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Should we ever give steroids to ARDS patients?

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Abstract

The development and severity of ARDS are closely related to dysregulated inflammation, and the duration of ARDS and eventual outcomes are related to persistent inflammation and abnormal fibroproliferation. Corticosteroids are potent modulators of inflammation and inhibitors of fibrosis that have been used since the description of the acute respiratory distress syndrome in attempts to improve outcomes. Randomized controlled trials of steroids for ARDS have answered some, but not all, questions regarding efficacy for prevention and treatment. First, there is no evidence that corticosteroids prevent the development of ARDS among patients at risk. Second, high dose and short course treatment with steroids does not improve the outcomes of patients with ARDS. And third, while there is compelling data that low dose and prolonged treatment with steroids improves pulmonary physiology in patients with ARDS, additional studies are needed to recommend treatment with steroids for ARDS.

Keywords

ARDS; corticosteroids; prevention; treatment; outcomes

Introduction: Why talk about steroids and ARDS?

The first report in the literature of the acute respiratory distress syndrome (ARDS) presents 12 patients who developed acute hypoxemic respiratory failure in response to overwhelming illness or injury, and concludes with the statement, “Corticosteroids appeared to have value in the treatment of fat emboli and possibly viral pneumonia¹.”

It has been nearly 50 years since this initial description of ARDS, during which time much has been learned about pathogenesis, epidemiology, supportive care, and long-term outcomes². However, the search for pharmacologic therapy has been disappointing, without

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convincing proof of a single agent to decrease mortality of patients with ARDS. And yet it seems so compelling that this syndrome that is defined by over-exuberant inflammation should be treated with corticosteroids—powerful anti-inflammatory agents that are part of the body's endogenous response to stress—that we continue to maintain hope. Do corticosteroids appear to have value in the treatment of ARDS, or possibly in specific settings?

In this review, we will briefly discuss the pathogenesis of ARDS and review the mechanism of action of corticosteroids. We will then review clinical data from studies of corticosteroids across the spectrum of ARDS—prevention, early, and late—focusing on results randomized trials. We will also discuss studies of corticosteroids in specific settings associated with ARDS, such as septic shock and pneumonia. Finally, we will conclude by making some recommendations for clinical practice and by identifying gaps that beg for future research.

Inflammation, fibrosis and the pathophysiology of ARDS

Histology early in the course of ARDS reveals interstitial and alveolar edema, infiltration of cells into the alveolar spaces (neutrophils, macrophages and red blood cells), and alveolar epithelial and endothelial injury. The alveolar basement membranes often become denuded; hyaline membranes form³. Dysregulated inflammation, both in the endothelial and epithelial spaces, is a key driver of the pathogenesis of ARDS. Ventilator-induced lung injury may further perpetuate both pulmonary and systemic inflammation⁴. Alveolar macrophages release pro-inflammatory cytokines, including neutrophil chemoattractants that promote neutrophilic activation and migration into the interstitial and alveolar spaces. These activated neutrophils release pro-inflammatory molecules, which contribute to and perpetuate the inflammatory environment⁵. Vascular permeability increases as these products released by neutrophils interrupt tight junctions and promote alveolar cell death, with loss of the normal function of the endothelial barrier⁶. There is also activation of local fibroblasts. Key homeostatic mechanisms to prevent injury due to uncontrolled inflammation, such as endogenous glucocorticoid secretion and the release of anti-inflammatory cytokines, are overwhelmed⁷. Degree of pulmonary and systemic inflammation, as measured by cytokine concentrations in the alveolar compartment and in serum, have been shown to be associated with severity and outcome in ARDS^{8,9}.

After the initial phase of ARDS, recovery may occur quickly, with reabsorption of the edema fluid, removal of the cellular infiltrates, and reparative epithelial proliferation with restoration of the alveolar barrier². However, for some patients with ARDS, recovery is complicated by persistent inflammation and fibroproliferation. Along with capillaries, fibroblasts proliferate in the alveolar and interstitial spaces, leading to collagen deposition and fibrosis¹⁰. The presence and magnitude of fibrosis in ARDS have been shown to be associated with outcome, using measurement of procollagen peptide III in bronchoalveolar lavage fluid as a marker of collagen deposition in the alveolar space¹¹.

