Intensive Care Med (2016) 42:931–933
DOI 10.1007/s00134-015-4135-0

EDITORIAL

Shailesh Bihari
Michael Bailey
Andrew D. Bersten

Steroids in ARDS: to be or not to be

Received: 28 October 2015
Accepted: 30 October 2015
Published online: 16 November 2015

S. Bihari · A. D. Bersten (✉)
Department of Critical Care Medicine, Flinders University, Bedford Park, SA, Australia
e-mail: andrew.bersten@flinders.edu.au
Tel.: +61-8-82044247

S. Bihari · A. D. Bersten
Department of Intensive Care Medicine, Flinders Medical Centre, Bedford Park, SA, Australia

M. Bailey
Department of Epidemiology and Preventive Medicine, Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Australia

Glucocorticoid treatment of acute respiratory distress syndrome (ARDS) remains contentious, and the available evidence remains contradictory [1–4]. In this context, the current analysis by Meduri et al. [5] is welcome. These authors conducted a two-part analysis—(1) individual patient data meta-analysis (IPDMA) from trials with methylprednisolone and (2) an updated trial-level meta-analysis including additional randomised controlled trials (RCTs) with hydrocortisone in early ARDS—and have reported that steroids accelerated the resolution of ARDS, leading to reduced ventilatory assistance, hospital mortality and health care utilisation [5]. However, these conclusions appear to contradict those of the ARDS Network LaSRS study [4], which contributed 56 % of the patients to the IPDMA. Furthermore, in addition to reporting no benefit from the routine use of methylprednisolone in patients with ARDS, the LaSRS investigators found that the use of methylprednisolone was associated with an increased risk of neuromuscular complications and that initiation of methylprednisolone treatment more than 2 weeks after the onset of ARDS led to an increase in the risk of death despite improved early cardiopulmonary physiology [4]. This discrepancy demands some consideration.

Meta-analysis offers some advantages over a single high-quality RCT, as the greater number of patients enrolled in the former, as well as the range of differing populations, circumstances and settings, facilitates generalisability. However, studies in critical care settings are particularly challenging due to the heterogeneity of both the cohort and the treatments, which can lead to misleading conclusions [6]. While this is minimised in IPDMA [7], which is considered the gold standard for meta-analysis [8], and therefore is the focus of our attention here, both the quality of the individual studies included in the IPDMA and of the analysis itself need to be considered.

Well-documented and published guidelines (PRISMA) for the conduct, reporting and transparency of meta-analysis [9]—and specifically for IPDMA [10]—have been developed. Despite Meduri et al.'s detailed description of the statistical methods used in their IPDMA [5], the information provided is insufficient to conclude that these guidelines were all followed. In addition, there was moderate heterogeneity in study outcomes (reported as an I^2 statistic, with likely wide 95 % confidence intervals), which the authors attribute to the LaSRS study. These methodological concerns suggest that the reader should be cautious in drawing conclusions.

There are important differences in trial design between the studies contributing data to the IPDMA of Meduri et al. [5]. The LaSRS study enrolled 180 patients (1:1 randomisation), with 60-day mortality as its primary

Table 1 Details of primary outcome, total number, tidal volume and plateau pressure for studies included in the individual patient data meta-analysis

Study	Primary outcome	Study arm	Number of participants in each study arm	Tidal volume		Plateau pressure[a]	
				n[a]	Mean ± SD (ml/kg/pbw)[b]	n[a]	Mean ± SD (cm H_2O)[b]
Meduri et al. [1]	Improvement in LIS by day 14	Placebo	8	7	10.1 ± 3.0	5	43.0 ± 2.2
		MP	16	14	10.9 ± 2.3	11	37.8 ± 6.3
Steinberg et al. [4]	60-day mortality	Placebo	91	77	7.2 ± 2.3	65	33.8 ± 9.7
		MP	89	77	7.1 ± 2.2	66	34.5 ± 10.0
Meduri et al. [3]	Improvement in LIS by day 7	Placebo	28	25	11.3 ± 2.8	13	29.0 ± 4.5
		MP	63	57	10.5 ± 2.8	30	29.9 ± 8.2
Rezk and Ibrahim [2]	Improvement in LIS by day 14	Placebo	9	–	–	–	–
		MP	18	–	–	–	–

LIS Lung injury score, *MP* methylprednisolone, *SD* standard deviation

[a] n is the number of patients for which tidal volume and plateau pressure data were available

