Corticosteroids for patients with acute respiratory distress syndrome: a systematic review and meta-analysis of randomized trials

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Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

**TITLE:** Corticosteroids for patients with acute respiratory distress syndrome: a systematic review and meta-analysis of randomized trials

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Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

What’s new?:

Acute respiratory distress syndrome (ARDS) is a life-threatening inflammatory pulmonary process characterized by rapid progression requiring respiratory support, without specific pharmacological therapy available. Corticosteroids have been proposed as a treatment for ARDS, prompting us to conduct a systematic review and meta-analysis on corticosteroids use in ARDS, with a critical appraisal and quality of evidence assessment of eligible studies. Our review of seven RCTs suggests that corticosteroid use may reduce mortality and ventilation duration, while increasing ventilator-free days. The case has grown stronger for corticosteroids in ARDS, and while enticing potentially to COVID-19 induced ARDS patients, the certainty of the evidence is limited by the low number of studies, low sample sizes, the clinical differences of the patient populations studied and the known harms due to corticosteroid use. Caution is urged in extrapolating these ARDS results to the bedside.
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

ABSTRACT:

Introduction:
Acute respiratory distress syndrome (ARDS) is a rapidly progressing inflammatory lung disease with a high mortality rate without specific pharmacological therapy.

Objective:
We conducted a systematic review and meta-analysis on corticosteroid use in ARDS.

Methods:
A search of four medical literature databases was conducted. We retained randomized trials (RCTs) of corticosteroids in hospitalized adults with ARDS in a search up to February, 2020. Two reviewers identified eligible studies, independently extracted data, and assessed risk of bias. Authors assessed the certainty of the evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.

Results:
We included seven RCTs (n=851 patients). Corticosteroids reduced all-cause mortality (risk ratio [RR] 0.75, 95% CI: 0.59 to 0.95, p=0.02, moderate certainty) and duration of mechanical ventilation (mean difference [MD] -4.93 days, 95% CI: -7.81 days to -2.06 days, p<0.001, low certainty), and increased ventilator-free days (VFD) (MD 4.28 days, 95% CI: 2.67 days to 5.88 days, p<0.001, moderate certainty), when compared to placebo.

Corticosteroids also increased the risk of hyperglycemia (RR 1.12%, 95% CI: 1.01 to 1.24, p=0.03, moderate certainty), and the effect on neuromuscular weakness was unclear (RR 1.30, 95% CI 0.80 to 2.11, p=0.28, low certainty).
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

Conclusions:

These results suggest that systemic corticosteroids may potentially improve mortality, ventilator duration, and VFD in patients with ARDS. However, the studies included different corticosteroid classes and initiated the corticosteroid doses at different times, as well as different dosing regimens. Thus caution in the actual clinical application of these results is recommended.

Short title: Corticosteroids in ARDS

Keywords: Acute Respiratory Distress Syndrome, corticosteroids, mortality, systematic review
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

INTRODUCTION:

Acute respiratory distress syndrome (ARDS) is a progressive life-threatening inflammatory pulmonary process characterized by alveolar injury leading to diffuse alveolar damage. Hospital mortality approaches 40%, with 200,000 cases occurring annually in the United States of America (USA). Timely diagnosis, treatment, and support may improve patient outcomes [1-3]. Corticosteroids have been proposed as a treatment for ARDS with particularly heightened interest in a potential role in reducing the pulmonary and systemic damage [4]. Corticosteroids reduce inflammatory responses and should act on the exudative, proliferative, and fibrotic phase in ARDS pathology [5, 6]. The efficacy of corticosteroid treatment in ARDS patients remains unclear. For example, a recent Cochrane review of randomized controlled trials (RCTs) revealed no significant difference in early all-cause mortality ≤ three months, and no significant reduction in mechanical ventilation duration[5]. However, a recently published RCT suggested a potential beneficial effect of dexamethasone in ARDS, with reduced mortality, increased ventilator-free days, and a decrease in the mechanical ventilation duration [4].

At this time, ARDS treatment is based on supportive care and management of the underlying illness, and currently, there are no approved pharmacological interventions for ARDS.

Given the clinical equipoise and pressing need for optimal patient management, our systematic review aimed to consider the body of RCT evidence and determine the efficacy and safety of corticosteroids in patients with ARDS.

METHODS:
**Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials**

**Data Sources and Searches**

The authors developed a protocol for this rapid review, with pre-determined eligibility criteria and methods. Given the global emergency situation and the present delay in PROSPERO registration, the authors proceeded with this rapid review without formal registration.

Our initial perusal of the literature suggested the existence of relevant systematic reviews on this clinical question. We planned to examine existing systematic reviews, and if judged methodologically strong, then we would incorporate them. We found two systematic reviews that we judged to be relevant.

We used the AMSTAR 2 critical appraisal tool for systematic reviews on this topic, the design and execution of the Lewis et al. (2019) review [2]. The Sun et al. (2019) systematic review also had an adequate methodology. However, we judged it overall to be of lower methodological quality to the Lewis et al. (2019) Cochrane review, and it also included methodologically weaker retrospective studies, which was not our focus [2, 7]. Therefore, we accepted and incorporated the Lewis et al. (2019) review data as part of our analysis [2].

We then updated the electronic database search spanning 2018 to February 14th, 2020, imposing an overlap search period to ensure that any publications that were in the publication pipeline were not missed by Lewis et al. (2019) [2]. For some searches, we also set earlier search periods as a means of quality assurance.

We searched i) MEDLINE/PubMed (1996 to February 14th, 2020) and applied a search filter for randomized controlled trials with no limits ii) EMBASE (2018 to February 14th, 2020), limiting the search to humans iii) Cochrane CENTRAL for trials (searched to February 14th,
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

2020), no limits and iv) CINAHL (2000 to February 14th, 2020, limiting to humans (see appendix for search strategy of MEDLINE and EMBASE).