Pharmacologic effects of corticosteroids

Synthetic corticosteroids, such as methylprednisolone and hydrocortisone, exert their clinical effects by mimicking natural glucocorticoids¹². Glucocorticoids are potent anti-

inflammatories which act primarily by binding to cytoplasmic glucocorticoid receptors. Once bound, the glucocorticoid-receptor complexes regulate the transcription of glucocorticoid-response elements (GRE) such as nuclear factor receptor- $\kappa\beta$ (NF- $\kappa\beta$). The transcription of many pro-inflammatory cytokines (including interleukins-1 α , -1 β , -2, -3, -5, -6, -8 and -12; tumor necrosis factor α ; and interferon γ) is modulated by NF- $\kappa\beta$ ¹³. Additionally, glucocorticoids act synergistically with natural anti-inflammatory cytokines, such as interleukin-4, -10, 13, and interleukin-1 receptor antagonist¹⁴. Glucocorticoids also have actions on fibrotic pathways, inhibiting fibroblast proliferation and decreasing collagen deposition¹⁵.

Regulated by the hypothalamic-pituitary-adrenal (HPA) axis, endogenous glucocorticoids are key effectors in the natural response to stress. Stressful stimuli, such as infection or injury, lead to hypothalamic release of corticotropin releasing hormone, which then acts on the anterior pituitary to produce adrenocorticotrophic hormone (ACTH). The adrenal cortex is stimulated by ACTH to release glucocorticoids into the blood. Glucocorticoids, such as cortisol, have myriad cardiovascular effects, including increasing vascular adrenergic receptor function, decreasing cytokine-induced nitric oxide synthetase, increasing endothelial integrity, decreasing vascular permeability, and increasing myocardial contractility; all of which help maintain blood pressure and cardiac output under stress¹³. In addition to anti-inflammatory and cardiovascular effects, glucocorticoids have profound metabolic effects, including inducing gluconeogenesis, increasing serum glucose levels, and altering protein, fat and bone metabolism¹².

Clinical trials of steroids in prevention and treatment of ARDS

In the 1970s, many clinical and animal studies demonstrated beneficial effects of corticosteroids on intermediate physiologic outcomes in the setting of sepsis and ARDS. Steroids were demonstrated to reduce inflammation by decreasing complement activation¹⁶ and neutrophil aggregation¹⁷, and were found to have potentially advantageous effects on oxyhemoglobin dissociation¹⁸, cardiac output¹⁹, pulmonary vascular pressure²⁰, and alveolo-capillary permeability²¹. In combination with case reports describing improved outcomes of patients with sepsis and ARDS after receipt of steroids, there was ample evidence to spur randomized clinical trials.

It is important to note that all randomized trials discussed here were conducted in the 1980s and 1990s—an era before low tidal volume ventilation⁴, an era with much higher ARDS-associated mortality². While considering each of these studies, it is also relevant to question if findings are generalizable to the treatment of ARDS today.

Clinical trials for ARDS prevention

There have been four randomized trials of corticosteroids that assessed the outcome of prevention of ARDS^{22–25}, as shown in Table 1. High dose methylprednisolone (30 mg/kg) was used in all trials, with number of doses ranging from 1 to 8 over up to 48 hours. Three studies enrolled only patients with septic shock with similar but not identical definitions; one study enrolled patients with respiratory failure “at high risk for ARDS”. ARDS was the

primary outcome measure for all studies, although definitions for ARDS were highly variable between the four studies.

The first study by Schein and colleagues began enrollment in 1979, and included patients with septic shock, both with and without ARDS at time of enrollment²⁴. Patients were randomized into three arms: methylprednisolone (30 mg/kg), dexamethasone (6 mg/kg), or no therapy (no placebo described). If shock persisted after four hours, a second dose of study drug was administered. This study found similar rates of ARDS across all three arms, and no difference in the intermediate outcome measure of plasma complement levels.