[b] Data for tidal volume and plateau pressure for Meduri et al. [1] and Meduri et al. [3] were retrospectively collected from respiratory flow sheets. No tidal volume and plateau pressure data were available from the study of Rezk and Ibrahim [2]

outcome [4]; the remaining studies used a 2:1 randomisation ($n = 24$ [1], 27 [2] and 91 [3]), with reduction in the lung injury score at day 7 [3] or day 14 [1, 2] as the primary outcome (Table 1) and only mortality at day 28 reported. Despite early improvements in cardiopulmonary physiology and an increased number of ventilator-free days, intensive care unit-free days and shock-free days during the first 28 days of treatment, patients treated with methylprednisolone in the LaSRS study did not show improved outcomes at day 60 and day 180 and had greater neuromuscular weakness and an increase in mortality if the treatment had been started after 14 days. While Meduri et al. [5] cogently argue that the rapid cessation of methylprednisolone resulted in an exacerbation of lung inflammation, contributing to these adverse effects, these data also emphasise the importance of examining longer-term outcomes [11]. Mortality is both unambiguous and unarguably important, but it does depend upon when it is measured [12], and current data are limited to treatment day 28 or hospital mortality. Long-term functional disability is an equally important legacy in ARDS survivors [13] and is an increasing focus for both researchers and clinicians.

There are also differences in routine care (co-interventions) in the studies included in the IPDMA that may contribute to heterogeneous outcomes. Lung protective mechanical ventilation has generally become the standard of care for ARDS patients. It is of note that barring the LaSRS study [4], the other three studies [1–3] used tidal volumes that would not be considered lung protective (Table 1). Other factors, such as use of neuromuscular blocking agents [14] and fluid balance, can also affect the outcome of patients with ARDS. Taken together, these factors raise the question of standardisation, where possible, and the potential bias of co-interventions during a clinical trial. For example, while magnesium was found to improve outcome from myocardial infarction in LIMIT-2 ($n = 2316$) [15], this was not confirmed in the ISIS-4 mega-trial ($n = 58{,}050$) [16]. An important difference between these latter two studies was the much greater use of aspirin and attempted revascularisation in ISIS-4 [16]. It is unknown whether protective ventilation mitigates the beneficial effects of steroids in ARDS, but clinicians should consider the possible bias introduced by unbalanced co-interventions when interpreting data from both RCTs and meta-analyses.

The potential adverse effects of therapeutic steroids go beyond neuromuscular weakness, immunosuppression, superadded infection and higher blood glucose levels [17]. The mineralocorticoid effect of steroids contributes to fluid and sodium retention [18, 19], with both a positive fluid and sodium balance associated with adverse outcomes in patients with lung injury [20–22]. Prospective data examining this potential confounder should be considered in future clinical trials.

On the principle of primum non nocere (first, do no harm), we feel that there is currently insufficient evidence to advocate the routine use of steroids in patients with ARDS as potential short-term improvements appear to be mitigated by later adverse effects. If steroids are used, however, abrupt cessation should be avoided.

Compliance with ethical standards

Conflicts of interest None.

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Intensive Care Med (2016) 42:918–920
DOI 10.1007/s00134-015-4162-x

EDITORIAL

Thomas Bein
Josef Briegel
Djillali Annane

Steroids are part of rescue therapy in ARDS patients with refractory hypoxemia: yes

Received: 12 November 2015
Accepted: 19 November 2015
Published online: 16 February 2016

For contrasting viewpoints, please go to
doi:10.1007/s00134-015-4160-z and
doi:10.1007/s00134-015-4255-1.

T. Bein (✉)
Department of Anesthesia, Operative Intensive Care, University Hospital Regensburg, 93042 Regensburg, Germany
e-mail: thomas.bein@ukr.de

J. Briegel
Department of Anesthesia, University Hospital of Munich, Ludwig-Maximilians-University, Munich, Germany

D. Annane
General Intensive Care Unit, Raymond Poincaré Hospital (AP-HP), Laboratory of Inflammation and Infection, UMR1173, University of Versailles SQY and INSERM, Versailles, France

