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Steroids are part of rescue therapy in ARDS patients with refractory hypoxemia: we are not sure

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acute respiratory distress syndrome; corticosteroids; diffuse alveolar damage; meta-analysis; rescue therapy

Many clinicians have ambivalence regarding the use of steroids in critical illness. In a survey of corticosteroid use in the ICU, more than half would use steroids in vasopressor-refractory septic shock while the majority of respondents almost-never use corticosteroids for ARDS [1]. Considering the nature of the injury, the high mortality and underlying pathogenesis of ARDS, this is somewhat surprising. Patients with ARDS with higher levels of lung and systemic inflammation have worse clinical outcome [2, 3]. Because of its inflammatory basis, corticosteroids have long been considered a potential therapy for ARDS.

In a recent article in *Intensive Care Medicine*, Meduri et al. [4] describe an intention-to-treat analysis of individual patient data (IPD) from four randomized trials of patients with ARDS treated with methylprednisolone or placebo either early (within 72 hours of onset) or late (after 5–7 days) after the onset of respiratory failure. They then performed a trial-level meta-analysis incorporating the IPD analysis with data from four randomized trials in which patients received seven days of hydrocortisone or placebo for early ARDS. They found decreased time to unassisted breathing with methylprednisolone as well as a reduction in hospital mortality in their meta-analysis. While their analysis is consistent with a potential benefit of prolonged corticosteroid therapy to improve outcomes in ARDS, the effects of corticosteroid dose on these variables is complicated by the different doses and duration of the corticosteroids used in the trials (Table 1).

Denoting steroids as rescue therapy assumes that usual care; reversing the underlying cause, limiting injury from mechanical ventilation and treating nosocomial infections, should be sufficient to decrease pulmonary inflammation and enhance survival. However, if these measures fail, rescue therapy with corticosteroids might be initiated to halt the decline in

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lung function and allow for recovery. If the mechanisms leading to organ injury and gas exchange abnormalities have some commonality, should steroids be considered as primary adjunctive therapy rather than rescue therapy?

The consensus definition of ARDS was developed as an epidemiologic tool and to facilitate the identification of consistent patient characteristics for clinical trials. However, it has limited fidelity to identify patients with lung injury who will benefit from anti-inflammatory therapy. The definition includes an amalgam of direct (i.e pneumonia, aspiration, inhalational injury, contusion, vasculitis, drowning) and indirect (i.e. non-pulmonary sepsis, trauma, pancreatitis, severe burns, non-cardiogenic shock, drug overdose, transfusion-associated lung injury) injuries to the lung [5]. Are the trials that assess the effects of steroids studying the same types of patients or are the underlying processes too diverse to be summarized as a single clinical entity? Attempts to address the effects of steroids on ARDS due to different etiologies has had only limited success because of the varying mix of patients included in current reports [6].

To add to the complexity of identifying patients who will benefit from steroid therapy, one might assume that the clinical definition of a syndrome that shares common mechanisms of injury would have consistent histologic manifestations with the hallmark finding of diffuse alveolar damage. Yet, autopsy studies of patients meeting the Berlin criteria for ARDS show that less than half of these patients had these findings at the time of death [7]. Other clinical diagnosis where ARDS criteria were met but no diffuse alveolar damage was found included pulmonary infections, cancer infiltration, pulmonary embolism, acute pulmonary edema, pulmonary hemorrhage, interstitial pneumonia/fibrosis, severe emphysema as well as the absence of any pulmonary lesions [7]. Thus, it should not be surprising that a uniform treatment strategy for patients meeting the consensus definition of ARDS has limitations and lacks sufficient accuracy to identify inflammatory lung processes amenable to modulation with steroids.

Corticosteroids have shown benefit in many infectious and noninfectious lung injuries that lead to ARDS. Patients with *Pneumocystis* pneumonia may develop ARDS, have evidence of diffuse alveolar damage and 21-day treatment with tapering doses of corticosteroids reduces mortality reduction in adults with significant hypoxemia due to *Pneumocystis* [8]. Diffuse alveolar hemorrhage (DAH) may present clinically as ARDS. Corticosteroids remain the standard treatment for DAH with capillaritis or DAH related to stem cell transplant or idiopathic pulmonary hemosiderosis [9].

However, corticosteroids are not a panacea for all lung inflammation. In immunosuppressed patients, such as hematopoietic stem cell transplant recipients, the anti-inflammatory effects of corticosteroids for treatment of ARDS are weighed against worsening co-existing infections (e.g. cytomegalovirus, adenovirus, fungal pneumonias) or increasing the risk of nosocomial infections. A lack of benefit is suggested from studies describing corticosteroid use in severe influenza pneumonia. Retrospective studies found an increase in mortality in critically ill patients with H1N1 influenza receiving corticosteroids compared to propensity matched controls [10, 11]. However these data are limited by their retrospective data and variability in the dose, timing and duration of antivirals as well as corticosteroids.