Around the same time, Weigelt enrolled 81 patients with hypoxemic respiratory failure ($\text{PaO}_2:\text{FIO}_2 < 350$) into a single-centered randomized controlled trial of methylprednisolone for the prevention of ARDS²³. The primary etiology of respiratory failure was sepsis and shock for three quarters of all patients enrolled. Patients received 30 mg/kg of intravenous methylprednisolone every 6 hours for a total of 8 doses in the intervention group; control subjects received mannitol. There was no evidence for benefit of steroids; ARDS, infectious complications and death were all significantly more common among patients randomized to methylprednisolone.

Between 1982 and 1985, Luce and colleagues randomized patients with septic shock to high-dose methylprednisolone or placebo within 2 hours of meeting criteria²⁵. This study was stopped early for safety²⁶. Eight-seven patients were enrolled and treated, but only the 75 patients with positive culture results were included in the analysis. There was no difference in proportion of patients meeting ARDS criteria between randomization groups, nor was there a difference in hospital mortality, which was over 50% for both groups. There was no significant association between development of ARDS and hospital mortality; there also was no association between randomization to corticosteroids and plasma complement levels.

Simultaneously, a large multicenter study was conducted by Bone and colleagues testing the efficacy of methylprednisolone on reducing mortality in patients with septic shock²⁶. This study found no benefit of high dose steroids on mortality, and a subgroup analysis found an association between randomization to steroids and increased mortality if serum creatinine was greater than 2 mg/dL (which led to the decision for early stopping in the Luce study). A secondary analysis was performed including patients who did not meet ARDS criteria before study enrollment; this analysis did not find that methylprednisolone either prevented ARDS or decreased its associated mortality²².

Several methodological issues complicate interpretation of these studies, both alone and in combination. Since these studies used different durations of therapy and varying definitions of ARDS, there is significant heterogeneity between trials. None of the three studies that prospectively sought to determine the effect of methylprednisolone on ARDS were adequately powered; to show a reduction in ARDS incidence from 40% to 20% in a two-arm study with 80% power would require a sample size of over 180 patients. When combined, these studies and the secondary analysis of Bone's trial suggest that there is no role for high-dose methylprednisolone early in septic shock for the prevention of ARDS²⁷. Peter's recent

meta-analysis concluded that there is an 86.6% probability that high dose steroid therapy may instead *increase* the incidence of ARDS²⁷.

There have been no recent randomized trials to inform the utility of corticosteroids for ARDS prevention. However, two recent cohort studies investigated the role of pre-hospital inhaled or systemic corticosteroid use on the subsequent development of ARDS in patients at risk^{28,29}. Investigators found no significant independent association between either inhaled or systemic corticosteroids on ARDS development.

Clinical trials for treatment of early ARDS

The first randomized controlled trial of corticosteroids for decreasing mortality in patients with established ARDS was conducted in the early 1980s. Bernard and colleagues used a similar protocol as the prevention trials, 30 mg/kg of intravenous methylprednisolone every six hours for a total of four doses, with the hypothesis that this treatment would reduce 45-day mortality³⁰. This study was stopped early for futility, with 60% mortality in the methylprednisolone group and 63% in control, after enrolling 99 patients. There was no increase in infectious complications noted in the steroid group, nor were there significant benefits in reduction of infiltrates on chest radiograph, lung compliance or oxygenation.

The end of the 1980s brought a close to the era of studies of high dose methylprednisolone both for ARDS prevention and early treatment. Excitement was renewed, however, after the publication of Annane's randomized controlled trial of treatment of refractory septic shock with low dose hydrocortisone and fludrocortisone³¹. This study investigated the effect of 50 mg of intravenous hydrocortisone given every six hours for one week, in combination with 50 mcg of enteral fludrocortisone once daily, on 28 day mortality. The authors hypothesized that there would be significant benefit in patients with critical illness related adrenal insufficiency³², diagnosed by non-response to a short corticotropin test ("non-responders"). While overall there was no significant effect on 28 day mortality, treatment with steroids was associated with decreased mortality among non-responders (53% versus 63%, $p=0.04$). Of the 300 patients in the study, 177 met criteria for ARDS³³ at study entry (59%), 129 of whom were non-responders.

A *post-hoc* analysis of this study tested the hypothesis that randomization to steroids was associated with decreased mortality among non-responders with ARDS, and found that non-responders with ARDS had lower mortality if randomized to steroids (53% versus 75%, $p=0.021$)³⁴. There was no mortality reduction associated with randomization to steroids among all ARDS patients, however. It is notable that a large subsequent study of hydrocortisone for septic shock found no mortality benefit, neither among non-responders nor the group as a whole. There has been no *post-hoc* analysis published to date looking at the ARDS subgroup in this study³⁵.

