Published in final edited form as:

Crit Care Med. 2013 July ; 41(7): 1813–1814. doi:10.1097/CCM.0b013e3182963cfb.

Corticosteroids and ARDS: The Debate Continues

Patrick Belvitch, M.D. and Steven M. Dudek, M.D.

Institute for Personalized Respiratory Medicine, Department of Medicine, University of Illinois Hospital & Health Sciences System

Keywords

ARDS; corticosteroids; mortality; prevention; propensity matching

The acute respiratory distress syndrome (ARDS) is a common cause of respiratory failure and death that is characterized by severe and persistent inflammation in the lung as well as systemically [1]. Mechanical ventilation with lung protective strategies decreases inflammation and improves survival [2, 3], but additional approaches are needed for optimal modification of the inflammatory process in ARDS. To that end, the potential utility of corticosteroids (CS) has been an active and controversial area of research for several decades. Early studies employing high dose CS demonstrated no significant benefit and possible harm [4, 5], while more recent controlled trials using prolonged, lower dose CS have yielded variable results on mortality and secondary outcomes [6, 7]. While some meta-analyses suggest an improvement in ARDS mortality and ventilator-free days with prolonged low dose therapy [8, 9], not all recent data have been positive. A cohort analysis of 208 patients with ARDS secondary to influenza A/H1N1 infection revealed that those treated with CS had higher rates of death, secondary infection, and ventilator duration [10]. Given the heterogeneous nature of ARDS and the pleiotropic effects of corticosteroids, it is not surprising that variable results have been observed in clinical trials. Thus, the optimal timing, duration, dose and discontinuation strategy of CS, as well as the appropriate selection of patients most likely to benefit, all remain incompletely defined.

In the current issue of *Critical Care Medicine*, Karnatovskaia and colleagues [11] address another aspect of clinical uncertainty pertaining to this topic: does prior CS use by those at risk for ARDS alter the clinical course? Several preventative trials in the 1980s employed high dose steroids in already hospitalized patients in an attempt to prevent or ameliorate ARDS [5, 12, 13]. A meta-analysis of these trials suggests increased risk of ARDS development and death in the CS treated patients [8]. In an observational cohort study of 688 ICU patients from a single center, prior CS use in a small subset of these patients did not alter risk for development of ARDS on multivariate analysis but was a significant predictor for increased mortality in those who did develop ARDS [14]. However, no definitive trial exists concerning the effects of prior CS use on ARDS risk and outcomes, and with the paucity of data in this area, equipoise remains.

The current study by Karnatovskaia and colleagues [11] investigates these questions through a pre-planned retrospective subgroup analysis of a prospectively identified cohort collected to determine the frequency and outcome of ARDS development in at risk patients and to validate the Lung Injury Prediction Score (LIPS) [15]. The original study enrolled 5584

hospitalized patients with risk factors for ARDS. Of these, 495 receiving inhaled corticosteroids at the time of enrollment (either alone or concomitantly with systemic CS) were excluded from further analysis, leaving 364 on systemic CS alone for comparison with 4725 patients not receiving any CS [11]. The authors hypothesized that pre-hospital CS therapy would have a protective effect on ARDS risk and outcomes given the beneficial effects of CS treatment in some previous trials [8, 9]. However, the incidence of ARDS was no different between those receiving pre-hospital systemic CS and those who did not (7.7% and 6.9%, respectively) [11]. To strengthen their analysis, the authors then performed propensity scoring to identify a subset of patients most closely matched for all available covariates except for CS therapy. 354 patients who received pre-hospital systemic CS were matched to 1093 that did not. After this adjustment, there were no significant differences in the risk of ARDS, invasive ventilation, or in-hospital mortality between the two groups. The authors conclude that prior systemic CS use did not affect risk for ARDS or its clinical course after development of the syndrome.

Interpretation of the clinical relevance of this study must begin with a review of its limitations. Although the subgroup analysis was pre-planned and involved a prospectively identified cohort, it does not rise to the level of evidence provided by a prospective, randomized, blinded, controlled trial. The propensity score matching strengthens the analysis but cannot control for all potential confounders. Another significant limitation is that the data collected do not provide any details concerning the specific medication, dose, or duration of systemic CS therapy being taken by patients prior to hospitalization. Patients were categorized as receiving CS based upon a review of the medical record at hospital admission. Pre-hospital compliance with the prescribed medication also was not determined. As a result, there likely existed a great deal of therapeutic heterogeneity within the systemic CS group, which serves to weaken the conclusions that can be drawn from these results. For example, is there any association between systemic CS dose and ARDS risk? Is there a difference in ARDS risk between patients chronically using CS and those receiving a brief steroid taper? Does the use of inhaled CS (these patients were excluded from analysis) affect ARDS incidence or outcomes? These questions cannot be answered by the current study.