Study Selection

Eligible studies were parallel-group RCTs that randomized patients with ARDS of any cause, to corticosteroid therapy versus placebo or standard treatment or no glucocorticoids. We sought studies reporting on at least one of the following outcomes: all-cause mortality, duration of mechanical ventilation (DMV), duration of hospitalization, ventilator-free days (VFD) (defined as the number of days alive free from mechanical ventilation), or adverse effects and complications of corticosteroid. We abstracted data for each outcome at the longest follow-up duration. A team of two reviewers independently screened titles and abstracts in duplicate, obtained full texts of articles that either reviewer considered potentially eligible, and determined final review eligibility from the full texts of studies.

Data Abstraction and Quality Assessment

Two reviewers independently extracted relevant data (study design, study demographics such as author, year, location and center status, patient demographics such as age, gender, sample size, intervention [corticosteroid class, the timing of corticosteroid initiation, and dosing regimens], comparator, and outcomes that included all-cause mortality, duration of mechanical ventilation, ventilator-free days and adverse events) and assessed risk of bias using the Cochrane risk of bias tool for RCTs [8]. We also assessed two additional domains for risk of bias that we felt were potential high risk of bias factors (stopping early for benefit and baseline imbalance). We also assessed the risk of bias of the RCTs included in the Lewis
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

et al. 2019 systematic review independent of the previously published reported assessment [2]. We sought this additional layer of quality assurance and independently appraised risk of bias as opposed to a blind acceptance of the included review’s risk of bias determination. In instances when a study was not available as a full manuscript, we defaulted to the Cochrane risk of bias determination and details. We adopted response options for risk of bias to be ‘yes’, ‘probably yes’, ‘probably no’, and ‘no’, to remove the often elevated ‘unclear’ responses reviewers often report, which hampers a more definitive interpretation of risk of bias [9].

For the overall risk of bias assessment, our approach was based on our judgement on whether key domains (randomization, allocation concealment, blinding of patients and health care providers, data loss and stopping early for benefit) were optimally reported. If any of the domains were not reported as an optimal execution, then we judged the study as high risk of bias.

Data Synthesis and Analysis

We used random-effects modeling for all analyses with Mantel–Haenszel, used risk ratio (RR) for dichotomous outcomes, and we used mean difference (MD) for continuous variables [10]. We hypothesized that the following would be associated with a more substantial treatment effect: greater ARDS severity, the timing of corticosteroid therapy (<7 days versus ≥7 days), and a higher risk of bias. When data were reported as medians and inter-quartile ranges, we converted these to means and standard deviations for meta-analytical pooling [11].
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

We decided that if continuous outcomes were reported using varying measurement scales that we would pool via the standardized mean difference (SMD) and not MD.

We planned to conduct subgroup analyses by ARDS severity as well as dose and early versus late administration of corticosteroids. We also planned to conduct sensitivity analyses based on a differential risk of bias. We would flag studies stopped early for benefit as being at high risk of biased estimates [12]. Our intent in sensitivity analysis was to separate these high risk of bias studies and examine their effect on the pooled estimate.

We conducted the meta-analyses using Review Manager 5.3 [13]. We assessed heterogeneity by visual inspection of forest plots, a Cochrane chi-square statistical test for heterogeneity, and the $I^2$ statistic (with $>50\%$ considered as significant heterogeneity warranting exploration and explaining) [8, 14].

We report 95% CI measures of uncertainty with presented estimates of effect. To estimate the absolute effects of the intervention, we sought large RCTs providing best estimates of these outcomes [15].

To estimate the baseline risk in computing the absolute effects, we used the control event rate. To compute the absolute effect, we multiplied the baseline risk by the relative effect (and 95% CIs).

GRADE Methods
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

We utilized the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to rate the certainty of the evidence for each outcome and for the entire body of evidence [16]. This outcome centric approach for rating effect estimate certainty considers the body of evidence via risk of bias, imprecision, inconsistency (heterogeneity), indirectness, and publication bias domains.

RESULTS:

We included 6 RCTs that informed the relevant meta-analyses obtained from the prior systematic review [2]. Our updated database searches identified 1,524 unique citations (MEDLINE/PubMed (n=253), EMBASE (n=371), CINAHL (n=463), and Cochrane CENTRAL (n=437). After reviewing references and following the screening of titles and abstracts as well as full-texts, one RCT was deemed firmly eligible to inform our systematic review (Figure S1 Flow diagram). We, therefore, included a total of seven RCTs as part of this updated review (n=851 patients) with relevant study characteristics shown in Table 1.

Study characteristics

Primary studies were conducted in multiple countries (China, Egypt, Kuwait, Spain, Thailand, and the USA), with 43% being multicenter trials. Non-profit sources funded nearly all the studies, except for Zhao et al. (2014), whose funding source was uncertain [17]. Sample sizes ranged from 26 to 277 of mostly male (51.5-85.2%), typically over 50 years of age, hospitalized patients. Patients received corticosteroid treatment with hydrocortisone [18, 19], methylprednisolone [5, 17, 20], dexamethasone [4], or inhaled budesonide. A placebo was used in five studies [5, 17-20], with two studies [4, 21] comparing typical ARDS
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

management with and without corticosteroid. Follow-up ranged from 28 days to 180 days from enrollment. Five studies [4, 17-20] initiated study treatment within seven days of ARDS diagnosis, one study [5] initiated study treatment after at least seven days after ARDS diagnosis, and one study [21] did not report the timing of study protocols concerning ARDS diagnosis.