In the late 1990's, Meduri and colleagues conducted a pilot randomized controlled trial to investigate the effect of a longer course of low dose methylprednisolone on pulmonary outcomes³⁶, including lung injury score³⁷ and ventilator-free days³⁸. This study enrolled 91 patients within the first 72 hours of onset of ARDS and randomized in a 2:1 ratio to 1 mg/kg of methylprednisolone followed by a prolonged infusion at 1 mg/kg/day or placebo. Most

patients had pneumonia, aspiration, or non-pulmonary sepsis. Randomization to steroids improved pulmonary outcomes, with a dramatic increase in ventilator-free days and improvement in lung injury score. Twelve of 28 patients in the placebo group died before hospital discharge (43%), compared with 15/63 in the steroid group (24%, $p=0.07$).

There have been no other randomized studies published to date that investigate the efficacy of low-dose steroids in decreasing hospital mortality for patients with early ARDS, although pilot studies in closely-related groups, such as severe community acquired pneumonia, may show promise³⁹. Despite the lack of clear evidence, the American College of Critical Care Medicine issued a recommendation in 2008 that “moderate dose glucocorticoids should be considered in the management strategy of patients with early severe ARDS ($\text{PaO}_2:\text{FIO}_2<200$)”, with a grade 2B³². In the recent Surviving Sepsis Campaign guidelines, no recommendations were made in this regarding the use of steroids in ARDS, despite 12 other recommendations specific to clinical management of ARDS in sepsis⁴⁰.

Clinical trials for treatment of late ARDS

While evidence was mounting against high dose, short-term treatment with corticosteroids for prevention and early treatment of ARDS, there were a number of case reports and small series describing treatment of “established” ARDS with longer courses and lower doses^{41–45}. These studies boasted remarkable improvements in lung function and patient outcome after treatment with steroids. Meduri, one of the early champions of this work, conducted a small randomized controlled trial of patients who had unresolving ARDS, defined as meeting ARDS criteria, requiring greater than 7 days of mechanical ventilation, and without significant improvement of lung injury since onset⁴⁶. Patients were excluded if they met ARDS criteria for over 3 weeks, or if they had untreated infection. Patients were randomized in a 2:1 ratio to methylprednisolone or placebo. Methylprednisolone was given with an initial loading dose of 2 mg/kg, which was followed by 14 days of 2 mg/kg/day in six hour intervals, which was then tapered over an additional 18 days. The protocol included a crossover, wherein patients without improvement in lung injury score by at least 1 point by the tenth day of treatment were blindly switched to the alternate treatment group. Primary outcomes were ICU survival and improvement in lung injury score. This study was stopped after enrollment of 24 patients when ICU mortality was significantly different between the groups: none of the 16 patients in the initial steroid group died before ICU discharge compared with 5 of 8 in the placebo group (0% versus 63%, $p=0.002$).

Despite a marked difference in ICU mortality between groups, a number of aspects of trial design give pause to clinical application of their results. First, the sample size is very small, with only 8 patients in the placebo group. This brings into question the statistical stability of the results, raising the likelihood of false positives. Second, half of the placebo group were crossed over and began receiving methylprednisolone on study day 10, late into the course of ARDS. All deaths in the placebo group occurred after crossover; it is unclear what role very late treatment with methylprednisolone might have played in patient outcome. Third, an ICU mortality of over 60% is considerably higher than expected from a late ARDS population.

In follow up, the NIH NHLBI ARDS Network conducted a multicenter randomized controlled trial of patients meeting ARDS criteria for at least 7 days, with continuous mechanical ventilation and persistent infiltrates on chest radiograph at study entry⁴⁷. Patients meeting ARDS criteria for longer than 28 days were excluded. The intervention was intravenous methylprednisolone, given as a 2 mg/kg loading dose, then 2mg/kg/day in 4 divided doses for 14 days, then tapered over 11 days. If a patient achieved 48 hours of unassisted breathing, study drug was tapered early, over 4 days. The primary outcome was 60 day mortality. It was estimated that the intervention would decrease mortality from 40% to 20%, with a sample size of 180 and 85% power. Sixty day mortality was lower than anticipated—29%—and was equal in both study groups.

