

# Corticosteroid therapy in acute respiratory distress syndrome

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## Competing interests:

François Lamontagne and Maureen Meade have received an award from the Canadian Institutes for Health Research for research on corticosteroids and acute respiratory distress syndrome. Roy Brower is a member of the Data and Safety Monitoring Board for AstraZeneca. No other competing interests were declared.

This article has been peer reviewed.

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CMAJ 2013. DOI:10.1503/  
cmaj.120582

**B**ecause acute respiratory distress syndrome (Figure 1) affects up to 150 000 patients and causes 60 000 deaths each year in the United States, the interest in potential therapies for this syndrome is high. Despite many candidate pharmacological interventions such as ketoconazole,<sup>1</sup> lisofylline<sup>2</sup> and inhaled nitric oxide,<sup>3</sup> no drug has conclusively been shown to reduce mortality associated with the condition. However, some experts believe that corticosteroids constitute an exception to this rule, and have recommended corticosteroid therapy for severe cases of early (< 14 d) disease.<sup>4</sup>

Although clinical practice recommendations provide a point of reference for clinicians, their impact is often limited by the lack of strong underlying evidence. Irregular use of corticosteroids by physicians who care for patients with this syndrome suggests there is a lack of certainty regarding their effects. This review focuses on the use of systemic corticosteroids to treat acute respiratory distress syndrome, and attempts to bring clinical context to current evidence. A summary of the evidence used in this review is found in Box 1. The review is based primarily on randomized controlled trials and meta-analyses (effects of corticosteroids), and observational studies (predicting responsiveness).

## What is the underlying rationale for corticosteroid therapy?

In the early 1980s, clinical investigators found that the inflammatory exudate from patients with adult respiratory distress syndromes could be

reduced with high doses of systemic corticosteroids.<sup>5</sup> More recently, in animal models of acute lung injury, Rocco and colleagues showed that corticosteroids reduce lung elastance and the deposition of collagen fibres in the extracellular matrix of the lung.<sup>6</sup> Meduri and colleagues have seen that peripheral blood leukocytes exposed to plasma from patients with acute respiratory distress syndrome produce inflammatory cytokines, and that giving methylprednisolone to these patients reduced this production.<sup>7</sup> Meduri and colleagues also found that procollagen aminoterminal propeptides (types I and III) in plasma and bronchoalveolar lavage increased in patients with nonresolving acute respiratory distress syndrome, and that the use of corticosteroids was associated with reductions in the levels of these markers. Moreover, the authors reported a substantial correlation between reductions in biomarker levels and improvements in lung injury scores.<sup>8</sup> These preclinical and clinical investigations are among the many supporting a therapeutic anti-inflammatory effect of corticosteroid therapy in acute respiratory distress syndrome in adults.

## Should corticosteroids be given to every patient with this syndrome?

Current systematic reviews addressing the role of corticosteroid therapy in acute respiratory distress syndrome have not conclusively shown a survival benefit, even among specific subgroups. Six randomized clinical trials (RCTs) specifically examined the effects of corticosteroids on mortality associated with acute lung injury or acute respiratory distress syndrome between 1985 and 2007.<sup>9-14</sup> The number of patients involved in these studies ranged from 16 to 180.<sup>10,13</sup> Mortality was measured at 45 days, at 180 days or after discharge from hospital. In early studies by Bernard and colleagues,<sup>9</sup> Laggner and colleagues,<sup>10</sup> and Weigelt and colleagues,<sup>14</sup> systemic corticosteroids had no impact on mortality; however, consistent with preliminary data showing reduced alveolar permeability with pharmacologic doses of corticosteroids, the tested therapies were short (limited to 1 or 2 d) and the doses were high (120 mg/kg

## KEY POINTS

- Routine use of corticosteroids for managing acute respiratory distress syndrome cannot be recommended because of insufficient scientific evidence to provide clinicians with clear and robust guidance.
- Meta-analyses of existing studies are largely underpowered to capture meaningful benefits or harmful effects of corticosteroids in patients with critical illness.
- Testing for corticosteroid responsiveness in acute respiratory distress syndrome has not been addressed by existing studies and should be incorporated in future research before this treatment is considered for clinical use.

