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REVIEW OF THERAPEUTICS

Corticosteroid use in ARDS and its application to evolving therapeutics for coronavirus disease 2019 (COVID-19): A systematic review

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Abstract

Data regarding the use of corticosteroids for treatment of acute respiratory distress syndrome (ARDS) are conflicting. As the coronavirus disease 2019 (COVID-19) pandemic progresses, more literature supporting the use of corticosteroids for COVID-19 and non-COVID-19 ARDS have emerged. Glucocorticoids are proposed to attenuate the inflammatory response and prevent progression to the fibroproliferative phase of ARDS through their multiple mechanisms and anti-inflammatory properties. The purpose of this systematic review was to comprehensively evaluate the literature surrounding corticosteroid use in ARDS (non-COVID-19 and COVID-19) in addition to a narrative review of clinical considerations of corticosteroid use in these patient populations. OVID Medline and EMBASE were searched. Randomized controlled trials evaluating the use of corticosteroids for COVID-19 and non-COVID-19 ARDS in adult patients on mortality outcomes were included. Risk of bias was assessed with the Risk of Bias 2.0 tool. There were 388 studies identified, 15 of which met the inclusion criteria that included a total of 8877 patients. The studies included in our review reported a mortality benefit in 6/15 (40%) studies with benefit being seen at varying time points of mortality follow-up (ICU survival, hospital, and 28 and 60 days) in the COVID-19 and non-COVID-19 ARDS studies. The two non-COVID19 trials assessing lung injury score improvements found that corticosteroids led to significant improvements with corticosteroid use. The number of mechanical ventilation-free days significantly were found to be increased with the use of corticosteroids in all four studies that assessed this outcome. Corticosteroids are associated with improvements in mortality and ventilator-free days in critically ill patients with both COVID-19 and non-COVID-19 ARDS, and evidence suggests their use should be encouraged in these settings. However, due to substantial differences in the corticosteroid regimens utilized in these trials, questions still remain regarding the optimal corticosteroid agent, dose, and duration in patients with ARDS.

KEYWORDS
acute respiratory distress syndrome, corticosteroids, COVID-19, mechanical ventilation

1 | INTRODUCTION

Prior to the coronavirus disease 2019 (COVID-19) pandemic, approximately 10% of patients presenting to the intensive care unit (ICU) were admitted for acute respiratory distress syndrome (ARDS).[1] This estimate has increased subsequent to the pandemic with approximately 33% of patients with COVID-19 developing ARDS.[2,3]

ARDS is a hypoxemic state caused by an inflammatory process resulting in alveolar damage (Figure 1) within 72 h following pulmonary insult.[2] Inflammatory mediators and chemokines are released in response to insult during the exudative phase where cellular injury is propagated by neutrophil accumulation, disrupting alveolar epithelial/endothelial barriers leading to fluid and debris accumulation. In the proliferative phase, restoration of endothelial and epithelial barriers occurs in addition to resorption of alveolar fluid.[2] Progression to the fibrotic phase results in fibrosis of the interstitium and within the alveoli. The mechanism of alveolar damage in both non-COVID-19 and COVID-19 ARDS is thought to be no different based on autopsy and clinical features.[4,5] Corticosteroids have been explored as a treatment for ARDS due to their anti-inflammatory and anti-fibrotic properties, however, their use in improving clinically meaningful outcomes remains controversial.[6-8] Herein, we provide a comprehensive review of the literature regarding corticosteroid use in non-COVID-19 and COVID-19 ARDS in addition to a narrative review of clinical considerations for these patient populations.

1.1 | Mechanism of corticosteroids in ARDS

Glucocorticoids have potent anti-inflammatory and immunomodulating effects via non-genomic and genomic mechanisms (Figure 2). Cytosolic glucocorticoid–glucocorticoid receptor (GC-GR) complexes directly modulate the transcription of glucocorticoid response elements and inhibit transcription factors nuclear factor-κB (NF-κB) and activating protein-1.[9,10] Through these mechanisms, glucocorticoids attenuate the production of pro-inflammatory cytokines.[11] They also work synergistically with natural anti-inflammatory cytokines, including IL-4, -10, and -13 and increase the expression of IL-1 receptor antagonist.[12] Glucocorticoids have inhibitory effects on fibrin pathways including inhibition of fibroblast proliferation and collagen deposition through inhibition of cytokines.[13] They stimulate T-cell, eosinophil, and monocyte apoptosis that may naturally work to decrease inflammation in ARDS and inhibit neutrophil activation that may otherwise potentiate inflammation in ARDS. It is postulated that relative glucocorticoid deficiency and unchecked inflammation further worsens inflammation in the setting of ARDS. Through the above mechanisms,