There were interesting differences between the treatment groups, however. Patients randomized to steroids liberated from mechanical ventilation sooner than those on placebo (14 days versus 23 days, $p=0.006$) and had significantly more ventilator free days at both 28 and 180 days. Yet, there was no difference in ICU length of stay between the groups, and return to mechanical ventilation was significantly more likely among patients randomized to steroids (20 versus 6, $p=0.008$). All nine serious adverse events of neuromyopathy were in the steroid group, but there was no significant difference between clinician recognition of neuromyopathy during the hospitalization between the two groups. There was no difference in infectious complications. Hyperglycemia was more common in the steroid group, however.

Two planned subgroup analyses were hypothesis generating. First, there was a significant interaction between duration of ARDS and randomization group. Among patients enrolled in after days 13 of ARDS, mortality was 12% in the placebo group compared with 44% in steroid group, suggesting that steroids may be harmful if begun too late in the course of ARDS. Conversely, benefit of steroids may be greatest while inflammation and fibroproliferation are still active. Supporting this theory, a second sub group analysis identified significant effect modification between treatment group and level of procollagen peptide III (PIIIP) in bronchoalveolar lavage fluid at study baseline. Patients with high levels of PIIIP who were randomized to steroids were less likely to die (4% versus 24% in placebo).

These findings raise at least three important questions. First, is there an identifiable subgroup of patients with late ARDS who may benefit from treatment with corticosteroids? Both studies suggest that treatment may be beneficial earlier and harmful later, inferring from the higher mortality in the ARDS Network treatment group enrolled after day 14, as well as in the placebo group of Meduri's study after late crossover to steroids. However, the evidence is sparse enough that a new randomized controlled trial targeting persistent ARDS between day 7–13 would be required to recommend this treatment clinically. It is possible that biomarkers, such as PIIIP could help identify the subgroup, but ideally such a biomarker would be available clinically with rapid turnaround. Also, measurement of the biomarker in the alveolar compartment significantly limits its clinical utility, since resource limitation and patient stability prevent widespread use. Even in the trial setting, only half of the patients in the ARDS Network study had bronchoalveolar lavages performed at study entry.

Second, why did so many patients in the steroid group develop recurrent respiratory failure requiring return to mechanical ventilation? It has been suggested that tapering methylprednisolone early after liberation from the ventilator led to recrudescence of lung inflammation and fibroproliferation, deteriorating compliance and oxygenation, increased work of breathing, and subsequent need for mechanical ventilation^{47,48}. Perhaps a protocol that continued treatment with steroids well beyond liberation from mechanical ventilation would prevent this mechanism of recurrent respiratory failure. However, a competing hypothesis is that complications from steroid therapy were responsible for return to mechanical ventilation, such as infection or neuromuscular weakness. While there is no compelling evidence to suggest higher infection rates, indeed recognition of neuromyopathy was higher in the steroid group, particularly within the first 28 days of the study⁴⁹. If weakness was a direct contributor to recurrent respiratory failure, then extending the course of steroids seems an unlikely solution.

The relationship between steroids and ICU-acquired neuromyopathy remains uncertain, however. Clinical evidence of neuromyopathy (weakness, deconditioning, myopathy and neuropathy) was very common in both arms of the ARDS Network trial (43 of 128 hospital survivors, 34%), with no significant increase in patients randomized to steroids (odds ratio 1.5, 95% CI 0.7–3.2)⁴⁹. Cohort studies have yielded conflicting results with regards to the association between steroids and ICU-acquired neuromyopathy⁵⁰. Interestingly, in the setting of intensive insulin therapy, which controls hyperglycemia and promotes muscle anabolism⁵¹, steroids may *reduce* the risk of ICU-acquired neuromyopathy⁵². Conflicting findings may reflect the complicated roles that steroids may play in muscle and nerve pathology and recovery⁵³.