methylprednisolone daily in 2 studies<sup>9,14</sup> and 8 g/d prednisolone in 1 study<sup>10</sup>). In 1998, Meduri and colleagues<sup>12</sup> published an RCT involving 24 patients, 16 of whom received a 32-day course of methylprednisolone (2 mg/kg daily), and 8 of whom were given a matching placebo. Mortality in hospital was lower for the group receiving corticosteroids (62.5% for placebo v. 12.5% for corticosteroids; relative risk [RR] 0.2,  $p = 0.04$ ).<sup>12</sup> This study uniquely focused on patients who had unresolved acute respiratory distress syndrome after 7 days of mechanical ventilation, and is one of the reasons systemic corticosteroids subsequently found a niche in the treatment of “late-phase acute respiratory distress syndrome.”

In an attempt to replicate these findings in a large, multicentre trial, the Acute Respiratory Distress Syndrome Network conducted the Late Steroid Rescue Study (LaSRS)<sup>13</sup> in which patients received a 25-day course of methylprednisolone (2 mg/kg daily) or a matching placebo after at least 7 days of mechanical ventilation. Although similar to the Meduri study in many ways, LaSRS differed in that corticosteroids were discontinued, rather than tapered, 3 days after extubation, potentially preventing recrudescence of respiratory failure. Moreover, the LaSRS protocol did not involve active screening for infection. Mortality at 60 days was similar between the 2 groups (28.6% for placebo v. 29.2% for corticosteroids; RR 1.0,  $p = 1.0$ ). In an a priori defined subgroup analysis, however, the duration of mechanical ventilation before the start of treatment with the study drug appeared to influence the effect of treatment. For the subgroup of patients given corticosteroids between 14 and 28 days after the start of mechanical ventilation, mortality was significantly higher compared with placebo (8% for placebo v. 35% for corticosteroids; RR 4.35,  $p = 0.02$ ). When corticosteroids were started within 7–13 days of mechanical ventilation, no significant difference in mortality was seen (36% for placebo v. 27% for corticosteroids; RR 0.75,  $p = 0.26$ ).

The most recent trial of corticosteroids for acute respiratory distress syndrome focused on early therapy (patients could be enrolled up to 72 h after meeting the criteria for a diagnosis of acute respiratory distress syndrome) and used a more modest dose of corticosteroids than in the previous trials (1 mg/kg daily for 28 d).<sup>11</sup> Enrolling 91 patients (28 in the placebo arm, 63 in the corticosteroid arm), this study failed to detect a statistically significant benefit in terms of mortality in hospital (42.9% for placebo v. 23.8% for corticosteroids; RR 0.56,  $p = 0.07$ ).

Just as clinical trials addressing this issue have varied both in their design and their results, systematic reviews vary in their selection of studies

for inclusion and in their results. Only 1 meta-analysis reported that corticosteroids reduce mortality in acute respiratory distress syndrome.<sup>15</sup> This conclusion hinged on the inclusion of a small number of available studies selected on the basis of illness-defining terms in use since the mid 1990s, and 3 of the studies might have been biased by stopping early for perceived benefit. Other meta-analyses have been inconclusive, unable to rule out the possibility of either benefit or harm with respect to patient mortality (Table 1).<sup>15–19</sup> Overall, meta-analyses have mostly shown that, even after pooling, existing studies lack power to measure meaningful effects of corticosteroids.

In light of the variation in study populations and corticosteroid regimens across trials, it is possible that steroids are harmful in some situations and helpful in others. Treatments of low dose and long duration appear most promising,<sup>20</sup> but determining whether corticosteroids truly reduce mortality associated with acute respiratory distress syndrome will require additional data. Meta-analyses of patient-level data offer the



**Figure 1:** Chest radiograph showing opacifications in both lung fields, compatible with acute respiratory distress syndrome.

