 72 hours of organ support, especially those who fail to wean from mechanical ventilation.
- And avoiding dopamine and starting PLR?

## Competing interests

The author declares that they have no competing interests.

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