Risk of bias assessment

Three [5, 19, 20] of seven trials (43%) enrolling 51.5% of the total sample had a low risk of bias (Table S1). The loss to follow-up was rare: six trials (85.7%) had a near-complete follow-up with loss that was deemed not biasing, and with only one study, we judged had attrition greater than 5%. Worst-case, best-case plausible modeling assumptions about the outcomes of patients lost to follow-up were not needed. No studies were stopped early for benefit. We also decided to develop no funnel plots or statistical tests for publication bias due to the limited interpretability when the study number is <10, as was our case. We used the comprehensiveness of the search strategy for this judgment and felt confident that it was exhaustive.

Outcomes

All-cause mortality

Seven trials [4, 5, 17-21] (n=851) reported on all-cause mortality, whereby 119 of 443 (26.9%) patients died in the corticosteroid groups compared with 151 of 408 (37.0%) in the control groups (RR 0.75, 95% CI 0.59 to 0.95), p=0.02; I² = 22%; moderate certainty) (Figure
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

1. Reported data did not optimally allow for sub-group analyses based on ARDS severity. Absolute effects were 93 fewer deaths per 1,000 affected individuals (from 152 fewer to 19 fewer) (GRADE evidence profile Table S2).

We conducted a sensitivity analysis by removing the high risk of bias studies [17, 18, 21]. The mortality benefit with corticosteroids was robust and consistent, RR 0.77 (95% CI 0.61 to 0.98), p=0.03. The sub-group test of the interaction of the timing of steroid therapy (Figure S2) showed no difference (p=0.13) for this outcome. Additional sub-group analysis by corticosteroid class had no impact on mortality (p=0.94).

Duration of mechanical ventilation

Five trials (n=645) reported on the DMV and the use of corticosteroids reduced ventilation duration (MD -4.93 days, 95% CI -7.81 to -2.06 days, p=0.0008; I² = 87%; low certainty) (Figure 2). The mean difference was 4.93 fewer days (from 7.81 fewer to 2.06 fewer days) (Table S2).

We performed a sensitivity analysis by removing a high risk of bias studies [4, 17, 21], and the results were robust and consistent (MD -4.09 days, 95% CI -7.76 to -0.42, p=0.03, I² = 86%). Substantial statistical heterogeneity was identified in the pooled data, and our various sensitivity analyses modeling were unable to explain this based on possible methodological or clinical study differences.

Ventilator-free days up to day 28
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

The five trials (n=771) that examined ventilator-free days up to day 28 revealed a significant increase in the mean number of ventilator-free days with corticosteroid treatment (MD 4.28 days, 95% CI 2.67 to 5.88 days, p<0.00001; I² = 21%; moderate certainty) (Figure 3). The mean difference was 4.28 more ventilator-free days (from 2.67 more to 5.88 more days) (Table S2).

We conducted a sensitivity analysis by removing the high-risk bias study [4, 18], and found the pooled estimate to be robust and consistent with a MD increase of 4.37 (95% CI 1.69 to 7.04), p=0.001. The sub-group test of interaction (Figure S3) of the timing of steroid therapy showed no difference (p=0.94) for this outcome.

**Hyperglycemia**

In 3 trials (n=565) that reported on hyperglycemia, 229 of 300 (76.3%) patients had significantly more hyperglycemia in the corticosteroid group compared with 182 of 265 (68.7%) in the control group (RR 1.12, 95% CI 1.01 to 1.24, p=0.03; I² =0%; moderate certainty) (Figure 4). The absolute effect was 82 more events per 1,000 affected individuals (from 7 more to 165 more) (Table S2).

**Infections**

We judged that the infection data where reported lacked clarity and could not be pooled for meaningful interpretation.

**Neuromuscular weakness**
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

In two trials (n=270) that examined neuromuscular weakness, 30 of 151 (19.9%) patients had neuromuscular adverse events in the corticosteroid group compared with 22 of 119 (18.5%) in the control group (RR 1.30, 95% CI 0.80 to 2.11, \( p=0.28; \hat{I}^2=0\%\); very low certainty) (Figure 5). The absolute effect was 55 more events per 1,000 affected individuals (from 37 fewer to 205 more) (Table 3).

DISCUSSION:

Our systematic review and meta-analysis examined the effect of corticosteroid use in hospitalized ARDS patients. We found a significant reduction in mortality and mechanical ventilation duration and an increase in ventilator-free days. However, there were increased hyperglycemia events, while the effect on neuromuscular weakness was uncertain. The prior 2019 Cochrane systematic review found low-certainty evidence that corticosteroids may reduce mortality within three months of the onset of ARDS, and their 95% confidence interval suggested both an increase and reduction of deaths. There was a similar presence of benefits and harms for mechanical ventilation. However, our improved power and precision found confidence interval boundaries fell on the benefit side for both mortality and mechanical ventilation duration.[2]. Despite the statistically significant findings, most of the outcomes were rated down to low or moderate or certainty of the evidence using GRADE methods. GRADE rates certainty of the evidence-based on issues of risk of bias, imprecision, and heterogeneity. Low certainty of the evidence implies one should have low confidence that an outcome’s effect estimates approximate the truth for a specific intervention. Low certainty of the evidence also suggests that there is the potential for future research to change the outcome’s effect estimates for a particular treatment. Estimates generated by our review
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

were more precise and yielded a significant treatment effect for several outcomes. Moderate certainty of the evidence suggests one should have moderate confidence that the direction and magnitude of an outcome’s effect estimates would change significantly with additional research.