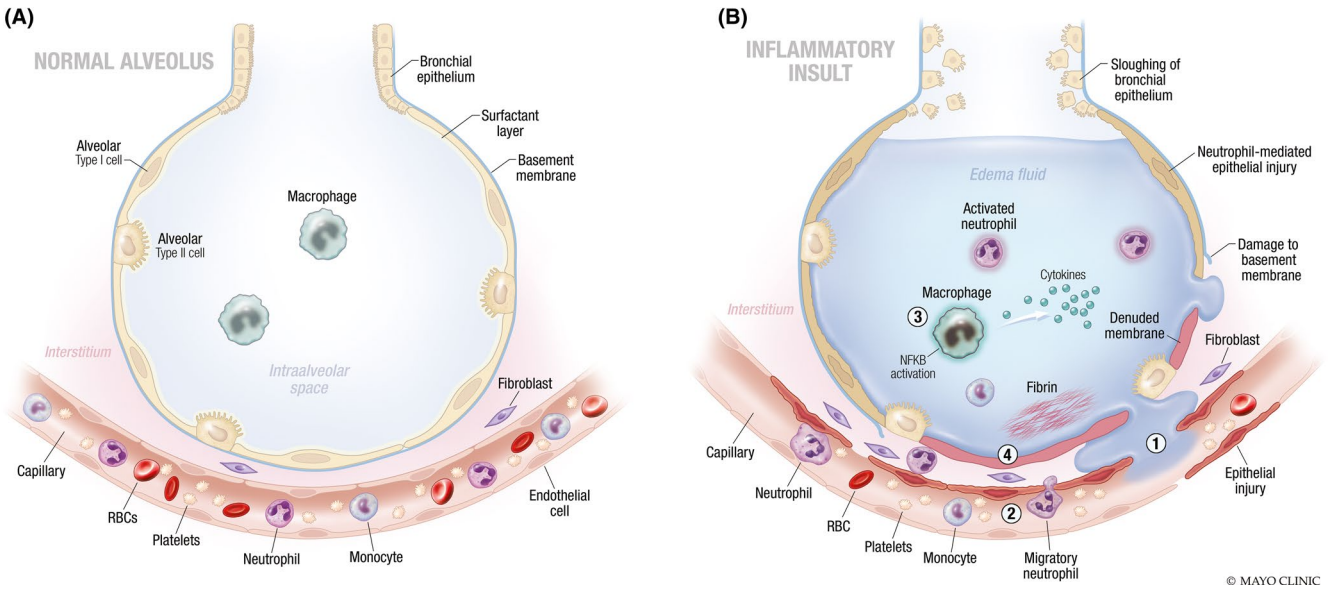

FIGURE 1 Actions of Corticosteroids in Acute Respiratory Distress Syndrome (ARDS). Panel A depicts a normal alveolus with intact alveolar cell structures and vascular epithelial membrane. Panel B shows alveolar changes following an acute inflammatory insult. Corticosteroids mitigate multiple pathways in the acute state. (1) Reduce extravasation of plasma through the intercellular junction. (2) Inhibit adhesion of neutrophils to the endothelial cell and migration across the capillary wall to into the alveoli. (3) Modulation of pro-inflammatory cytokines through genomic and non-genomic pathways. (4) Inhibition of fibroblast proliferation and collagen disposition

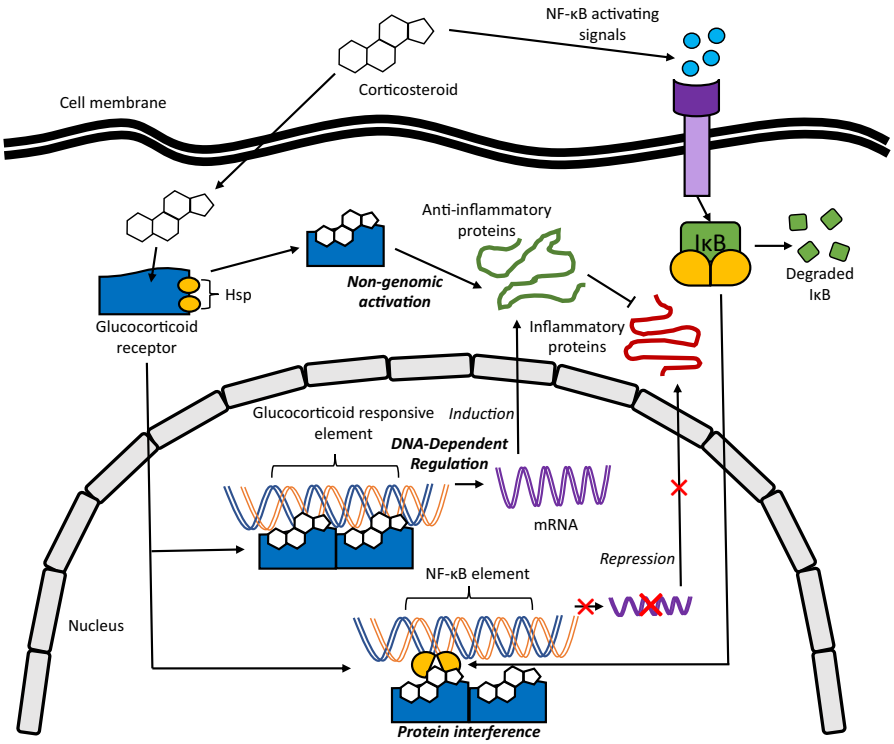

FIGURE 2 Pharmacology of Glucocorticoids. NF-κB, nuclear factor-kappa B, Hsp, heat shock protein, IκB, inhibitor-kappa B. The three main pathways of glucocorticoid pharmacology include DNA-dependent regulation of anti-inflammatory proteins, non-genomic modulation of inflammation, and direct protein interference of transcription factors such as nuclear factor-kappa B (NF-κB). Corticosteroids diffuse across cell membranes and bind with cytosol-bound glucocorticoid receptors. Activated glucocorticoid-glucocorticoid receptor (GC-GR) complexes trigger both non-genomic and genomic pathways. In the nucleus, the GC-GR complex dimerizes and activates glucocorticoid-responsive elements, stimulating production of mRNA and induction of anti-inflammatory proteins, such as Annexin I. Non-genomic effects are not fully elucidated but are thought to be dose dependent. Inflammatory signals such as tumor necrosis factor-alpha, interleukin-1, microbial pathogens, and viral proteins activate membrane-bound receptors leading to degradation of inhibitor-kappa B and NF-κB release. In the absence of the GC-GR complex, NF-κB binds NF-κB elements in DNA sequences which activates the production of pro-inflammatory mediators and cyclooxygenase 2. The GC-GR complex directly binds NF-κB transcription factors causing repression of mRNA and inflammatory proteins. Adapted from Rhen et al[6]