If steroids are considered only as rescue therapy, when should therapy be initiated and what would the clinical signs be to demonstrate failure of other treatments? Histologic data from autopsies suggest that exudative lesions predominate during the first week and by the third week fibroproliferative changes become dominant [12]. As lung histology is rarely available in early ARDS, blood biomarkers (e.g. type III procollagen) may provide the clinical signal to initiate anti-inflammatory therapy [13]. Analysis of trial data from the current study suggests that if corticosteroids are used to treat ARDS, treatment should be initiated prior to day 14.

We believe the question of primary or rescue steroid therapy for ARDS needs to be reframed. Significant gaps remain in the randomized trial data. The dose and duration of corticosteroids providing benefit in ARDS differed by 2 to 5 fold and 1 to 4 weeks in duration, respectively. These data suggest that one treatment strategy may not fit all patients fulfilling the clinical criteria of ARDS. Many investigators on both sides of this debate agree that the current clinical definition is limited in identifying patients with lung injuries that may be responsive to corticosteroids [14, 15]. Expanding the current physiologic definition of ARDS with disease-specific biomarkers may help focus the debate [14]. In the absence of a specific tissue diagnosis or real-time biomarker signatures reflecting the etiology and stage of lung injury, the uncertainty and reservations regarding steroid use in ARDS will persist.

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Table 1

Dose and Duration of Methylprednisolone or Hydrocortisone given to Patients with ARDS[a]

Studies cited in Meduri et al.	Total Number of Patients Treated with	Total Number of Patients Treated with	Total Dose (mg) of Corticosteroid Days 1–7	[c] Total HydrocortisoneEquivalents (mg) Days 1–7	Maximum duration of steroid therapy (days)
	Placebo	Methylprednisolone	[b] Methylprednisone		
Meduri 1998	8	14	1120	5600	31
Steinberg 2006	92	85	1120	5600	25
Meduri 2007	28	63	560	2800	28
Rezk 2013	9	18	560	2800	28
Total	**137**	**180**			
	Placebo	Hydrocortisone	Hydrocortisone		
Confaloneri 2005	19	15	1880	1880	7
Annane 2006	66	66	1400	1400	7
Sabry 2011	34	26	2100	2100	7
Liu 2012	12	14	2100	2100	7
Total	**131**	**121**			

[a] patient numbers derived from Figure 4 [4],

[b] estimate for 70 kg (body weight) patient,

[c] equivalent dose of hydrocortisone 20 mg equals 4 mg methylprednisolone

Intravenous dosing strategy for methylprednisolone studies:
Meduri 1998 *– Loading dose 2mg/kg followed by 2 mg/kg/day from days 1 – 4, then 1 mg/kg/day days 15 – 21, the 0.5 mg/kg/day from day 22 – 28, 0.25 mg/kg/day on days 29 and 30, then 0.125 mg/kg/day on days 30 and 31*
Steinberg 2006 *- Loading dose 2mg/kg followed by a dose of 0.5 mg/kg of predicted body weight every 6 hours for 14 days, a dose of 0.5 mg/kg of predicted body weight every 12 hours for 7 days, and then tapering of the dose. Study drug was tapered over a period of 4 days if 21 days of treatment had been completed and the patient was unable to breathe without assistance for a period of 48 hours*
Meduri 2007 *- Loading dose of 1 mg/kg was followed by an infusion of 1 mg/kg/day from day 1 to day 14, 0.5 mg/kg/day from day 15 to day 21, 0.25 mg/kg/day from day 22 to day 25, and 0.125 mg/kg/day from day 26 to day 28. If the patient was extubated between days 1 and 14, the patient was advanced to day 15 of drug therapy and tapered according to schedule.*
Rezk 2013 *- Load 1 mg/kg, then days 0–14; 1mg/kg/day, days 15–21; 0.5 mg/kg/day, days 22–25; 0.25 mg/kg/day, days 26–28; 0.125 mg/kg/day*

Intravenous dosing strategy for hydrocortisone studies:
Confaloneri 2005 *– 200 mg bolus then 10 mg/h for 7 days*
Annane 2006 *– 50 mg hydrocortisone every 6h and 50 mcg fludrocortisone for 7 days*
Sabry 2011 *– 12.5 mg/h hydrocortisone for 7 days*
Liu 2012 *– 100 mg hydrocortisone, three times per day for 7 days*