Specifically, based on our findings, we have moderate certainty that there is an absolute risk reduction of 9.3% fewer deaths in adults with ARDS being treated with corticosteroids (Figure 1 and Table S2). We also have low certainty that the duration of mechanical ventilation in hospital is reduced by approximately five days on average (Figure 2, Table S2), and moderate certainty that ventilator-free days increased by an average four days (Figure 3, Table S2) with corticosteroid treatment for ARDS. The review also found, with moderate certainty, an absolute increase of 8% more hyperglycemia adverse events in patients being treated with corticosteroids (Figure 4 and Table S2). However, there was a very low certainty of a plausible yet non-significant increase in the neuromuscular weakness events of 5.5% (Figure 5, Table S2). The timing of corticosteroid therapy may be a factor in its benefits. Our subgroup analysis revealed increased mortality at 60 days with the use of corticosteroids when initiated ≥14 days from ARDS diagnosis (increased RR was 4.35 (95% CI 1.03 to 18.39), p=0.05 for > 14 days) (Figure S4).

Our study has several strengths. Firstly, we developed explicit eligibility criteria based on patients with ARDS and conducted a comprehensive search of four electronic databases. Moreover, we assessed the eligibility of all studies and risk of bias in replicate and independently, addressing essential outcomes, and performed a small number of plausible sub-group and sensitivity analyses. In addition, we used the GRADE approach to assess the certainty of the evidence. Our study differs from the prior Cochrane review in that we
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

included seven RCTs (as opposed to six RCTs included in the Cochrane review), which improved the precision, sample size, and the number of events that led to detecting important differences. This translated to increased confidence in the estimates of effect. We found our sensitivity analysis results were robust and consistent with the removal of high-risk studies, therefore, we did not rate down for risk of bias for all-cause mortality, the duration of mechanical ventilation and ventilator-free days, in contrast. Additionally, we modified the responses of the risk of bias tool that assigns either a “probably no” or “probably yes” for a risk of bias instead of uncertain. This is in contrast to Cochrane review, which did rate the risk of bias high for those outcomes, due to the risk of bias assignment of “uncertain” to certain studies and did not perform a sensitivity analysis with removal of high risk studies to assess robustness of results. We also reported on additional outcomes on adverse events that the prior review did not report on, such as hyperglycemia and neuromuscular weakness.

Our review also has limitations worth mentioning, which include the use of various corticosteroid agents with different doses, leaving the optimal choice of agent and dosing open to question. Moreover, we were unable to search the gray literature or conference abstracts for pragmatic reasons, and thus we may have missed unpublished studies. Furthermore, we noted significant statistical heterogeneity in the pooled estimates of mechanical ventilation duration. We were unable to explain the differences by any methodological or overt clinical heterogeneity between the five studies, except that the outlier study in many outcomes, Rezk (2013), which reported the lowest patient number, had the least duration of ventilation and was at a high risk of biased estimates. We were limited in the exploration of heterogeneity due to the sub-optimal reporting overall.

While infectious pneumonia is the most common inciting factor leading to ARDS, ARDS is a heterogeneous disease with other possible etiologies including severe sepsis, gastric
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

aspiration, trauma, severe acute pancreatitis, transfusion-associated lung injury and drug reactions [1, 22]. The various etiologies leading ARDS result in progressive inflammatory damage to the lung tissue: In the acute phase (at 1-6 days), there is increased interstitial and alveolar edema. In the subacute phase (at 7-14 days), there is a proliferation of alveolar epithelial type II cells, with fibroblast proliferation and collagen deposition. In the chronic phase (>14 days), there is more fibrosis and continued epithelial repair [22]. Corticosteroids may function to reduce the inflammation found in the acute and subacute phases more than ameliorate the fibrotic changes in the chronic phase [6, 20, 22].

There is a significant variation in the use of corticosteroids for ARDS treatment amongst those who treat ARDS. A 2013 survey of North American intensivists (n=103 responses) investigating the use of corticosteroids in ARDS found that responses varied by intensity and etiology: with 12% asserting using corticosteroids “sometimes” or “most always” in ARDS, 22% using corticosteroids “sometimes” or “most always” in severe ARDS, but 90% using corticosteroids “sometimes” or “most always” in ARDS with an undifferentiated etiology [23]. A systematic review of community-acquired pneumonia in hospitalized adults suggests treatment with corticosteroids reduces mortality, the need for mechanical ventilation, and length of hospital stay [24]. Guidelines published by the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) suggest the use of corticosteroids in patients with moderate to severe ARDS within 14 days of onset with moderate certainty [25].

The research evidence on the use (benefits) of corticosteroids in ARDS patients is highly ambivalent and complex and based largely on observational, non-randomized evidence. For example, a recently published multicenter retrospective cohort study in medical center ICUs
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials across Taiwan by Tsai et al. (2020) sought to assess the effectiveness of corticosteroids in patients presenting with influenza-associated ARDS [26]. The study revealed that of the 241 patients with influenza-associated ARDS, those receiving early corticosteroids had a significantly higher hospital mortality rate than those who did not get early corticosteroid (43.5% (37/85) versus 19.2% (30/156), p < 0.001). Early corticosteroid treatment was independently associated with increased hospital mortality in overall patients [an adjusted OR of 5.02 (95% CI 2.39-10.54), p < 0.001] and among all examined subgroups. Researchers found that a higher dose and earlier treatment was linked to higher hospital mortality. Moreover, they found that earlier treatment was related to a significantly increased odds of subsequent bacteremia [an adjusted OR of 2.37 (95% CI 1.01-5.56)].

The Tsai et al. (2020) study raises important questions and underscores the urgency for robust comparative research to add clarity since these findings are based on observational evidence that is confounded by selection bias [26]. This suggests that while estimates may be potentially biased (even when using adjusted analysis estimates), they do underscore the potential harms of corticosteroids in the population of influenza linked ARDS. In a similar light, a meta-analysis that focused on influenza pneumonia and included ten observational studies (n=6,548), revealed an increased risk of death when patients were given corticosteroids (RR 1.75 (95% CI 1.3 to 2.4, p=0.0002)[27].