Third, given the consistent increase in ventilator-free days across both the Meduri and ARDS Network studies, do we have ample evidence to recommend widespread clinical use of corticosteroids for late ARDS? The problem is that ventilator-free days may not represent a truly patient centered outcome; despite a nearly 5 day difference in ventilator free days between the groups, there was no significant difference in mortality or even ICU length of stay. While decreasing duration of mechanical ventilation among survivors is a positive outcome, the associated long-term risks are not known. There are concerns that long-term physical function may be worse among patients treated with steroids in the ICU^{54,55}. The relationship between steroids and long-term mental health is also unclear, with studies suggesting beneficial actions of steroids on depression⁵⁶ and post-traumatic stress⁵⁷.

While the American College of Critical Care Medicine recommends consideration of steroid treatment for unresolving ARDS before day 14³², new randomized controlled trials are needed to increase certainty of efficacy, inform patient choice and timing of treatment, duration of therapy and approach to taper, and effect of treatment on long-term patient outcomes^{13,58}. Additionally, information is needed regarding the clinical utility of steroids in the era of low tidal volume ventilation⁴. Ventilator-induced lung injury is an important contributor to both inflammation and fibrosis^{59–62}, which are mitigated by treatment with steroids^{63–65}. It may be that the beneficial effects of steroids are diminished in patients managed with low tidal volume ventilation. The effects of low tidal volume ventilation on the natural history are still largely undescribed, but it may be the case that preventing

ventilator-induced lung injury decreases fibroproliferation. If so, the incidence of unresolving ARDS may be falling—benefiting patients but complicating future attempts to study the effect of steroids (or anything else) in this population.

Meta-analyses of steroids for ARDS

Meta-analytic techniques are often useful for integrating information across small or conflicting studies. However, the approach to meta-analysis may introduce additional heterogeneity, as each author may incorporate different definitions, different studies, and different sub-groups. This is the case for the five meta-analyses of steroids for ARDS published in the last decade^{27,48,66–68}. Table 4 presents the inclusion criteria, eligible studies, primary findings and conclusions from each of these recent meta-analyses; conclusion differ markedly based on studies and subgroups included in each report. These meta-analyses found high degrees of heterogeneity among studies, and significant quality issues, such as inclusion of studies with frequent and early stopping. It is notable that several of these conclusions include estimates that rely on *post hoc* subgroup analyses, for they may be inconsistent and imprecise⁶⁷. However, a recent survey suggests that clinicians may recognize the limitations of current evidence, with only 12% endorsing that they “sometimes” use systemic corticosteroids for treatment of ARDS⁶⁷.

Specific ARDS etiologies and steroids

On the whole, clinical trials provide little evidence supporting the use of steroids for the prevention of ARDS and for early treatment. However, ARDS is heterogeneous; steroids may be beneficial for some etiologies of ARDS, and not for others. ARDS associated with *Pneumocystis carinii* (jirovecii) pneumonia, for example, should be treated with steroids, since high quality randomized controlled trials have demonstrated that steroid treatment decreases both the risk of respiratory failure and death^{73–75}. Unfortunately, this level of evidence is lacking for most other etiologies of ARDS. It has been suggested that steroids improve outcomes from ARDS associated with acute monocytic leukemia⁷⁶, but no randomized trials have been published to support this observation. Clinical trials of steroids for treatment of sepsis⁷⁷ and pneumonia⁷⁸—among the most common ARDS risk factors—are inconclusive to date. And despite significant interest in the use of steroids in treatment of pandemic H1N1 influenza-associated ARDS, most reports from careful observation cohort studies suggest that such treatment was associated with harm^{79–81}.

Conclusion

So, should we ever give steroids for treatment of ARDS? In a word: may be... but not yet. Certainly there is no evidence to suggest that a short course of high dose steroids is helpful for either prevention or ARDS treatment. Work still needs to be done to determine if there are benefits to prolonged treatment with low dose corticosteroids for unresolving ARDS in the current era, with well-designed randomized controlled trials. These trials must determine if potential benefits outweigh short and long-term risks, including delayed recovery and impairments in physical function and health-related quality of life.

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Key Points

1. No studies support the use of corticosteroids for the prevention of ARDS.
2. High dose and short course treatment with steroids does not improve the outcomes of patients with ARDS.
3. There is compelling data that low dose and prolonged treatment with steroids improves pulmonary physiology in patients with ARDS, but additional studies are needed to recommend treatment with steroids for ARDS.