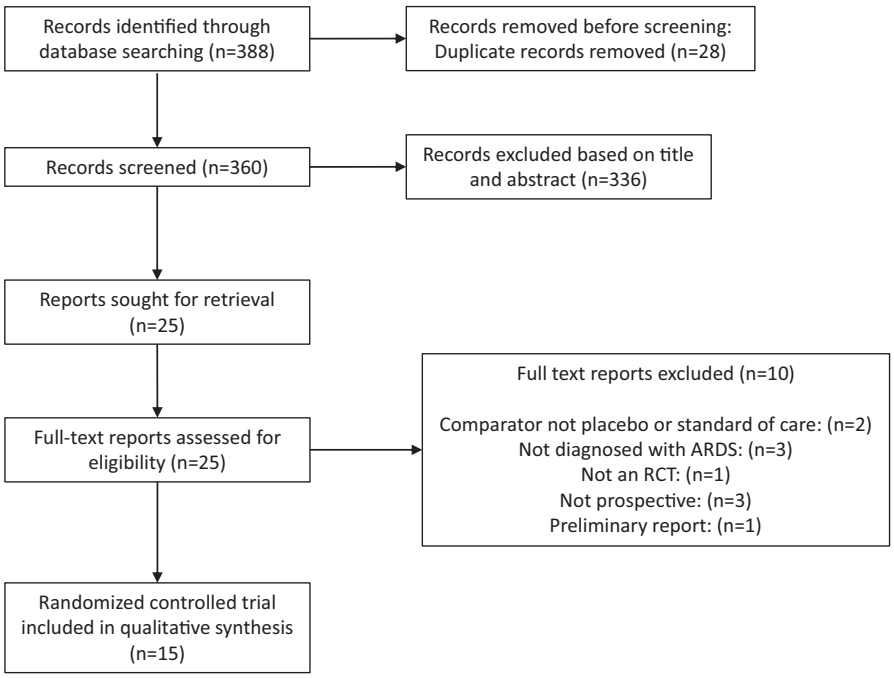

FIGURE 3 Flow diagram of the number of studies included in the systematic review literature search and reasons for study exclusion

TABLE 1 Trials of corticosteroids in acute respiratory distress syndrome

Trial	Study Period	Design	Patient Population
Bernard et al. *N Engl J Med* 1987[29]	Jun. 1983–Nov. 1985	Prospective placebo-controlled RCT, DB, Multicenter (7 centers) *N* = 99	Patients with ARDS defined by: 1) PaO_2 ≤ 70 mmHg on 40% oxygen or PaO_2: partial pressure of alveolar O_2 ≤ 0.3; 2) bilateral diffuse infiltrates on chest X-ray compatible with pulmonary edema; and 3) PAWP </=18 mmHg
Meduri et al. *JAMA* 1998[30]	Oct. 1994-Nov. 1996	Prospective placebo-controlled RCT, DB, Multicenter (6 centers) *N* = 24	Patients with ARDS for <3 weeks: 1) defined by AECC; 2) failure to improve LIS by day 7 of MV (LIS ≥2.5 and <1 point LIS reduction from day 1); and 3) no evidence of untreated infection
Meduri et al. *CHEST* 2007[32]	Apr. 1997-Apr. 2002	Prospective placebo-controlled 2:1 RCT, DB, Multicenter (6 centers) *N* = 91	Patients with early ARDS (≤ 72 h) defined by AECC while on PEEP
ARDS Clinical Trials Network. *N Engl J Med* 2006[16]	Aug. 1997-Nov. 2003	Prospective, placebo-controlled RCT, DB, Multicenter (25 centers) *N* = 180	ARDS (P:F < 200, bilateral infiltrates)
Confalonieri et al. *Am J Respir Crit Care Med* 2005[31]	Jul. 2000-Mar. 2003	Prospective placebo-controlled RCT, DB, Multicenter (6 centers) *N* = 46	Severe pneumonia based on modified 1993 ATS criteria or 2 of the following: 1) respiratory rate >30 bpm, 2) P:F < 250, 3) chest radiograph bilateral or multilobar involvement, 4) sbp <90 mmHg, and 5) DBP <60 mmHg
Annane et al. *Crit Care Med* 2006[35]	Oct. 1995-Feb. 1999	Post hoc analysis of a placebo controlled RCT, DB, Multicenter (19 ICUs) *N* = 177 with ARDS	Septic shock-associated early ARDS (P:F < 200, bilateral infiltrates)