#### Box 1: Evidence used in this review

- We conducted a literature search of MEDLINE and Embase for the following terms appearing in the article text: “acute lung injury,” “shock lung,” “acute respiratory distress,” “adult respiratory distress,” “acute respiratory distress syndrome,” “pneumonia,” “glucocorticoid,” “methylprednisolone,” and “hydrocortisone.” In addition, we searched for the following medical subject headings: “adult respiratory distress syndrome,” “pneumonia,” “adrenal cortex hormones,” “steroids” and “glucocorticoids.” We made no language-based restrictions to our literature search.
- To address each question, we identified the highest level of evidence from randomized controlled trials and meta-analyses, when available, or from observational studies.

advantages of powerful subgroup analyses, which could resolve the problem of heterogeneous populations. Unfortunately, it is likely that even an individual patient meta-analysis would require more data than are currently available in studies of this syndrome. However, trials of corticosteroid therapy in septic shock, either already completed or currently underway, may provide sufficient data for this purpose if subgroups with acute respiratory distress syndrome are clearly delineated. In the meantime, corticosteroid therapy cannot be recommended for the routine management of acute respiratory distress syndrome.

### Is corticosteroid therapy an option for specific subsets of patients?

As long as the effect of corticosteroid therapy on mortality remains uncertain, other potential benefits may have greater influence on a clinical decision to give or withhold corticosteroids. The most compelling additional outcome for which current research suggests potential benefit relates to the duration of mechanical ventilation. In a meta-analysis of the subset of studies that reported this outcome, corticosteroids were associated with 4.05 more ventilator-free days (95% confidence interval [CI] 0.22–8.71).<sup>16</sup>

Moreover, the broad criteria defining acute res-

piratory distress syndrome are similar to those of other illnesses that could respond to steroid therapy. These may simply accompany the syndrome or constitute the underlying cause of the syndrome. Thus, despite the lack of evidence to suggest improved survival for the general population of patients with acute respiratory distress syndrome, there are some situations in which careful consideration of corticosteroid therapy is prudent. In the setting of diagnostic uncertainty, clinicians must consider the response to steroids of illnesses that can masquerade as acute respiratory distress syndrome (i.e., profound hypoxemia and diffuse bilateral opacification on chest radiography). Examples of such conditions include cryptogenic organizing pneumonia and acute eosinophilic pneumonia, for which corticosteroids are a mainstay of therapy, and acute interstitial pneumonia, for which the role of corticosteroids remains uncertain. Pneumonia caused by specific infectious agents such as *Pneumocystis jiroveci* and tuberculosis are additional steroid-responsive illnesses to consider.<sup>21</sup> Although these illnesses are uncommon, in the absence of a clear risk factor for acute respiratory distress syndrome, their likelihood increases, and the potential for steroid responsiveness is an important consideration.

Other illnesses more commonly seen in the intensive care unit, such as severe bronchoconstriction and vasopressor-refractory septic shock,

**Table 1:** Reviews on corticosteroids in acute lung injury and acute respiratory distress syndrome

Review	Total no. of studies (no. of included RCTs)	Populations of interest in primary studies	Primary outcome	Results	Comments on subgroup analyses
Meduri et al. 2008 <sup>15</sup>	5 (5)	Acute lung injury, acute respiratory distress syndrome	Mortality	RR 0.76 (0.62–0.93)	Size of primary studies, no interaction test
Peter et al. 2008 <sup>16</sup>	5 (5) addressed therapeutic use	Acute respiratory distress syndrome or patients at risk of syndrome	Mortality	OR 0.62 (0.23–1.26)	Timing, dose and year of study completion not significant
Lamontagne et al. 2009 <sup>17</sup>	12 (12)	Acute lung injury, acute respiratory distress syndrome, severe pneumonia	Mortality	RR 0.84 (0.66–1.06)	9 trials of low-dose corticosteroids RR 0.68 (0.49–0.96); <i>p</i> = 0.047
Tang et al. 2009 <sup>18</sup>	9 (4)	Acute lung injury, acute respiratory distress syndrome	Mortality	RCTs RR 0.51 (0.24–1.09)	Timing, tapering, drug formulation, year of study completion, crossover design not significant
Agarwal et al. 2007 <sup>19</sup>	6 (4)	Acute lung injury, acute respiratory distress syndrome	Mortality	Early acute respiratory distress syndrome OR 0.57 (0.25–1.32) Late acute respiratory distress syndrome OR 0.58 (0.22–1.53)*	Not available

Note: OR = odds ratio, RCT = randomized control trial, RR = relative risk.  
\*The authors only reported analyses resulting from statistical pooling of observational and experimental studies.

may also be reasonable indications for the use of corticosteroids. Co-occurrence of steroid-responsive illnesses and acute respiratory distress syndrome renders trials even more difficult to interpret. Future research should be powered to distinguish the effects of corticosteroids on acute respiratory distress syndrome from their effects on co-presenting illnesses.