Despite these limitations, Karnatovskaia and colleagues have advanced the debate about the role of CS in ARDS by providing the first study specifically focused upon the effects of pre-hospital CS on ARDS risk and outcomes. Their data suggest that outpatient CS therapy does not alter the natural clinical course in patients at risk for the development of ARDS. However, given the multiple beneficial effects of CS on ARDS pathophysiology and the positive results in some clinical trials of low dose CS early in ARDS, there remains some uncertainty about the potential use of CS as a prophylactic agent in high risk patients. The recently announced NHLBI Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network is one potential avenue for providing the randomized control trial needed to determine which at risk patients, if any, may benefit from CS therapy. Until such data are available, the debate is likely to continue.

Acknowledgments

Drs. Dudek and Belvitch have received funding from the National Institutes of Health.

References

1. Meduri GU, Annane D, Chrousos GP, Marik PE, Sinclair SE. Activation and regulation of systemic inflammation in ARDS: rationale for prolonged glucocorticoid therapy. *Chest*. 2009; 136(6):1631–1643. [PubMed: 19801579]

2. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Eng J Med*. 2000; 342(18):1301–1308.
3. Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. *The J Clin Invest*. 2012; 122(8):2731–2740.
4. Bernard GR, Luce JM, Sprung CL, Rinaldo JE, Tate RM, Sibbald WJ, Kariman K, Higgins S, Bradley R, Metz CA, et al. High-dose corticosteroids in patients with the adult respiratory distress syndrome. *N Eng J Med*. 1987; 317(25):1565–1570.
5. Bone RC, Fisher CJ Jr, Clemmer TP, Slotman GJ, Metz CA. Early methylprednisolone treatment for septic syndrome and the adult respiratory distress syndrome. *Chest*. 1987; 92(6):1032–1036. [PubMed: 3315478]
6. Meduri GU, Golden E, Freire AX, Taylor E, Zaman M, Carson SJ, Gibson M, Umberger R. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. *Chest*. 2007; 131(4):954–963. [PubMed: 17426195]
7. Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, Thompson BT, Ancukiewicz M. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Eng J Med*. 2006; 354(16):1671–1684.
8. Peter JV, John P, Graham PL, Moran JL, George IA, Bersten A. Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis. *BMJ*. 2008; 336(7651):1006–1009. [PubMed: 18434379]
9. Tang BM, Craig JC, Eslick GD, Seppelt I, McLean AS. Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis. *Crit Care Med*. 2009; 37(5):1594–1603. [PubMed: 19325471]
10. Brun-Buisson C, Richard JC, Mercat A, Thiebaut AC, Brochard L. Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2011; 183(9):1200–1206. [PubMed: 21471082]
11. Karnatovskaia LV, Lee AS, Gajic O, Festic E. The influence of pre-hospital systemic corticosteroid use on development of Acute Respiratory Distress Syndrome and hospital outcomes. *Crit Care Med*. 2013 in press.
12. Luce JM, Montgomery AB, Marks JD, Turner J, Metz CA, Murray JF. Ineffectiveness of high-dose methylprednisolone in preventing parenchymal lung injury and improving mortality in patients with septic shock. *Am Rev Respir Dis*. 1988; 138(1):62–68. [PubMed: 3202402]
13. Schein RM, Bergman R, Marcial EH, Schultz D, Duncan RC, Arnold PI, Sprung CL. Complement activation and corticosteroid therapy in the development of the adult respiratory distress syndrome. *Chest*. 1987; 91(6):850–854. [PubMed: 3556054]
14. Gong MN, Thompson BT, Williams P, Pothier L, Boyce PD, Christiani DC. Clinical predictors of and mortality in acute respiratory distress syndrome: potential role of red cell transfusion. *Crit Care Med*. 2005; 33(6):1191–1198. [PubMed: 15942330]
15. Gajic O, Dabbagh O, Park PK, Adesanya A, Chang SY, Hou P, Anderson H 3rd, Hoth JJ, Mikkelsen ME, Gentile NT, et al. Early identification of patients at risk of acute lung injury: evaluation of lung injury prediction score in a multicenter cohort study. *Am J Respir Crit Care Med*. 2011; 183(4):462–470. [PubMed: 20802164]