



## Evidence-Based Medicine Journal Club

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Journal club critique

### Steroids in early ARDS?

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#### Expanded Abstract

##### Citation

Annane D, Sebille V, Bellissant E: Effect of low doses of corticosteroids in septic shock patients with or without early acute respiratory distress syndrome. *Crit Care Med* 2006, 34:22-30 [1].

##### Background

Experimental evidence suggests that corticosteroids may be beneficial in early acute respiratory distress syndrome (ARDS).

##### Methods

**Objective:** To investigate the efficacy of low doses of corticosteroids in septic shock patients with or without early ARDS by *post hoc* analysis of a previously completed clinical trial.

**Design:** Retrospective analysis of a placebo-controlled, randomized, double-blind trial of low doses of corticosteroids in septic shock.

**Setting:** Nineteen intensive care units in France.

**Subjects:** Among the 300 septic shock patients enrolled, we selected those meeting standard criteria for ARDS at inclusion.

**Intervention:** Seven-day treatment with 50 mg of hydrocortisone every 6 hrs and 50 µg of 9-alpha-fludrocortisone once a day.

**Measurements and main results:** There were 177 patients with ARDS (placebo, n = 92; corticosteroids, n = 85) including 129 (placebo, n = 67; corticosteroids, n = 62) nonresponders and 48 (placebo, n = 25; corticosteroids, n = 23) responders. In nonresponders, there were 50 deaths (75%) in the placebo group and 33 deaths (53%) in the steroid group (hazard ratio 0.57, 95% confidence interval

0.36-0.89, p = .013; relative risk 0.71, 95% confidence interval 0.54-0.94, p = .011). The number of days alive and off the ventilator was 2.6 +/- 6.6 in the placebo group and 5.7 +/- 8.6 in the steroid group (p = .006). There was no significant difference between groups in responders. There was no significant difference between groups in the two subsets of patients without ARDS. Adverse events rates were similar in the two groups.

##### Conclusion

This *post hoc* analysis shows that a 7-day treatment with low doses of corticosteroids was associated with better outcomes in septic shock-associated early ARDS nonresponders, but not in responders and not in septic shock patients without ARDS.

##### Commentary

It is difficult to imagine a topic that generates a more heated debate than that of the role of corticosteroids (steroids) in ARDS. First described in 1967 [2,3], ARDS is an acute life threatening condition characterized by excessive and protracted systemic inflammation. Given their anti-inflammatory properties, steroids have been evaluated as a potential treatment for ARDS using a variety of doses and durations and at various time points in the course of ARDS. Short courses of high dose steroids in ARDS are not beneficial [4,5]. Interest in this therapy was renewed when an apparent survival benefit was demonstrated in a single-center randomized trial of low dose prolonged steroids in late ARDS [6].

In the current study, Annane and colleagues explored the effect of seven days of treatment with low dose steroids in septic shock patients with or without early ARDS [1]. This study was a *post hoc* subgroup analysis of data obtained previously in another completed clinical trial [7]. Among the 300 subjects enrolled in the original trial, there were 177

patients with early ARDS, including 129 non-responders to the short cosyntropin stimulation test (steroids, n = 62; placebo, n = 67) and 48 responders (steroids, n = 23; placebo, n = 25). The steroid-treated and placebo groups were well balanced at baseline. Among non-responders with early ARDS, 28-day mortality was significantly lower in those receiving steroids (53% vs. 75%, p=0.01). There was no significant difference between groups in the rates of adverse events, such as superinfection, gastrointestinal bleeding, or psychiatric disorders. Interestingly, there were no differences in clinical outcomes between the steroid and placebo groups for the subgroup of early ARDS responders or for those without early ARDS, regardless of responder status. These results persisted after adjustment for baseline cortisol, cortisol response, McCabe class, Logistic Organ Dysfunction score, arterial lactates, and PaO<sub>2</sub>/FiO<sub>2</sub> ratios. The authors conclude that their findings should be confirmed in multicenter trial.

This was a well-done study and an insightful application of existing clinical trial data to inform the "steroids for ARDS" debate. An obvious limitation is one inherent in any *post hoc* subgroup analysis: multiple comparisons can lead to misleading conclusions. To emphasize the danger of *post hoc* subgroup analysis, one group demonstrated in data from a randomized trial that there was a statistically significant association between astrological birth sign and the effect of aspirin on mortality in acute myocardial infarction [8]. Such statistical aberrations are more likely when multiple combinations of subgroups are examined, especially if the approach is not hypothesis driven. This was *not* the case in the current study. Because this study was conducted before publication of the ARDS Network low tidal volume trial [9], the mean ventilator tidal volume in each group was 9 mL/kg of observed body weight. Since lower tidal volumes reduce inflammation and improve outcome in ARDS, it is not known whether steroids would still be beneficial when a low tidal volume strategy is utilized.

This and other recent trials raise several interesting issues. In the current study, steroids were of no benefit in septic shock patients without ARDS, which might lead one to conclude that the benefit of steroids in septic shock [7] is due to treatment of ARDS rather than adrenal insufficiency. This might explain the failure of the 500 patient multicenter CORTICUS trial to show a mortality benefit for steroids in patients with septic shock, although other explanations have been offered [10]. Supporting the findings of the current study, Meduri and colleagues recently reported the results of a five-center 91 patient randomized trial of low-dose prolonged steroid infusion in early severe ARDS. The authors found significantly improved lung function and ICU mortality in steroid treated subjects, and a trend toward lower hospital mortality [11]. Mean tidal volume was not reported in this trial, but was likely greater than 6 mL/kg since the study was conducted between years 1997 and 2002. While the authors did assess adrenal function at entry, the small size of the trial limited any meaningful subgroup analysis by cosyntropin responsiveness. Furthermore, the large late crossover rate (control subjects

received steroids if they failed to improve by study days 7 to 9) could have biased results in favor of the steroid group, given the results of another recent trial which suggested harm when steroids were given late in the progression of ARDS [12]. This latter trial, in turn, has also been criticized, with some suggesting too rapid weaning of steroids or the permitted use of neuromuscular blockers might explain the failure to find a benefit.

## Recommendation

As suggested by the authors of the current study [1] as well as the more recent Meduri and colleagues study [11], a larger randomized controlled trial of low-dose prolonged steroids in patients with early ARDS is warranted. Such a trial should stratify patients according to cosyntropin responsiveness and, perhaps, whether they have shock at study entry. Furthermore, close attention must be paid to infection surveillance, tight blood glucose control, avoidance of neuromuscular blockers, and the use of low tidal volume ventilation.

## Competing interests

The authors declare no competing interests.

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