## What are the potential harms of corticosteroid therapy?

Physicians have been prescribing corticosteroids for decades and have learned to recognize and anticipate many of their harmful effects, such as severe secondary infections, stress ulceration, poor wound healing, psychoses and hyperglycemia.<sup>22</sup> Most of these complications can have severe consequences for patients with critical illness. Because these patients are at risk of a variety of serious complications related to their acute or chronic illnesses, it is often challenging to establish causality between therapies and potential adverse effects outside of clinical trials.<sup>23</sup>

To date, the harms of corticosteroids have received insufficient attention in critical care clinical trials.<sup>23</sup> A systematic review of corticosteroid therapy for acute respiratory distress syndrome found that high-dose regimens were associated with increased risk of infection (RR 1.77, 95% CI 1.23–2.54).<sup>17</sup> In contrast, data from LaSRS suggest no increase in severe infections with a low-dose regimen.<sup>13</sup> Unfortunately, definitions and screening protocols for infections vary considerably between studies,<sup>16</sup> and most did not adequately define, systematically screen for or adjudicate infectious complications.<sup>17</sup> Exceptions are 2 clinical trials by Meduri and colleagues, which involved vigilant protocols to screen for new infections; however, with a total of 24 and 91 patients, the studies were underpowered to detect differences in rates of infection.<sup>11,12</sup>

The association between corticosteroid therapy and weakness acquired during intensive care remains uncertain. An important concern that corticosteroids may affect the nerves and muscles of patients with critical illness comes from the largest trial of corticosteroids for patients with acute respiratory distress syndrome, in which neuromyopathy was reported in 9 patients, all of whom were in the corticosteroid arm ( $p = 0.001$ ).<sup>13</sup> Although the number of events in this study are too few to form firm conclusions, the results are supported by a recent case–control study that reported a statistically significant association between corticosteroid therapy and neuromuscular disability in patients in intensive care.<sup>24</sup>

Overall, research programs focusing on the efficacy of corticosteroid therapy in acute respiratory distress syndrome have insufficiently addressed the harm it causes in this highly vulnerable population. Designs of future trials of corticosteroids in acute respiratory distress syndrome will have to incorporate rigorous measures of clinically relevant new infections, weakness acquired during intensive care, gastrointestinal bleeding, and metabolic and psychiatric disorders. Equally important will be the implementation of systematic screening or independent adjudication based on a priori defined criteria for each adverse event. In an analogous situation, a large multicentre trial of steroid therapy for traumatic brain injury was stopped early after the investigators measured excess death and severe disability in the treatment arm.<sup>25,26</sup> Before that study, statistical pooling of the results from 16 smaller studies had not shown excess death or harm with high-dose corticosteroids.<sup>26</sup>

## Can we predict responsiveness to corticosteroid therapy?

In an ideal world, clinicians could access a test for steroid responsiveness in the heterogeneous population of patients with acute respiratory distress syndrome. Several assays of corticosteroid sensitivity are currently available for clinical research purposes.<sup>27–34</sup> One *ex vivo* assay measures suppression by dexamethasone of phytohemagglutinin-induced proliferation of lymphocytes in peripheral blood. Other *ex vivo* assays measure dexamethasone suppression of lipopolysaccharide-induced production of pro-inflammatory cytokines, such as interleukin-6 and tumour necrosis factor  $\alpha$ , and stimulation of anti-inflammatory proteins, such as the glucocorticoid-induced leucine zipper and FKBP51, from mononuclear cells in peripheral blood.<sup>34–36</sup>

Two important observations are apparent in previous studies of corticosteroid responsiveness. First, there is great variability between peoples' sensitivities to corticosteroids.<sup>27–31,33,35,37–39</sup> For example, the normal range of dexamethasone-induced inhibition of lymphocyte proliferation (after stimulation with phytohemagglutinin) is 10%–98%.<sup>28</sup> There are several reasons for such highly variable responses. Some polymorphisms of the gene encoding the glucocorticoid receptor can diminish or enhance sensitivity to glucocorticoids,<sup>40,41</sup> but these polymorphisms are uncommon and unlikely to explain such wide variations in sensitivity. Most differences in corticosteroid sensitivity between people are related to variations in transcription of the glucocorticoid recep-



tor gene and to posttranscriptional and posttranslational modifications. These differences depend on several factors, including specific tissue and inflammatory milieu.<sup>42-45</sup> The range of variation in corticosteroid responsiveness among people suggests that, in previous trials, corticosteroids may have had beneficial effects in some patients, but not beneficial (or even harmful) effects in others.