A retrospective study that adjusted for known confounders examined a coronavirus linked syndrome, the Middle East Respiratory Syndrome (MERS), and found corticosteroid use was associated with delayed RNA clearance of the coronavirus without a difference in mortality [28].
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

Similarly, Zhou et al. (2020) examined the use of corticosteroids in influenza-associated ARDS and severe pneumonia via a meta-analysis and included 15 studies (n=6,427 patients) examining mortality (comprised of observational studies, except for one RCT) [29]. They found that corticosteroid therapy was associated with significantly higher mortality (OR 1.53, 95% CI (1.16, 2.01)) and incidence of nosocomial infection (OR 3.15, 95% CI (1.54, 6.45)).

Moreover, Baek et al. (2020) looked at the impact of corticosteroid therapy in the early phase of acute respiratory distress syndrome by employing a propensity-matched cohort study design [30]. In this Korean study, the researchers compared patients treated with methylprednisolone 40 to 180 mg/day or equivalent (n = 404) to those who did not receive steroids (n = 161), and found the overall mortality at 28 days was not significantly different between the corticosteroid-treated and control groups (43.8% versus 41%, p = 0.541). At 90 days, the overall mortality rate was higher in the corticosteroid-treated group than in the control group (59.2% versus 48.4%, p = 0.021). However, on propensity score matching, corticosteroid therapy was not associated with a higher 28-day mortality rate (odds ratio, 1.031; 95% confidence interval, 0.657 to 1.618; p = 0.895). And corticosteroid therapy was not associated with a higher 90 days mortality (odds ratio, 1.435; 95% confidence interval, 0.877 to 2.348; p = 0.151).

Additionally, a well-conducted, recently published Cochrane review by Lansbury et al. (2020) that explored corticosteroids as adjunctive therapy in the treatment of influenza, raises additional concerns of corticosteroids in influenza-like illnesses [31]. Researchers found increased odds of mortality with corticosteroid therapy (OR 3.90, 95% CI 2.31 to 6.60) and increased odds of hospital-acquired infection in people treated with corticosteroids (unadjusted OR 2.74; 95% CI 1.51 to 4.95).
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

A very recent study out of a hospital in Wuhan, China [32] sought to describe the clinical characteristics and outcomes in patients with COVID-19 pneumonia who developed ARDS or died and offers a depiction of the COVID-19 patients. They retrospectively examined 201 patients with confirmed COVID-19 pneumonia admitted up to January 26, 2020 with follow-up to mid-February and found that the median age was 51 years (IQR range, 43-60 years), and 128 (63.7%) patients were male. Eighty-four patients (41.8%) developed ARDS, and of those 84 patients, 44 (52.4%) died. In those 84 who developed ARDS, compared with those who did not, more patients presented with dyspnea (59.5%) versus 25.6%, respectively, and had comorbidities such as hypertension (27.4%) patients versus 13.7% of patients, respectively. Moreover, 19.0% of patients had diabetes versus 5.1% of patients, respectively. Researchers employed a bivariate Cox regression analysis and found that the risk factors associated with the development of ARDS and progression from ARDS to death included older age (hazard ratio [HR], 3.26; 95% CI 2.08-5.11; and HR, 6.17; 95% CI, 3.26-11.67, respectively), neutrophilia (HR, 1.14; 95% CI, 1.09-1.19; and HR, 1.08; 95% CI, 1.01-1.17, respectively), and organ and coagulation dysfunction, e.g. higher lactate dehydrogenase (HR, 1.61; 95% CI, 1.44-1.79; and HR, 1.30; 95% CI, 1.11-1.52), respectively and D-dimer (HR, 1.03; 95% CI, 1.01-1.04; and HR, 1.02; 95% CI, 1.01-1.04, respectively). High fever (39 °C) was associated with a higher likelihood of ARDS development (HR, 1.77; 95% CI, 1.11-2.84) and a lower likelihood of death (HR, 0.41; 95% CI, 0.21-0.82). Researchers also found that administration of methylprednisolone significantly decreased the risk of dying (HR, 0.38; 95% CI, 0.20-0.72), suggestive of a potential benefit.

Comparative effectiveness research performed on specific patient populations is urgently required since accumulated evidence thus far is weak and argues overall against
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials
corticosteroids in virus-induced ARDS. We also caution in making the extrapolation of using corticosteroids in other virus linked ARDS without the additional evidence in the patient population. For example, although the use of corticosteroids for COVID-19 (SARS-Cov 2 coronavirus) induced ARDS is controversial, there are estimates that presently approximately 40-50% of patients with COVID-19 are receiving corticosteroids treatment [33].

Our systematic review findings in critically ill patients with ARDS do provide some evidence and promise for the use of corticosteroids in ARDS patients. We argue that the case has been made stronger by our review of RCTs. While one may also speculate on the evidence being indirect and potentially applicable to COVID-19, one should do so timidly, especially in the context of observational research examining corticosteroids in viral-induced ARDS.

Furthermore, critical consideration of issues around dosing and administration details, in the context of harmful side effects known to occur with higher doses and more prolonged steroid use is required. This demands urgent, robust, trustworthy, and direct evidence on the effectiveness of corticosteroid use in COVID-19 patients to help inform much needed clinical practice and public health guidance. We urge caution in the interpretation of any of these results as directly applicable to COVID-19 patients. Moreover, we are largely dealing with small numbers of studies with small sample sizes and thus much uncertainty.