In recent years, three important topics have been frequently addressed in terms of scientific efforts and clinical management of the acute respiratory distress syndrome (ARDS): (1) the demand for a new definition which underlines more precisely the acute character of this syndrome [1], (2) the identification of the typical inflammatory pathways at onset of ARDS resulting in early management recommendations [2], and (3) a 'shift' from mortality as the golden standard of outcome parameter to the health-related quality of life of surviving ARDS patients [3]. The Berlin definition—despite some current critiques—enables a grading of the severity of the syndrome, i.e., severe ARDS means 'acute hypoxemic' and life-threatening, resulting in a high mortality rate. The three major causes of death in ARDS are refractory hypoxemia, multiple organ failure secondary to sepsis or hemodynamic compromise, or ventilator-induced lung injury. It has been shown that early ARDS is characterized by an overshooting systemic and pulmonary inflammatory response within 48 h triggered by various cytokines and inflammatory pathways. Furthermore there is an imbalance between excessive nuclear factor κB (NF-κB) activity and deficient glucocorticoid receptor α (GC-GRα) inducing resistance or insensitivity of the stressed host to endogenous corticosteroids [4]. As a result patients develop not only systemic inflammation and hemodynamic instability but also pulmonary inflammation and fibroproliferation with subsequent loss in lung function, increased mortality rate, and reduced health-related quality of life in survivors. Failure to repair tissue damage results in an ongoing and self-perpetuating inflammation: lung biopsies demonstrated fibroproliferation in 60 % of ARDS patients [5]. Typical clinical findings include persistent increased levels of inflammatory biomarkers, decreased compliance of the lungs, and reticular densities in radiographic imaging.

Consequently, from recent interventional randomized studies we have learned that early therapeutic interventions in ARDS (lung [ultra-]protective strategies, adequate high PEEP, prone positioning) are critical points in setting the direction for survival: the first 48 h present the most vulnerable period in an ARDS's life! The early downregulation of inflammation is essential for reduction of the influx of neutrophils, monocytes, macrophages, and lymphocytes into the lung to restore the lung's homeostasis [6].

What is the role of glucocorticoid (GC) therapy in early management of ARDS? Meduri and coworkers have impressively shown that low-dose GC have potent anti-inflammatory and antifibroproliferative effects in this specific clinical setting [4]. Furthermore, the expression of high levels of type III procollagen in the immediate

phase of ARDS was identified as a strong predictor for fibrosis and it was argued that the beneficial effect of GC could be in preventing rather than in reversing lung fibrosis [7]. In a small randomized controlled trial [8], early infusion (≤72 h after onset of ARDS) of low-dose methylprednisolone was associated with significant improvement in pulmonary and extrapulmonary organ dysfunction. On the other hand, former studies investigating the effects of GC on a large patient database were not convincing: Bernard et al. administered four pulses of high-dose GC within 24 h after ARDS onset, but they found no benefit in terms of the 45-day mortality [9], and the concept of 'supraphysiologic' high GC doses in this study was criticized in the aftermath. A randomized clinical trial led by the ARDS Network failed to show survival benefit of prolonged low-dose methylprednisolone in patients with persistent ARDS. Of note in this trial, 27 % of patients were recruited beyond 14 days from disease onset [10].

A recent analysis of individual patient data from four randomized trials combined with a trial-level meta-analysis of the updated literature demonstrated that early and prolonged GC treatment accelerated resolution of ARDS, decreased hospital mortality and healthcare utilization without increasing the risk of infection [11]. The suggested mechanism underlying these beneficial effects is that prolonged treatment with low-dose GC may overcome ARDS-associated deficient GC-GRα activity [12].

The take-home message from the meta-analysis by Meduri et al. is that glucocorticoids in severe ARDS—early, low-dosed, and prolonged—act as an important part of the management bundle (Fig. 1). Indeed, the observed number needed to treat in this meta-analysis is rather low and side effects rather rare. Although retrospective analyses suggested negative effects of steroids (at various doses) on neuromuscular function, this aspect could not be confirmed by the prospective study of the ARDS Network [13]. Nevertheless, a number of unanswered issues include choice of drug (hydrocortisone or methylprednisolone), dose (moderate or low), and main mechanisms of genomic versus non-genomic effects.

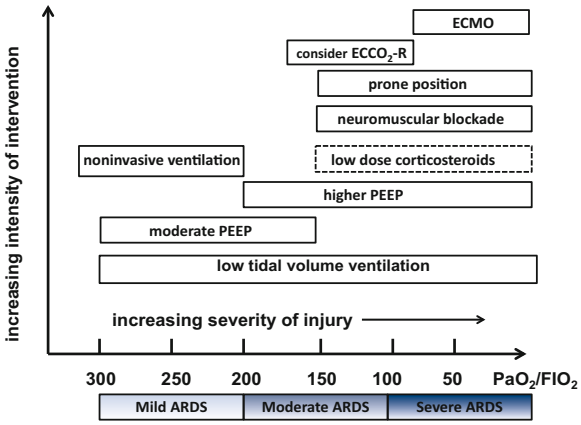

Fig. 1 Modification of an algorithm for therapeutic management of mild, moderate, and severe ARDS, adopted from Ferguson et al. [1]. Low-dose glucocorticoid infusion is included. High-frequency oscillation ventilation was deleted because of recent negative studies

In patients with refractory hypoxemia, an early and bundle-guided management is not only crucial for survival but also for quality of survival. Such a management should include lung protective ventilation, adequate PEEP, prone positioning, early and low-dose glucocorticoids (methylprednisolone initially 1 mg/kg/day, then dose tapering), and a short course of a short-acting neuromuscular blocker (Fig. 1). Steroids are part of rescue therapy in ARDS patients with refractory hypoxemia: yes!