Table 1

Randomized trials of methylprednisolone for ARDS prevention

Author (dates)	Patients	Intervention (drug, dose, duration)	ARDS definition	Number enrolled	Outcome: steroids	Outcome: control	Notes
Schein (1979–1982) ²⁴	Septic shock	MP 30 mg/kg; DX 6 mg/kg, redosed after 4 hours if shock persisted	CXR: diffuse bilateral infiltrates Hypoxemia: PaO ₂ :FIO ₂ ratio<160 PAOP<15 mmHg	59 enrolled, 42 without ARDS at time of first study drug	ARDS 4/16 (MP) 3/13 (DX)	ARDS 2/13	Steroid treatment did not affect complement levels
Weigelt (1980–1985) ²³	Hypoxemic respiratory failure	MP 30 mg/kg q6 hours for 48 hours	“Pulmonary failure” and ARDS, including hypoxemia, shunt and CXR infiltrates	81 enrolled	ARDS 25/39 Died 18/39	ARDS 14/42 Died 13/42	Increased infectious complication in MP group
Bone (1982–1985) ²²	Septic shock	MP 30 mg/kg q6 hours for 24 hours	CXR: bilateral infiltrates Hypoxemia: PaO ₂ <70 on FIO ₂ 40% PAOP<18 mmHg	304 enrolled	ARDS 50/152 Died by day 14 26/50 (ARDS only)	ARDS 38/152 Died by day 14 23/38 (ARDS only)	Secondary analysis of study with primary endpoint of mortality
Luce (1983–1986) ²⁵	Septic shock	MP 30 mg/kg q6 hours for 24 hours	CXR: 4 quadrant infiltrates Hypoxemia: arterial to alveolar oxygen tension <0.3 PAOP 18 mmHg	87 enrolled, 75 confirmed with sepsis and analyzed	ARDS 13/38 Died 22/38	ARDS 14/37 Died 20/37	Stopped early (safety)

Abbreviations: MP=methylprednisolone. DX=dexamethasone. CXR= chest radiograph. PaO₂=partial pressure of arterial oxygen. FIO₂= fractional inspired oxygen. PAOP= pulmonary artery occlusion pressure.

Table 2

Randomized trials of corticosteroids for treatment of early ARDS

Author (dates)	Patients	Intervention (drug, dose, duration)	ARDS definition	Number enrolled	Outcome: steroids	Outcome: control	Notes
Bernard (1982–1985) ³⁰	ARDS, risk factor, no shock	MP 30 mg/kg MP q 6 for 24 hours	CXR: bilateral infiltrates Hypoxemia: PaO ₂ <70 on FIO ₂ 40% OR arterial to alveolar oxygen tension <0.3 PAOP<18 mmHg	99	45-day mortality: 30/50	45-day mortality: 31/49	Stopped early for futility. No difference in infectious complications; MP associated with hyper-glycemia
Annane (1995–1999) ³⁴	Septic shock, ARDS	HC 50mg q6 hours for 7 days, plus FC 50 meg qd	AECC criteria with PaO ₂ :FIO ₂ ratio <200	300 with sepsis, 177 with ARDS, 129 nonresponders	28-day mortality: 49/85 33/62 (non-responders)	28-day mortality 62/92 50/75 (non-responders)	Post-hoc secondary analysis of RCT
Meduri (1997–2002) ³⁶	ARDS, first 72 hours	MP 1 mg/kg load then 1 mg/kg/d infusion for 14 days or until extubation, then tapered over 14 days	AECC definition	91	Hospital mortality: 15/63 VFDs at 28: 16.5 (10.1)	Hospital mortality: 12/28 VFDs at 28: 8.7 (10.2)	Primary endpoint: reduction in lung injury score 2:1 randomization protocol

Abbreviations: MP=methylprednisolone. CXR= chest radiograph. PaO₂=partial pressure of arterial oxygen. FIO₂= fractional inspired oxygen. PAOP= pulmonary artery occlusion pressure. HC=hydrocortisone. FC=fludrocortisone. AECC=American European Consensus Conference. RCT=randomized controlled trial. VFD=ventilator free day