Conclusion

In this updated systematic review and meta-analysis of RCTs, we found that the early use of systemic corticosteroids in ARDS patients may improve mortality, ventilator duration, and ventilator-free days. However, the overall evidence landscape, driven mainly by weaker non-
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

randomized observational type studies, is very conflicted. Adequately powered, well-designed, robust RCTs with longer-term follow up that includes harm outcomes are needed to confirm or refute our systematic review findings. Until then, clinicians may consider the balance between potential desirable and undesirable effects of corticosteroids when managing patients with ARDS. Caution is urged given potential harms of corticosteroid use and particularly in extrapolating these findings beyond ARDs patients used in this analysis. Specifically, we urge careful reflection when considering using corticosteroids in COVID-19 despite observational evidence suggesting benefits. Such non-randomized evidence is plagued with confounding.

Author Contributions

Study design [MJM, WA, PEA], data abstraction and risk of bias [MJM, KA, PEA], statistical analysis [MJM, WA, PEA], data interpretation [MJM, WA, PEA]. All authors participated in drafting the manuscript and approved the final version.

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Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

Conflict of interest

None declared.

DISCLOSURE STATEMENT:

Authors have disclosed no conflicts of interest, and have received no funding of any means for this study. Authors do work in guideline development as well as are part of the GRADE Working Group.

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Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

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Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

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**TABLES:**

**Table 1: Study characteristics**

| Author, year, location, single versus multicenter | Sample size total n; intervention arm n; control arm n | % males | Inclusion criteria | Duration of follow-up | Treatment intervention arm/dose versus treatment control arm/dose | Degree of hypoxemia or lung injury | Reported cause of ARDS | Reporte d comorbidities (any notable findings) |
|-----------------------------------------------|------------------------------------------------------|---------|-------------------|----------------------|---------------------------------------------------------------|-----------------------------------|------------------------|---------------------------------------------|
| Steinberg 2006; USA, multicenter[5]            | 180; 89; 91                                          | 54.4%   | Patients intubated and receiving mechanical ventilation 7 to 28 days after the onset of acute respiratory distress syndrome (ARDS) Continuous mechanical ventilation and persistent bilateral | After at least seven days after ARDS diagnosis Intravenous methylprednisolone sodium succinate (methylprednisolone) diluted in 50 ml of 5 percent dextrose in water; single dose of 2 mg of methylprednisolone per kilogram (kg) of predicted body weight was followed by a dose | Corticosteroid arm: lung injury score mean (± standard deviation [±SD]): 3.3 (± 0.9), PaO2/FiO2, lung injury score mean | Both arms reported multiple trauma, sepsis, multiple transfusions; aspiration, pneumonia, other, and both groups were roughly | Note, there was a higher number of serious adverse events (neuromyopathy) in the corticosteroid group (9 versus 0). |
### Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

| Meduri 2007; USA, multicenter[20] | Rando
mized 51.6% | Adult intubated patients receiving mechanical ventilation; meeting criteria for ARDS according to American- | Up to 28 days | 2:1 randomization protocol, with per-protocol analysis | Within 72 hours of ARDS diagnosis Corticosteroid methylprednisolone; loading dose of 1 mg/kg, then | Both arms reported multiple trauma, sepsis, pancreatitis, multiple Sepsis in both intervention and control arms; 66% sepsis |
|-----------------------------------|-------------|--------------------------------------------------|--------------|-------------------------------------------------|---------------------------------------------|------------------------------------------------------------------|
| Per-protocol | | Infiltrates were required from the onset of ARDS to study entry. On the day of study entry, the PaO2/FiO2 ratio had to be less than 200. | | Of 0.5 mg per kg of predicted body weight every 6 hours for 14 days, a dose of 0.5 mg per kg of predicted body weight every 12 hours 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 hours. Tapering occurred over a two-day period if disseminated fungal infection or septic shock developed or the patient was able to breathe for a period of 48 hours without assistance versus placebo (50 ml of 5 percent dextrose in water), 50 mL of 5% dextrose in water of 0.5 mg/kg. | | Balanced as to predisposing cause (7-28 days) (yes) | |
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

| Liu, 2012, China, single-center[18] | Per Cochrane Randomized, 26; 12; 14 | 73.0% | Per Cochrane “Inclusion criteria: 18 to 80 years of age; fulfils criteria of ARDS according to the AECC (Bernard 1994); ARDS diagnosis within 3 days of admission; fulfils CIRCI diagnosis according to Society of Critical Care Medicine Guidelines” | Unclear | Per Lewis et al. (2019): **Within 72 hours of ARDS diagnosis** “hydrocortisone 100 mg IV 3 times a day for 7 days” versus “normal saline; 0.9% IV 100 mg 3 times a day for 7 days” | Unclear | Unclear | Unclear |
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

| Study                        | Country | Year | Participants | Exclusion Criteria | Inclusion Criteria | Treatment | Outcome Measures                                                                 |
|------------------------------|---------|------|--------------|--------------------|-------------------|-----------|----------------------------------------------------------------------------------|
| Rezk, Kuwait, single-center  | Kuwait  | 2013 | 27; 18; 9    | PaO2/FIO2 more than 200 | All patients must get criteria of ARDS. (2) All patients must be on mechanical ventilation. (3) Methyl prednisolone must be started randomly in first 48 hours. | 2:1 randomization protocol, with per-protocol analysis. **Within 48 hours of ARDS diagnosis** Corticosteroid methylprednisolone; loading dose of 1 mg/kg, then infusion of 1 mg/kg/day from day 1 to day 14; 0.5 mg/kg/day on days 15 to day 21; 0.25 mg/kg/day on days 22 to day 25; then 0.125 mg/kg/day from day 26 to day 28. VS. normal saline in the same manner of methyl prednisolone. | Unclear | Unclear | Unclear | Corticosteroid group FIO2, lung injury score mean (±SD): 91.67(±1 2.49); PEEP, lung injury score mean (±SD): 11.00(±3 1.14) versus Control group FIO2, lung injury score mean (±SD): 77.78(±2 2.79); PEEP, lung injury score mean (±SD): 8.44(±2. 55) |
| Zhao, China, single-center   | China   | 2014 | Per Cochrane randomized; 53; 24; 29 | Reference not provided | Reference not provided | Reference not provided | Reference not provided | Reference not provided | Unclear | Unclear | Unclear |
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