Compliance with ethical standards

Conflicts of interest All authors declare that there are no conflicts of interest.

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Intensive Care Med (2016) 42:921–923
DOI 10.1007/s00134-016-4255-1

EDITORIAL

Steroids are part of rescue therapy in ARDS patients with refractory hypoxemia: no

B. Taylor Thompson[1*] and V. Marco Ranieri[2]

Rescue therapies for acute respiratory distress syndrome (ARDS) usually target patients with severe hypoxia and/or hypercarbia refractory to conventional therapies and are considered when rapid deterioration in the patient's condition over a period of hours suggests an increased risk of death. Under these circumstances conventional mechanical ventilation will almost certainly cause additional lung injury if "rescue therapies" are not implemented. Inhaled nitric oxide, inhaled epoprostanol, high-frequency ventilation, prone positioning, or immediate cannulation for extracorporeal membrane oxygenation (ECMO) or extracorporeal carbon dioxide removal (ECCO2R) are often considerations in this setting. Three thoughtful views on the value, if any, of rescue therapies were published in *Intensive Care Medicine* last year [1–3]. None of these expert commentaries recommended corticosteroids as a rescue option. Should they have? Are the known effects of corticosteroids on the injured lung likely to reverse or stabilize lung injury in these catastrophically ill patients in a timely way?

When confronted with such dramatic cases clinicians should first ensure that the underlying cause of ARDS has been identified and effectively treatment started, such as appropriate antibiotics and source control for patients with sepsis and prompt management of volume overload for hypervolemic patients. Because rescue therapies are, in essence, life support or lung protective measures that do not treat the underlying disease processes leading to these catastrophic cases, intensivists must consider specific causes of ARDS or ARDS mimics that may benefit from specific therapies, including corticosteroids. ARDS mimics should be suspected when no identifiable risk factors for ARDS are apparent [4]. Examples include severe ARDS from *Pneumocystis jiroveci* pneumonia presenting as an AIDS-defining illness, diffuse alveolar hemorrhage from vasculitis, acute hypersensitivity pneumonitis, cryptogenic organizing pneumonia, or acute eosinophilic pneumonia. These uncommon diseases may rarely present with fulminate ARDS and have specific treatments, including corticosteroids (Table 1) [4–7].

Corticosteroids have not been systematically studied as rescue therapy for acute ARDS, so much of the evidence that bears on this question is indirect. Four randomized trials of high-dose steroids for prevention of ARDS (methyprednisolone at, for example, 30 mg/kg every 6 h for 24 h, or equivalent doses dexamethazone) showed no effect or harm of this therapeutic strategy and were the subject of a contemporary Bayesean meta-analysis [8]. This analysis determined that the probability for an odds ratio of ≥ 1 for developing ARDS and for death was 86 and 78 %, respectively. These probabilities suggest steroids are ineffective for prevention and probably harmful—although the credible intervals both include 1. Accordingly, treatment with high doses of corticosteroids for short periods early in the course of critical illness has largely been abandoned. Recent meta-analyses and a systematic review of studies of lower dose corticosteroids for established ARDS show substantial heterogeneity of the pooled trials along with short-term improvement in lung physiology and outcomes, including earlier achievement of unassisted breathing [8, 9, reviewed in 10]. Additional studies of corticosteroids for patients with ARDS and sepsis are ongoing and needed (Clinical Trials.gov identifiers NCT01731795 and NCT01448109).

Do these short-term improvements in lung physiology with corticosteroids support their use as rescue therapies? To do so, a relevant improvement of physiological variables would need to be observed in a matter of minutes or hours to "rescue" a patient from fulminant

*Correspondence: thompson.taylor@mgh.harvard.edu
[1] Division of Pulmonary and Critical Care, Department of Medicine, Massachusetts General Hospital–Harvard Medical School, 55 Fruit Street, Boston, MA 02114, USA
Full author information is available at the end of the article

For contrasting viewpoints, please go to doi:10.1007/s00134-015-4160-z and doi:10.1007/s00134-015-4162-x.