Timing of Initiation	Intervention	Primary outcome	Other Outcomes
Time from symptoms: 32.5 hrs in MP vs. 28.9 hrs placebo Time from MV: 2.8 ± 0.5 hrs MP vs. 1.9 ± 0.4 hrs placebo	MP 30 mg/kg IV every 6 hrs for 4 doses Duration: 1 day	No difference in 45-day mortality: 60% MP vs. 63% placebo, $p = 0.74$	No difference in reversal of ARDS: 36% steroids MP vs. 39% placebo, $p = 0.77$
Unresolving ARDS (7 days of MV with LIS of 2.5 or greater and less than 1-point reduction from day 1 of ARDS)	MP loading dose of 2 mg/kg, then 2 mg/kg/day days 1 to 14, 1 mg/kg/day days 15 to 21, 0.5 mg/kg/day days 22 to 28, 0.25 mg/kg/day days 29 to 30, and 0.125 mg/kg/day days 31 to 32 Dosed as IV push every 6 hours Duration: 32 days	Improvement in LIS by >1 point: 100% MP vs. 25% placebo, $p < 0.001$ Survivors of ICU admission: 100% MP vs. 37% placebo, $p = 0.002$	MODS score: 0.7 (0.2) MP vs. 1.8 (0.3) placebo, $p < 0.001$ Survivors at hospital discharge in 87% MP vs. 37% placebo, $p = 0.03$
Day 7	MP IV loading dose of 1 mg/kg, then 1 mg/kg/day days 1 to 14, 0.5 mg/kg/day days 15 to 21, 0.25 mg/kg/day days 22 to 25, and 0.125 mg/kg/day days 26 to 28 Dosed as continuous infusion If extubated days 1–14, then advanced to day 15 of therapy and followed taper If failure to improve LIS days 7–9, left treatment arm and received MP 2 mg/kg/day Duration: 28 days	Improvement in LIS[11] or extubation by study day 7: 69.8% MP vs. 35.7% placebo, $p = 0.02$	Improvement in MV-free days: 16.5 ± 10.1 MP vs. 8.7 ± 10.2 days placebo, $p = 0.001$ MODS score at 7 days: 0.90 ± 1.1 MP vs. 1.9 ± 1.4 placebo, $p = 0.002$ ICU LOS:7 (6–12) MP vs. 14.5 (7–20.5) days placebo, $p = 0.007$ P:F 256 ± 19 MP vs. 179 ± 21 placebo, $p = 0.006$ ICU mortality: 20.6% MP vs. 42.9% placebo, $p = 0.03$
7–28 days after ARDS onset	MP IV loading dose of 2 mg/kg then 0.5 mg/kg q6h for 14 days, 0.5 mg/kg q 12h, for 7 days, followed by taper over 2–4 days Duration: 23–25 days	60-day mortality: 29.2% MP vs. 28.6% placebo, $p = 1.0$	Improvement in MV-free days at 28 days: 11.2 ± 9.4 vs. 6.8±8.5 days placebo, $p < 0.001$ No. of ICU-free days at day 28: 8.9 ± 8.2 MP vs. 6.2 ± 7.8 days placebo, $p = 0.02$ Organ failure-free days at day 28: 20.7 ± 8.9 vs. 17.9 ± 10.2 days placebo, $p < 00001$
Unclear	HCT 200 mg IV followed by infusion at 10mg/h Duration: 7 days	P:F > 300 at day 8: 70% HCT vs. 22% placebo, $p = 0.003$ P:F ≥ 100 increase from study entry at day 8: 87% HCT vs. 35% placebos, $p = 0.0007$ MODS score at day 8: 0.3 ± 0.5 HCT vs. 1.0 ± 0.9 placebo, $p = 0.003$	MV-free days at day 8: 4 (0–7) HCT vs. 0 (0–6) placebo, $p = 0.01$ 60-day mortality: 0% HCT vs. 38% placebo, $p = 0.001$
Within 8 hrs of the onset of shock	HCT 50 mg IV every 6 hrs +fludrocortisone 50 mcg orally daily or placebo Duration: 7 days	28-day survival in non-responders: 33/62 (53%) steroid vs. 50/67 (75%) placebo, $p = 0.013$	ICU mortality in non-responders: RR 0.73 (0.57–0.94), $p = 0.010$ Days alive and free of MV HCT group of non-responders: 5.7±8.6 steroids vs. 2.6±6.6 placebo, $p = 0.006$ 28-day survival in non-responders: RR 0.71 (0.54–0.94), $p = 0.011$ Hospital mortality in non-responders: RR 0.75 (0.59–0.96), $p = 0.016$

(Continued)

TABLE 1 (Continued)

Trial	Study Period	Design	Patient Population
Tongyoo et al. *Crit Care* 2016[36]	Dec. 2010-Dec. 2014	Prospective placebo-controlled parallel-group RCT, DB, Single-center *N* = 197	Severe sepsis or septic shock receiving MV meeting AECC criteria for ARDS
DEXA-ARDS *Lancet Respir Med* 2020[38]	Mar. 2013–Dec. 2018	Prospective standard care controlled RCT, open label, Multicenter (17 centers) *N* = 277	Moderate-to-severe ARDS based on AECC/Berlin criteria (P:F < 200) on FiO_2 ≥ 0.5 and PEEP ≥10 cm H_2O

Abbreviations: AECC, American European Consensus Conference; AEs, adverse events; ARDS, acute respiratory distress syndrome; bpm, breaths per minute; DB, double blind; DEX, dexamethasone; FiO_2, fraction of inspiratory oxygen; HCT, hydrocortisone; hrs, hours; IV, intravenously; LIS, lung injury score; MODS, multiorgan dysfunction syndrome; MP, methylprednisolone; MV, mechanical ventilation; NS, non-significant; P, F, partial pressure of oxygen/fraction of inspired oxygen, partial pressure of arterial oxygen; PAWP, pulmonary artery wedge pressure; RCT, randomized controlled trial; RR, relative risk; SD, standard deviation.

glucocorticoids have broad effects to mitigate the pathogenesis of ARDS (Figure 1). Anti-inflammatory properties of glucocorticoids with the potential for glucocorticoid-resistant states in the setting of severe systemic inflammation are proposed to dampen the deranged inflammatory response and prevent progression to the fibroproliferative phase of ARDS. Increased GC-GR binding for patients with non-COVID-19 or COVID-19 ARDS pathophysiology through the above mechanisms may shorten the time for disease resolution and improve outcomes.[14]