Second, some assays predicted clinical response to corticosteroids of inflammatory conditions such as ulcerative colitis,<sup>31</sup> asthma,<sup>27,29,44,46,47</sup> psoriasis<sup>48</sup> and rheumatoid arthritis.<sup>49</sup> An assay of corticosteroid responsiveness may provide critical information to distinguish patients with acute respiratory distress syndrome who will respond well to corticosteroid therapy from those who will not.

### Gaps in knowledge

Editorialists have emphasized the need for more conclusive data,<sup>50</sup> but future studies on the efficacy of corticosteroid therapy for acute respiratory distress syndrome will face many challenges. Competing indications and contraindications for corticosteroid therapy among patients with this syndrome threaten their eligibility to participate in such studies and ongoing adherence to protocol by causing many patients in the control arm to also receive corticosteroids. The evolving literature on the role of corticosteroids in sepsis, in particular, will constitute a substantial challenge if patients who also have septic shock are not enrolled in trials.

Firmly held beliefs about the role of corticosteroids in acute respiratory distress syndrome and entrenched practice patterns may affect decision-making among some intensive care specialists, compromising the feasibility of future RCTs.

Other challenges include the need for complex, data-heavy, resource-intensive measurement of myriad potential adverse effects of corticosteroid therapy in the intensive care unit. The lack of evidence concerning the potential harm caused by corticosteroids represents the largest gap in previous studies, but rigorous measures of these outcomes are costly. In addition, complex and resource-intensive measurement of the multiple effects of corticosteroids is required, specifically those pertaining to the immune regulatory, metabolic, endocrine, vasoregulatory and neurocognitive functions. Validating ways of obtaining more reliable measurement will thus generate considerable costs.

There are essentially 3 potential paths forward. Investigators could consider a large pragmatic RCT comparing early, prolonged corticosteroid therapy to placebo, and providing liberal criteria for giving steroids in the placebo arm. This

approach might be acceptable to most intensivists, but a prohibitively large sample may be required. Alternatively, investigators could target a distinct, as yet unspecified, subgroup of patients with acute respiratory distress syndrome who have no competing indications for corticosteroids, thus dealing with the problem of heterogeneous patient populations in previous studies. A disadvantage of this strategy is that it would impose new feasibility challenges and limit generalizability. A third option is to conduct a review of individual patient data, with meta-analysis including all trials of corticosteroid therapy in acute respiratory distress syndrome, in addition to trials of corticosteroids in sepsis, for which discreet subgroups of acute respiratory distress syndrome are clearly defined. An example of this option is the Adjunctive Corticosteroid Treatment in Critically Ill Patients With Septic Shock study (clinicaltrials.gov registry no. NCT01448109) currently underway in Australia and New Zealand, with a target enrolment of 3800 patients.

### Conclusion

The role of corticosteroids in managing acute respiratory distress syndrome remains uncertain. Despite a strong physiologic rationale with supporting evidence from laboratory research, clinical trials have yet to establish that the therapy improves survival, and the threat of important and long-term complications looms large. Specific subgroups with a high likelihood of responding to treatment remain undefined, and bedside tests for responsiveness in this setting are not sufficiently developed for use in routine clinical care.

Although current evidence does not support routine use of corticosteroids to treat this syndrome, there are specific situations where their use is prudent; for example, when an alternative diagnosis or underlying cause will respond to treatment with steroids (e.g., cryptogenic organizing pneumonia). Special challenges to conducting definitive trials in this field have thwarted investigators in the past. For the near future, clinicians can look forward to the completion of related clinical trials.

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**Contributors:** All of the authors contributed to the conception and design of this review, the acquisition and interpretation of the data and the writing of the manuscript. All of the authors approved the final version submitted for publication.