| Tongyoo, 2016, Thailand, single-center[19] | 197; 98; 99 | 51.5% | Hospitalized, patients aged 18 years or older meeting the criteria for severe sepsis or septic shock, receiving mechanical ventilation (MV) for hypoxemic respiratory failure, if, **within 12 hours of study entry**, they met the diagnostic criteria for acute lung injury the 2012 Berlin criteria for the diagnosis of ARDS. | 60 days | **Within 12 hours of ARDS diagnosis** Hydrocortisone was given daily as an intravenous bolus (50 mg in 10 ml of normal saline) every 6 h for 7 days VS. the control group received a comparable volume of normal saline on the same time schedule. | lung injury score (mean ±SE), hydrocortisone 2.2 ±0.9; control 2.2 ± 1.0 PaO2/FiO2 (lung injury score) ranges from 0 to 4; 0.1-2.5 is | Severe sepsis associated ARDS or septic shock (<12 hrs) (yes) | Hypertension, diabetes mellitus, CAD, stroke, chronic kidney disease, chronic lung disease, cancer/immunosuppression

**ARDS management algorithm according to the 2006 Chinese Society for Critical Care Medicine Guidelines**

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### Corticosteroids for patients with acute respiratory distress syndrome: a rapid update
systematic review and meta-analysis of randomized trials

| Author(s) and Location | Study Details | Outcomes | Treatments |
|------------------------|---------------|----------|------------|
| Villar, 2020, Spain, multicenter[4] | Hospitalized, 18 years or older; intubated and mechanically ventilated; had acute onset of ARDS (defined by the Berlin criteria as moderate-to-severe ARDS; includes having an initiating clinical condition (e.g. pneumonia, aspiration, inhalation injury, sepsis, trauma, or acute pancreatitis) within one week of the known clinical insult, or new or worsening respiratory symptoms; bilateral pulmonary infiltrates on 60 days | Within 7 days of ARDS onset: Dexamethasone intravenous dose of 20 mg once daily from day 1 to day 5, which was reduced to 10 mg once daily from day 6 to day 10 versus continued routine intensive care (control group). Patients in both groups were ventilated with lung-protective mechanical ventilation. | Treatment group: (moderate (100 < PaO2/FiO2 ≤ 200) n=118, (severe (PaO2/FiO2 ≤ 100)) n=21) vs. control group: (moderate (100 < PaO2/FiO2 ≤ 200) n=121, (severe (PaO2/FiO2 ≤ 100)) n=17 | Pneumonia, sepsis, aspiration, trauma, others Authors report that more than 75% of patients had ARDS associated with pneumonia or sepsis Reported to have excluded patients with major co-morbidities (antibiotic therapy and haemodynamic support) |
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

| Footnote: | chest imaging (x-ray or computed tomography scan); |
|-----------|--------------------------------------------------|

Footnote:
ARDS: acute respiratory distress syndrome
kg: kilogram
mg: milligram
mmHg: millimeters of mercury
mL: milliliter
SD: standard deviation

FIGURES:

NOTE:
*Figures:*
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

Figure 1: Effect of corticosteroids on all-cause mortality

| Study or Subgroup | Corticosteroids | Control | Risk Ratio |
|-------------------|-----------------|---------|------------|
|                   | Events Total    | Events Total | M-H, Random, 95% CI |
| 1.1.1 Methylprednisone |                 |         |             |
| Meduri 2007       | 15 63           | 12 28   | 0.56 [0.30, 1.03] |
| Rizk 2013         | 0 18            | 3 9     | 0.68 [0.30, 1.52] |
| Steinberg 2006    | 26 89           | 26 91   | 1.02 [0.65, 1.62] |
| Subtotal (95% CI) | 170 128         | 128 32.9 | 0.67 [0.32, 1.40] |
| Total events      | 41 41           |         |             |
| Heterogeneity: Tau² = 0.23; Chi² = 5.10, df = 2 (P = 0.08); I² = 61% |
| Test for overall effect: Z = 1.06 (P = 0.29) |

1.1.2 Hydrocortisone

| Study or Subgroup | Corticosteroids | Control | Risk Ratio |
|-------------------|-----------------|---------|------------|
|                   | Events Total    | Events Total | M-H, Random, 95% CI |
| Liu 2012          | 2 12            | 7 14    | 0.33 [0.08, 1.31] |
| Tongue 2016       | 34 98           | 40 99   | 0.86 [0.50, 1.43] |
| Subtotal (95% CI) | 110 113         | 29.8%   | 0.68 [0.30, 1.52] |
| Total events      | 36 47           |         |             |
| Heterogeneity: Tau² = 0.19; Chi² = 1.74, df = 1 (P = 0.19); I² = 42% |
| Test for overall effect: Z = 0.94 (P = 0.35) |