1.2 | Selection of corticosteroids

Given the physiologic benefits derived from glucocorticoid activity, corticosteroids with glucocorticoid effects are preferred in ARDS.[15,16] Methylprednisolone, a potent glucocorticoid, leads to increased concentrations in the lung compared to other corticosteroids due to its larger volume of distribution and tendency to be retained in the lungs for a longer period.[17-19] When used for ARDS, guidelines suggest weaning methylprednisolone over days to weeks because a rebound increase in pro-inflammatory cytokines may precipitate the recurrence of cytokine storm.[19] Recent clinical trials comparing dexamethasone to methylprednisolone in COVID-19 patients suggest greater benefit with methylprednisolone in terms of recovery time/length of hospital stay, intensive care need, and mechanical ventilation.[20-22] Of note, these trials used relatively higher doses of methylprednisolone compared to dexamethasone making it unclear if benefit is due to higher dose or corticosteroid selected. Dexamethasone, also a potent glucocorticoid, has a biological half-life up to 54 h allowing concentrations to auto-taper, decreasing the potential for a rebound effect upon discontinuation and need for a prolonged taper when treating ARDS.[23,24] Corticosteroids with more potent mineralocorticoid effects, such as hydrocortisone, increase the expression of epithelial sodium channels and activate the basolateral Na^+/K^+ ATPase pump in the distal portion of the nephron. This promotes sodium reabsorption and increases effective circulating volume, which may lead to pulmonary edema, worsening lung function, and increased duration of mechanical ventilation (MV).[25,26]

2 | METHODS

A systematic review was completed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[27] The investigators used OVID MEDLINE and EMBASE databases to identify relevant prospective, randomized control trials (RCTs) conducted in humans ≥18 years old published in English from 1987 up to August 19, 2021. Search terms included: acute respiratory distress syndrome or adult respiratory distress syndrome or COVID-19 and dexamethasone or methylprednisolone or hydrocortisone or glucocorticoid or corticosteroid. Titles and abstracts identified in the literature search were reviewed, with further screening of inclusion criteria, and then retrieval of full-text articles for review. Studies meeting the following PICO (population, intervention, comparator, and outcome) qualities were included: P—adults with COVID or non-COVID-19 ARDS; I—receiving systemic glucocorticoids; C—placebo, standard of care, or other steroid; and O—mortality. Assessment of bias was completed using the Risk of Bias (RoB) 2.0 tool for RCTs.[28] Studies were assessed for bias by two investigators for domains including bias from: the randomization process, deviations from the intended interventions, missing outcome data, risk of bias in measurement of the outcome, and risk of bias in selection of the reported result.

Timing of Initiation	Intervention	Primary outcome	Other Outcomes
Within 12 hrs of meeting ARDS criteria	HCT 50 mg IV every 6 h Duration: 7 days	28-day mortality: 22.5% HCT vs. 27.35 placebo; $p = 0.51$	Duration of MV: 0.4 ± 9.4 days HCT vs. 12.4 ± 11 days placebo, $p = 0.16$ Duration vasopressor support: (4.8 ± 3 days HDCT vs. 6.8 ± 5.7 days placebo, $p = 0.16$) Patients alive at day 28 without organ support: (HCT 11.9 ± 9.7 days vs. placebo 9.5 ± 9.8, $p = 0.13$).
Within 30 hrs after ARDS onset	DEX 20 mg IV daily days 1–5 10 mg IV daily days 6–10 Duration: 10 days or until extubation (if before 10 days)	Ventilator-free days at day 28: 12.3 (SD 9.9) DEX vs. control 7.5 (SD 9.0), $p < 0.0001$	All-cause mortality at 60 days: 29 (21%) DEX vs. 50(36%) control, $p = 0.0047$ Hospital mortality: 33 (24%) DEX vs. 50 (36%) control, $p = 0.0235$

3 | RESULTS

A total of 360 articles were identified via database search after removing duplicates (Figure 3). Full text of 25 articles were reviewed and 15 met inclusion criteria including 8877 patients. Data evaluated in these articles are in Tables 1 and 2. RoB assessment was completed for all studies with 8 (53.3%) assessed to have low risk, 6 (40%) with some concerns, and 1 (6.7%) with high risk of bias (Table 3). All included studies were RCTs, with one being a post hoc analysis of an RCT. Of these, 11 (73.3%) studies were multicentered and 4 (2.7%) single-centered. There were 10 (66.7%) double-blinded trials and 5 (33.3%) unblinded. Comparing regimens, 5 (33.3%) studied methylprednisolone, 4 (26.7%) hydrocortisone, 1 (6.7%) hydrocortisone and fludrocortisone, 4 (26.7%) dexamethasone, and 1 (6.7%) methylprednisolone compared to dexamethasone. Dosing regimens varied between methylprednisolone studies and between hydrocortisone studies. Dexamethasone was dosed as 20 mg daily for 5 days followed by 10 mg daily for 5 days in 3/5 studies, 2 studies incorporated 6 mg daily for 10 days. All studies reported mortality as a primary or secondary outcome, with 6 (40%) reporting 28-day mortality. Adverse effects are reported in Table 4.

3.1 | Corticosteroids for non-COVID-19-related ARDS

Standard of care for ARDS and management of MV have changed drastically across the time continuum of corticosteroid trials, influencing baseline mortality rates, and efficacy of co-interventions. Outcomes studied have changed from Lung Injury Score (LIS) to difference in PaO_2/FiO_2 and MV-free days (Table 1). Controversy has continued in the role of corticosteroids in improving clinically meaningful outcomes like mortality, potentially due to overall sample sizes, differences in ARDS definitions, timing of corticosteroid initiation, dosing, and duration, and treatment crossover.

