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

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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 the 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 h 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 7 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 (i.e., 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 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

Table 1 Dose and duration of methylprednisolone or hydrocortisone given to patients with ARDS

Studies cited in Meduri et al. [4]	Total number of patients treated with placebo	Total number of patients treated with methylprednisolone	Total dose (mg) of corticosteroid days 1–7 methylprednisone ^a	Total hydrocortisone equivalents (mg) days 1–7 ^b	Maximum duration of steroid therapy (days)
Meduri et al. [16]	8	14	1120	5600	31
Steinberg et al. [17]	92	85	1120	5600	25
Meduri et al. [18]	28	63	560	2800	28
Rezk et al. [19]	9	18	560	2800	28
Total	137	180			
Studies cited in Meduri et al. [4]	Total number of patients treated with placebo	Total number of patients treated with hydrocortisone	Total dose (mg) of corticosteroid days 1–7 hydrocortisone	Total hydrocortisone equivalents (mg) days 1–7 ^b	Maximum duration of steroid therapy (days)
Confaloneri et al. [20]	19	15	1880	1880	7
Anname et al. [21]	66	66	1400	1400	7
Sabry et al. [22]	34	26	2100	2100	7
Liu et al. [23]	14	12	2100	2100	7
Total	133	119			

Patient numbers derived from Fig. 3 in [4]

Intravenous dosing strategy for methylprednisolone studies:

Meduri et al. [16]—Loading dose 2 mg/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 et al. [17]—Loading dose 2 mg/kg followed by a dose of 0.5 mg/kg of predicted body weight every 6 h for 14 days, a dose of 0.5 mg/kg of predicted body weight every 12 h 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 h

Meduri et al. [18]—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 et al. [19]—Load 1 mg/kg, then days 0–14; 1 mg/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 et al. [20]—200 mg bolus then 10 mg/h for 7 days

Anname et al. [21]—50 mg hydrocortisone every 6 h and 50 mcg fludrocortisone for 7 days

Sabry et al. [22]—12.5 mg/h hydrocortisone for 7 days

Liu et al. [23]—100 mg hydrocortisone, three times per day for 7 days

^a Estimate for 70 kg (body weight) patient

^b Equivalent dose of hydrocortisone 20 mg equals 4 mg methylprednisolone

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, and 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 and have evidence of diffuse alveolar damage, while 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 nature and the 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 that 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 two- to fivefold and 1–4 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.

Compliance with ethical standards

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