1.1.3 Dexamethasone

| Study or Subgroup | Corticosteroids | Control | Risk Ratio |
|-------------------|-----------------|---------|------------|
|                   | Events Total    | Events Total | M-H, Random, 95% CI |
| Villar 2020       | 33 139          | 50 138  | 0.66 [0.45, 0.95] |
| Subtotal (95% CI) | 139 138         | 26.0%   | 0.66 [0.45, 0.95] |
| Total events      | 33 50           |         |             |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 2.23 (P = 0.01) |

1.1.4 Inhaled Budenoside

| Study or Subgroup | Corticosteroids | Control | Risk Ratio |
|-------------------|-----------------|---------|------------|
|                   | Events Total    | Events Total | M-H, Random, 95% CI |
| Zhao 2014         | 9 24            | 13 29   | 0.84 [0.43, 1.61] |
| Subtotal (95% CI) | 24 29           | 11.3%   | 0.84 [0.43, 1.61] |
| Total events      | 9 13            |         |             |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 0.33 (P = 0.59) |

Total (95% CI): 443 408 100.0% 0.75 [0.59, 0.95]
Total events: 129 151
Heterogeneity: Tau² = 0.02; Chi² = 6.99, df = 6 (P = 0.25); I² = 22%
Test for overall effect: Z = 1.56 (P = 0.02)
Test for subgroup differences: Chi² = 0.41, df = 1 (P = 0.54), I² = 0%
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

**Figure 2**: Effect of corticosteroids on duration of mechanical ventilation

| Study or Subgroup | Corticosteroids | Control | Mean Difference | Mean Difference |
|-------------------|-----------------|---------|-----------------|-----------------|
|                   | Mean SD Total   | Mean SD Total | IV, Random, 95% CI | IV, Random, 95% CI |
| Madari 2007       | 5.25 1.46 63    | 11.1 3.9 28 | 21.9% -5.85 (-7.34, -4.36) |  
| Rask 2013         | 10.6 4.4 16    | 20.3 1.9 9  | 20.1% -8.70 (-12.06, -5.32) |  
| Tonge 2016        | 11.8 7.5 98    | 13.9 9 99  | 20.1% -2.10 (-4.45, 0.25) |  
| Villar 2020       | 14.3 13.1 139  | 20.2 14 138 | 18.0% -5.90 (-9.32, -2.48) |  
| Zhao 2014         | 10.5 4.6 24    | 11.6 4.6 29 | 19.8% -1.90 (-3.58, 0.78) |  
| Total (95% CI)    | 103 100.0%     | -4.93 (-7.81, -2.06) |  

Heterogeneity: Tau² = 9.22; Chi² = 31.72, df = 4 (P < 0.00001); I² = 87% 
Test for overall effect: Z = 3.37 (P = 0.0008) 

Favours corticosteroids, Favours control
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

Figure 3: Effect of corticosteroids on ventilator-free days up to 28 days

| Study or Subgroup | Corticosteroids Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|----------------------|----|-------|--------------|----|-------|--------|----------------------------------|----------------------------------|
| Liu 2012          | 13.9                 | 11.3| 12    | 12.8         | 11.3| 14    | 3.3%   | 1.10 [-7.61, 9.81]                |                                  |
| Medari 2007       | 16.5                 | 10.1| 63    | 8.7          | 10.2| 28    | 11.3%  | 7.60 [1.27, 12.93]                |                                  |
| Steinberg 2006    | 11.2                 | 9.4 | 89    | 8.8          | 8.5 | 91    | 26.9%  | 4.40 [1.78, 7.02]                 |                                  |
| Tengsøe 2016      | 12                   | 9.7 | 98    | 9.7          | 10  | 99    | 25.1%  | 2.30 [-0.45, 5.05]                |                                  |
| Villar 2020       | 12.3                 | 9.9 | 139   | 7.5          | 9   | 138   | 33.8%  | 4.80 [2.57, 7.03]                 |                                  |

Total (95% CI): 401 470 100.0% 4.28 [2.67, 5.88]

Heterogeneity: $I^2 = 0.69$, $Q = 5.04$, $df = 4$ ($p = 0.28$), $I^2 = 21$
Test for overall effect: Z = 5.23 ($p < 0.00001$)
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

**Figure 4:** Effect of corticosteroids on adverse events and complications (hyperglycemia)

| Study or Subgroup | Corticosteroids | Control | Risk Ratio |
|-------------------|-----------------|---------|------------|
|                   | Events          | Events  | M-H, Random, 95% CI |
| Medun 2007        | 45              | 63      | 1.11 [0.81, 1.53]   |
| Tongyee 2016      | 79              | 98      | 1.12 [1.01, 1.24]   |
| Villar 2020       | 100             | 119     | 1.07 [0.93, 1.24]   |
| Total (95% CI)    | 300             | 265     | 1.12 [1.01, 1.24]   |

Total events: 229

Heterogeneity: Tau^2 = 0.00, Chi^2 = 0.84, df = 2 (P = 0.66); I^2 = 0%

Test for overall effect: Z = 2.18 (P = 0.03)
Corticosteroids for patients with acute respiratory distress syndrome: a rapid update systematic review and meta-analysis of randomized trials

**Figure 5:** Effect of corticosteroids on adverse events and complications (neuromuscular weakness)

| Study or Subgroup | Corticosteroids Events Total | Control Events Total | Weight | Risk Ratio M-H, Random, 95% CI |
|-------------------|-----------------------------|---------------------|--------|--------------------------------|
| Medium 2007       | 4                           | 63                  | 1      | 28 5.0% 1.78 [0.21, 15.20]    |
| Steinberg 2006    | 26                          | 88                  | 21     | 91 95.0% 1.28 [0.78, 2.10]    |

Total (95% CI) 151 119 100.0% 1.30 [0.80, 2.11]

Total events 30 22

Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.77); I² = 0%

Test for overall effect: Z = 1.07 (P = 0.28)