3.2 | Bernard et al. *N Engl J Med* 1987

Bernard and colleagues studied the effects of high-dose methylprednisolone (30 mg/kg intravenously (IV) every 6 h for 24 h) on mortality in ARDS to understand the effect of corticosteroids on chest radiograph, oxygenation, and lung compliance.[29] Notably, there was no difference in the rate of mortality between the corticosteroid [60%; (95% CI, 46–74%)] and placebo groups [63%; (95% CI, 49–77%)], with no difference during 45-day follow-up. In the subgroup analysis of patients with ARDS secondary to sepsis, patients treated with methylprednisolone had a lower reversal of chest radiograph and arterial blood gases vs. placebo (9% vs. 56%, $p < 0.018$) but no difference in survival. Contemporary ventilation practices recommend that patients with ARDS receive lung protective ventilation strategies; however, it is unlikely that such strategies were employed in this study. Criteria for reversal of blood gas were not fully elucidated, so we are unable to apply this finding to clinical practice. Furthermore, the study did not specify the duration, and frequency chest radiographs were evaluated for resolution of bilateral pulmonary edema.

3.3 | Meduri et al. *JAMA* 1998

In 1998, Meduri and colleagues looked at the effect of prolonged IV methylprednisolone therapy (2 mg/kg/day days 1–14, 1 mg/kg/day days 15–21, 0.5 mg/kg/day days 22–28, 0.25 mg/kg/day days 29–30,

and 0.125 mg/kg/day days 31–32) in late (≥7 days of MV with LIS ≥2.5 and <1 point reduction from ARDS day 1) ARDS on improvement in lung function and mortality.[30] Methylprednisolone therapy was associated with improvement in ARDS defined as >1-point reduction in LIS (1.7 vs. 3; $p < 0.001$) and also led to more ICU survivors (16/16 vs. 3/8 survivors; $p = 0.002$) and survivors of hospital admission (14/16 vs. 3/8, $p = 0.03$). The trial was stopped early and included a small sample size ($n = 24$). There were numerical differences in severity of illness at baseline between treatment and placebo groups. The study protocol allowed for crossover to the other treatment arm in patients who did not have a 1-point reduction in LIS by study day 10. Four patients in the placebo group crossed over to methylprednisolone but 0 patients in the methylprednisolone group crossed over.

3.4 | Confalonieri et al. *Am J Respir Crit Care Med* 2005

This RCT evaluated the effects of hydrocortisone (200 mg loading dose IV followed by a 7-day infusion at 10 mg/h) on improvement in PaO_2/FiO_2, MODS score by study day 8, and reduction in septic shock.[31] While this study did not evaluate ARDS patients specifically, it assessed patients with severe community-acquired pneumonia with a high predisposition to systemic inflammation. This study, suspended after interim analysis of 46 patients, identified a greater improvement in PaO_2/FiO_2 at day 8 as well as hospital mortality (30% vs. 0%). While this study is encouraging, it is limited by a small sample size, including only three patients with ARDS at day 8 in the placebo group and had unbalanced groups at randomization.

3.5 | Meduri et al. *Chest* 2007

Since systemic inflammatory response is established early in the ARDS course, Meduri and colleagues investigated prolonged administration of low-dose methylprednisolone (1 mg/kg/day IV days 1–14, 0.5 mg/kg/day IV days 15–21, 0.25 mg/kg/day IV days 22–25, and 0.125 mg/kg/day days 26–28) in early ARDS (≤72 h of diagnosis) with a primary outcome of LIS at day 7.[32] By day 7, 44/63 (69.8%) patients receiving methylprednisolone attained a 1-point reduction in LIS compared with 10/28 (35.7%) in the placebo group ($p = 0.002$) (Table 1). Mortality and ICU length of stay (LOS) were significantly reduced in the methylprednisolone group (20.6% vs. 42.6%; $p = 0.03$ and 7 vs. 14.5 days; $p = 0.007$, respectively) but hospital mortality and LOS failed to reach statistical significance (23.8% vs. 42.9%; $p = 0.07$ and 13 vs. 20.5 days; $p = 0.09$, respectively). Despite the positive results, important limitations include the small sample size and the higher incidence of catecholamine-dependent shock in the placebo group which likely contributed to increased mortality. Furthermore, crossover design obscured the analysis as 10 patients in the placebo and 5 in the methylprednisolone group received high-dose methylprednisolone 2 mg/kg/day.

3.6 | ARDS Clinical Trials Network. *N Engl J Med* 2006

As early data demonstrating corticosteroid benefit were mixed using heterogeneous regimens, the ARDSNET trial attempted to better delineate the role of corticosteroids in ARDS on their primary outcome of 60-day mortality.[16] Patients were enrolled 7–28 days after the onset of ARDS and randomized to placebo or 3 weeks of IV methylprednisolone (2 mg/kg followed by 0.5 mg/kg q6h for 14 days followed by 0.5 mg/kg q12h for 7 days followed by taper over 2–4 days if 21 days of corticosteroids completed). The primary outcome of 60-day mortality was not different between placebo and corticosteroid arms (28.6% vs. 29.2%; $p = 1.0$). Patients treated with corticosteroids had a greater incidence of serious adverse events associated with myopathy/neuropathy (9 (10%) vs. 0 (0%), $p = 0.001$). Those randomized after 13 days of ARDS onset had increased mortality (8% vs. 35%, $p = 0.02$). Relative to other studies, this trial employed short taper schedules ranging from 2 to 4 days. Subsequent analyses have suggested a positive interaction with prolonged tapering and MV-free days.[33] The treatment group included more females, and a small percentage of total eligible patients were enrolled, bringing into question the generalizability of these results.[34]