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Table 1 Steroid-responsive conditions which may present with severe acute respiratory distress syndrome

ARDS mimics
Acute eosinophilic pneumonia (AEP)
Diffuse alveolar hemorrhage from vasculitis
Crytogenic organizing pneumonia
Acute hypersensitivity pneumonitis (HSP)
Pneumocystis jiroveci pneumonia complicating human immunodeficiency virus (HIV)
Nonspecific interstitial pneumonitis and pneumonitis associated with connective tissue disease

Some diseases, such as granulomatosis with polyangiitis leading to diffuse alveolar hemorrhage, require additional immunosupressive treatment with cyclophosphamide or rituximab [7]. Other conditions require removal of the offending antigen [heat shock proteins (HSP); asparagine endopeptidase (AEP)]. Acute interstial pneumonia (Hamman Rich) is often treated with corticosteroids but efficacy has not been established

ARDS Acute respiratory distress syndrome

ARDS. In a recently published study, Meduri et al. carefully observed the patterns of response to corticosteroids in patients with established and presumed fibroproliferative ARDS [11]. Of the 25 patients enrolled in their study, 15 demonstrated a "rapid" response to corticosteroids. Unfortunately "rapid" meant that in these responders the partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2) had improved on day 3 following initiation of steroid therapy and that static respiratory system compliance had improved on day 5. One-third of the patients did not improve at all. Similarly, the ARDS network noted improvement in PaO_2/FiO_2 and plateau airway pressure after 3 and 4 days, respectively, of steroid therapy and more rapid liberation from mechanical ventilation [12]. Recent studies of steroids for community acquired pneumonia (CAP) also document beneficial acute responses, but the time course is relatively slow for the purposes of immediate rescue. For example, in one study of patients with severe CAP the median time to clinical stability was shorter in the steroid group [3.0 days, interquartile range (IQR) 2.5–3.4 days] than in the placebo group (4.4 days, IQR 4.0–5.0 days) [12], and in a second study of patients with CAP, time to treatment failure was reduced but the difference appeared after 4 days [13]. These encouraging data suggest corticosteroids at lower doses early in the course of pneumonia or ARDS improve lung function but that the onset of action is too slow and inconsistent and the magnitude of the effect too small to be recommended as a reliable life-saving rescue therapy. Furthermore, corticosteroids have been associated with late complications, such as secondary infections and new shock [14, 15].

Because of the modest, delayed, and inconsistent physiologic improvement observed with the use of corticosteroids for ARDS and CAP and the concern for late complications, we do not recommend the use of corticosteroids as rescue therapy for patients with immediately life-threatening early ARDS. Clinicians should remain vigilant for steroid-responsive diseases that may masquerade as ARDS, especially in patients without identifiable risk factors for the syndrome of ARDS. Some of these patients will require corticosteroids and other disease-specific treatments for optimal outcomes.

Author details
[1] Division of Pulmonary and Critical Care, Department of Medicine, Massachusetts General Hospital–Harvard Medical School, 55 Fruit Street, Boston, MA 02114, USA. [2] Policlinico Umberto I, Anesthesia and Critical Care Medicine, "Sapienza" Università di Roma, Rome, Italy.

Compliance with ethical standards

Conflicts of interest
Both authors do not have any relevant conflicts of interest to disclose.

Received: 13 January 2016 Accepted: 28 January 2016
Published online: 16 February 2016

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Intensive Care Med (2016) 42:924–927
DOI 10.1007/s00134-015-4160-z

EDITORIAL

Nitin Seam
Anthony F. Suffredini

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

Received: 14 November 2015
Accepted: 19 November 2015
Published online: 29 January 2016

For contrasting viewpoints, please go to
doi:10.1007/s00134-015-4162-x and
doi:10.1007/s00134-015-XXXX-X.

N. Seam · A. F. Suffredini (✉)
Critical Care Medicine Department, Clinical Center,
National Institutes of Health, Building 10, Room 2C145,
10 Center Drive, Bethesda, MD 20892-1662, USA
e-mail: asuffredini@cc.nih.gov

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
Annane 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
Annane 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

Funding Supported by the Intramural Program, Clinical Center, National Institutes of Health.

Disclosures Dr. Seam and Suffredini serve on the Executive Committee of the US Department of Veterans Affairs Cooperative Studies Program (CSP) #574: Evaluate the Safety and Efficacy of Methylprednisolone in Hospitalized Veterans with Severe Community-Acquired Pneumonia (NCT01283009).

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