Table 3

Randomized trials of corticosteroids for treatment of late ARDS

Author (dates)	Patients	Intervention (drug, dose, duration)	ARDS definition	Number enrolled	Outcome: steroids	Outcome: control	Notes
Meduri (1994–1996) ⁴⁶	ARDS on ventilator for 7 days, no improvement in lung injury score	MP: 2 mg/kg/day × 14 days, then tapered over 18 days	AECC	24	Died in ICU: 0/16	Died in ICU: 5/8	Met early stopping rules on second look. 4/8 placebo patients crossed to MP treatment on day 10
Steinberg (1997–2003) ⁴⁷	ARDS criteria, on ventilator 7–28 days	MP: 2 mg/kg/day × 14 days, then tapered over 11 days (or over 4 days after 2 days off ventilator)	AECC	180	60 day mortality: 26/91 VFDs at day 28: 11.2 (9.4)	60 day mortality: 26/89 VFDs at day 28: 6.8 (8.5)	

Abbreviations: MP=methylprednisolone. VFD=ventilator free day

Table 4

Overview of meta-analyses of steroids and ARDS

Author	Inclusion criteria	Strata	Studies included	Effects of steroids on outcome	Conclusion
Agarwal ⁶⁶	RCT or observational cohorts of patients with ARDS treated with steroids	Early and late ARDS	Early: Bernard ³⁰ Annane ³⁴ Lee ⁶⁹ Late: Meduri ⁴⁶ Steinberg ⁴⁷ Keel ⁷⁰	Early: OR 0.57 (0.25–1.32) Late: OR 0.58 (0.22–1.53)	“Current evidence does not support a role for corticosteroids in the early or late stages of the disease”
Meduri ⁴⁸	RCT of 7 days of treatment with steroids for ARDS	Study size, duration of ARDS <14 days and duration of therapy > 7 days (including subgroups)	Meduri ⁴⁶ Confalonieri ³⁹ Annane ³⁴ Steinberg ⁴⁷ Meduri ³⁶	Larger: OR 0.84 (0.68–1.04) ARDS<14 days: OR 0.78 (0.64–0.96) ARDS<14 days and Rx> 7 days: OR: 0.62 (0.43–0.90)	“Prolonged glucocorticoid treatment substantially and significantly improves meaningful patient-centered outcome variable, and has a distinct survival benefit when initiated before day 14 of ARDS”
Peter ²⁷	RCT of steroid for ARDS prevention or treatment between 1966–2007	Prevention and treatment	Weigelt Bone ²² Schein ²⁴ Luce ²⁵ Bernard ³⁰ Meduri ⁴⁶ Steinberg ⁴⁷ Annane ³⁴ Meduri ³⁶	Prevention: OR 1.55 (0.58–4.05) Treatment: 0.62 (0.23–1.26)	“A definitive role of corticosteroids in the treatment of ARDS is not established. A possibility of reduced mortality and increased ventilator free days with steroids started after the onset of ARDS was suggested”
Tang ⁶⁸	RCTs and cohort studies that used low dose steroids to treat ARDS	Cohort and RCT	Keel ⁷⁰ Varpula ⁷¹ Huh ⁷² Lee ⁶⁹ Annane ³⁴ Meduri ⁴⁶ Confalonieri ³⁹ Steinberg ⁴⁷ Meduri ³⁶	Overall: OR 0.62 (0.43–0.91) Cohort: OR 0.66 (0.43–1.02) RCT: 0.51 (0.24–1.09)	“The use of low-dose corticosteroids was associated with improved mortality and morbidity outcomes without increased adverse reactions. The consistency of results in both study designs and all outcomes suggests they are an effective treatment for ARDS.”
Lamontagne ⁶⁷	RCTs of steroids for ARDS, limited to ARDS < 14 days at enrollment	Definition of ARDS	Annane ³⁴ Bernard ³⁰ Meduri ⁴⁶ Meduri ³⁶ Steinberg ⁴⁷	OR 0.79 (0.61–1.01)	“Our analysis suggests that low-dose corticosteroid therapy administered within 14 days of disease onset may reduce all-cause mortality in patients with ARDS... [but] the mortality benefits we recorded rely on analyses of subgroups, which are both inconsistent and imprecise.”