3.7 | Annane et al. *Crit Care Med* 2006

Annane and colleagues completed a post hoc analysis of their trial using hydrocortisone 50 mg IV every 6 h and enteral fludrocortisone 50 μg daily in patients with septic shock and relative adrenal insufficiency to assess the primary outcome of 28-day mortality.[35] Fifty-nine percent of the study population had mild ARDS (mean PaO_2/FiO_2 270 mmHg) on inclusion. In post-hoc analysis of non-responders (cortisol response ≤9 μg/dl) with ARDS, 28-day mortality was 50/67 (75%) in the placebo group and 33/62 (53%) in the corticosteroid group (adjusted RR 0.71 [0.54–0.94, $p = 0.011$]). Hospital and ICU mortality were lower in the corticosteroid group compared to placebo (adjusted OR 0.38; 95% CI 0.16–0.88 and adjusted OR 0.35; 95% CI 0.15–0.82, respectively). In responders (cortisol response >9 μg/dl from baseline) with ARDS and patients without ARDS, there was no difference in mortality, and days alive and MV-free. The mean tidal volume in all patients with ARDS was >8 ml/kg, indicating not all patients received lung protective ventilation. The results of this study may not be generalizable to ARDS patients without septic shock.

3.8 | Tongyoo et al. *Crit Care* 2016

Sepsis-associated ARDS confers higher mortality rate compared to sepsis without ARDS or in non-sepsis-related ARDS. Tongyoo and colleagues conducted a prospective RCT studying hydrocortisone 50 mg IV every 6 h for 7 days on 28-day mortality.[36] There was no difference in 28-day mortality, 22/98 (22.5%) vs. 27/99 (27.3%);

RR 0.82 (95% CI 0.5 to 1.34); and day 60, 34/98 (34.7%) vs. 40/99 (40.4%); RR 0.86(95% CI 0.6 to 1.23), which persisted after adjustment for covariates in the multivariate survival model. By day 7 of treatment, the corticosteroid group had a higher PaO_2/FiO_2, 319.1 ± 9.7 vs. 266.3 ± 11.7 ($p = 0.001$), and lower LIS score, 1.1 ± 0.1 vs. 1.4 ± 0.1 ($p = 0.01$), compared to placebo. This was a single-center study where patients were diagnosed with ARDS according to the American-European Consensus definition, however, these criteria changed in 2012 with the Berlin Criteria. Although pragmatic in their choice of corticosteroids for the treatment of sepsis, the study may have been limited by utilizing a corticosteroid with greater mineralocorticoid activity and lower lung penetration than alternatives.

3.9 | Villar et al. *Lancet Respir Med* 2020

A prior meta-analysis including small, randomized trials assessed the use of corticosteroids for the treatment of ARDS, showing increased MV-free, ICU-free, and hospital-free days. Decreased mortality was only found in those treated before day 14 of ARDS.[19,37] The DEXA-ARDS study is the largest, randomized, multicenter study assessing the efficacy of dexamethasone (20 mg IV daily for 5 days followed by 10 mg IV daily for 5 days) compared to routine care in patients with moderate-to-severe non-COVID-19 ARDS defined by the Berlin criteria and used a standardized approach to assess a primary outcome of MV-free days.[38] The dexamethasone group had more MV-free days than the control group: mean difference 4.8 days [95% CI 2.57–7.03]. More patients in the dexamethasone group developed extubation failure in the 28-day period [12(8.6%) vs. 7(5.1%)]. There was no difference in adverse effects or complications in the two groups. The study ended early due to low enrollment, was unblended, and had a high rate of excluded patients, potentially decreasing external validity. However, investigators assessed PaO_2/FiO_2 for inclusion at 24 h after ARDS onset as a strategy to decrease heterogeneity and to restrict enrollment of patients at a higher risk of death or those with rapid improvement in oxygenation after ARDS onset. Fifty-nine percent of patients in both groups received neuromuscular blockers (NMB) and only 20% of patients in the dexamethasone group and 30% of patients in the control group received proning.

3.10 | Corticosteroids for COVID-19-related ARDS

During initial stages of the COVID-19 pandemic, corticosteroids were not recommended for use due to previous evidence from the SARS and MERS outbreaks suggesting delayed viral clearance and worse outcomes.[39] Patients with COVID-19 often progress to systemic inflammatory response syndrome, furthering lung injury and damaging multiple organ systems which similarly to non-COVID-19 ARDS may be attenuated by anti-inflammatory properties of corticosteroids.[40,41] Heterogeneous steroid regimens were studied among COVID-19 patients with a wide range of illness severity (Table 2).

3.11 | RECOVERY Collaborative Group *N Engl J Med* 2020

The Randomized Evaluation of COVID-19 Therapy (RECOVERY trial) is the largest of the COVID corticosteroid trials.[42] This pragmatic, adaptive RCT was designed to evaluate the effects of several different therapies for COVID-19, including low-dose dexamethasone (6 mg daily oral or IV for up to 10 days or until hospital discharge) on the primary outcome of 28-day mortality. Overall, 22.9% of patients in the dexamethasone group died within 28 days of randomization compared to 25.7% of patients in the usual care group (rate ratio, 0.83; 95% CI, 0.75–0.93; $p < 0.001$). Greatest mortality benefit was seen among patients who were receiving invasive MV at baseline (29.3% vs. 41.4%; rate ratio 0.64; 95% CI, 0.51–0.81). A reduction in mortality was also seen in patients receiving oxygen therapy without invasive MV (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72–0.94). This study was limited by its open-label design and did not specify ARDS diagnosis. Patients receiving invasive MV were on average 10 years younger than those not receiving any respiratory support. Finally, patients receiving MV prior to randomization had symptoms an average of 7 days longer and the mortality benefit of dexamethasone was only significant for those with symptoms longer than 7 days.

