Steroids for Acute Respiratory Distress Syndrome?

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KEYWORDS

• ARDS • Corticosteroids • Prevention • Treatment • Outcomes

KEY POINTS

- No studies support the use of corticosteroids for the prevention of acute respiratory distress syndrome (ARDS).
- High-dose and short-course treatment with steroids does not improve the outcomes of patients with ARDS.
- There are 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.

INTRODUCTION: WHY TALK ABOUT STEROIDS AND ACUTE RESPIRATORY DISTRESS SYNDROME?

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 that, "Corticosteroids appeared to have value in the treatment of fat emboli and possibly viral pneumonia."[1]

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 outcomes.[2] However, the search for pharmacologic therapy has been disappointing, without convincing proof of a single agent to decrease the mortality of patients with ARDS. However, it seems so compelling that this syndrome, which is defined by overexuberant inflammation, should be treated with corticosteroids (powerful antiinflammatory agents that are part of the body's endogenous response to stress) that clinicians continue to maintain hope. Do corticosteroids have value in the treatment of ARDS, or possibly in specific settings?

This article discusses the pathogenesis of ARDS and reviews the mechanism of action of corticosteroids. It then reviews clinical data from studies of corticosteroids across the spectrum of ARDS (prevention, early, and late), focusing on the results of randomized trials. Studies of corticosteroids in specific settings associated with ARDS, such as septic shock and pneumonia, are also discussed. In addition, the article concludes by making some recommendations for clinical practice and by identifying gaps that require future research.

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INFLAMMATION, FIBROSIS, AND THE PATHOPHYSIOLOGY OF ACUTE RESPIRATORY DISTRESS SYNDROME

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 form.[3] 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 inflammation.[4] Alveolar macrophages release proinflammatory cytokines, including neutrophil chemoattractants that promote neutrophilic activation and migration into the interstitial and alveolar spaces. These activated neutrophils release proinflammatory molecules, which contribute to and perpetuate the inflammatory environment.[5] 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 barrier.[6] There is also activation of local fibroblasts. Key homeostatic mechanisms to prevent injury caused by uncontrolled inflammation, such as endogenous glucocorticoid secretion and the release of antiinflammatory cytokines, are overwhelmed.[7] Degree of pulmonary and systemic inflammation, as measured by cytokine concentrations in the alveolar compartment and in serum, has 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 barrier.[2] 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 fibrosis.[10] 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 space.[11]

PHARMACOLOGIC EFFECTS OF CORTICOSTEROIDS

Synthetic corticosteroids, such as methylprednisolone and hydrocortisone, exert their clinical effects by mimicking natural glucocorticoids.[12] Glucocorticoids are potent antiinflammatories that act primarily by binding to cytoplasmic glucocorticoid receptors. Once bound, the glucocorticoid-receptor complexes regulate the transcription of glucocorticoid-response elements such as nuclear factor receptor-$\kappa\beta$ (NF-$\kappa\beta$). The transcription of many proinflammatory cytokines (including interleukins 1α, 1β, 2, 3, 5, 6, 8, and 12; tumor necrosis factor alpha; and interferon gamma) is modulated by NF-$\kappa\beta$.[13] In addition, glucocorticoids act synergistically with natural antiinflammatory cytokines, such as interleukins 4, 10, 13, and interleukin-1 receptor antagonist.[14] Glucocorticoids also have actions on fibrotic pathways, inhibiting fibroblast proliferation and decreasing collagen deposition.[15]

Regulated by the hypothalamic-pituitary-adrenal 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 adrenocorticotropic 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 stress.[13] In addition to antiinflammatory and cardiovascular effects, glucocorticoids have profound metabolic effects, including inducing gluconeogenesis; increasing serum glucose levels; and altering protein, fat, and bone metabolism.[12]

CLINICAL TRIALS OF STEROIDS IN PREVENTION AND TREATMENT OF ACUTE RESPIRATORY DISTRESS SYNDROME

In the 1970s, many clinical and animal studies showed beneficial effects of corticosteroids on intermediate physiologic outcomes in the setting of sepsis and ARDS. Steroids were shown to reduce inflammation by decreasing complement activation[16] and neutrophil aggregation,[17] and were found to have potentially advantageous effects on oxyhemoglobin dissociation,[18] cardiac output,[19] pulmonary vascular pressure,[20] and alveolocapillary permeability.[21] In combination with case reports describing improved outcomes of patients with sepsis and ARDS after receipt of steroids, there was enough evidence to spur randomized clinical trials.