3.12 | REMAP-CAP *JAMA* 2020

A Randomized, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) was a pragmatic, international adaptive platform design to test multiple interventions for COVID-19, including a three-arm hydrocortisone trial.[43] REMAP-CAP randomized patients to (1) fixed-dose HCT group (50 mg or 100 mg IV every 6 h); or (2) a shock-dependent group, where physicians prescribed HCT for patients in shock (50 mg IV every 6 h when shock evident); or (3) a no-HCT group. The study was reported with a Bayesian logistic model, adjusting for enrolling site, age, sex, and time, and estimated an intervention-specific treatment effect. A >99% probability of superiority is to be interpreted as significant. The primary outcome was the number of organ failure-free days at 28 days and was not different among the groups 0 (IQR, −1 to 15), 0 (IQR, −1 to 13), and 0 (IQR, −1 to 11). Compared to the no-HCT group, the median adjusted odds ratio (aOR) was 1.43 (95% credible interval (CrI), 0.91–2.27) for fixed-dose and 1.22 (95% CrI, 0.76–1.94) for shock dependent. There was no difference between groups, with a 93% and 80% probability of superiority, respectively. Mortality rates in fixed dose, shock dependent, and placebo are as follows: 30% ($n = 41/137$), 26% ($n = 37/141$), and 33% ($n = 33/99$). Median adjusted OR 1.03 (95% CI 0.53–1.95); 1.10 (95% CI, 0.58–2.11), yielding a probability of superiority of 54% and 62%, as compared to the no-HCT group, which was not different among groups. Overall, 95% of patients received their first dose within the day of enrollment. In the fixed-dose group, 97% received ≥1 dose, higher than the shock-dependent group; 43% receiving ≥1 dose. Follow-up

TABLE 2 Trials of corticosteroids in COVID-19 ARDS

Trial	Study period	Design	Patients	Background therapy	% MV or ARDS at baseline
RECOVERY *N Engl J Med* 2020[42]	Mar.–Jun. 2020	RCT Open label *N* = 6425 Multicenter	Hospitalized adult patients with clinically suspected or laboratory-confirmed SARS-CoV–2 infection	REM = 3 patients Anti-IL6: 0–3% Azithromycin ~25% both arms CP: 0%	%MV: 1007/6425 (16%) DEX: 324/2104 (15%) Placebo: 683/4321 (16%) P:F not reported
REMAP-CAP *JAMA* 2020[43]	Mar.–Jun. 2020	RCT open label *N* = 384 Multicenter	Adults with severe COVID–19 69–81% confirmed infection	Co-enrolled with antibiotic arm, anti-viral arm, details unavailable CP: 0% Anti-IL6: 0%	% MV: Fixed dose: 87/137 (63.5%) Shock dependent: 73/146 (50%) No HCT: 53/ 101 (52.5%) Baseline P:F 141
CAPE-COVID *JAMA* 2020[44]	Mar.– Jun. 2020	RCT DB *N* = 149 Multicenter	Adult ICU patients with respiratory failure secondary to COVID–19	>40% both groups received hydroxychloroquine and azithromycin Anti-IL6: ~2% both groups CP: 0% REM: ~3% both groups	% MV: HCT: 81.6% Placebo: 80.8% Mean P:F HCT: 130 Placebo: 133
CoDEX *JAMA* 2020[45]	Apr.–Jun. 2020	RCT open label *N* = 299 Multicenter	Adult MV patients within 48 hrs of meeting criteria for moderate-to-severe ARDS	REM not available ~20% both arms HCQ >65% both arms Azithromycin 0% anti-IL 0% CV 0% REM	%MV: 100% Moderate-to-severe ARDS
Metcovid *Clin Infect Dis* 2020[46]	Apr.–Jun. 2020	RCT DB *N* = 393 (mITT population—all pts who received >1 dose of study drug) Single center	Hospitalized adults with suspected COVID–19* with SpO2 ≤ 94%, or requiring supplementary oxygen or MV 81.3% confirmed by SARS-CoV–2 PCR	0% REM 0% anti-IL6 0% CP HC for shock MP vs. placebo: 8.7% vs. 7.0%	%MV: 33.8% MP: 53/66 (80.3%) Placebo: 57/67 (85.1%) % non-invasive O2: 188/393 47.8% Median P:F 158 MP: 160 Placebo: 156
Jamaati et al. *Eur J Pharmacol* 2021[47]	Mar. 2020	RCT Open label *N* = 50 Single center	Laboratory-confirmed SARS-CoV–2 infection Mild-to-moderate ARDS (P:F 100–300 mmHg) Excluded: CKD, chronic liver disease, and hyperglycemic	100% lopinavir/ritonavir 400/100 mg BID REM not reported Anti-IL6 not reported	%MV: not reported 100% ARDS
Ranjbar et al. *BMJ Inf Dise* 2021[20]	Aug.–Nov. 2020	RCT TB *N* = 86 Single center	Hospitalized adults with confirmed COVID–19 with SpO2 ≤ 92%	Standard of care, specific therapies not listed	Not reported

Abbreviations: anti-IL, interleukin inhibitor; CKD, chronic kidney disease; CP, convalescent plasma; CT, computed tomography; DEX, dexamethasone; HCQ, hydroxychloroquine; HCT, hydrocortisone; ICU, intensive care unit; IV, intravenous; MP, methylprednisolone; MV, mechanical ventilation; P:F, partial pressure of oxygen/fraction of inspired oxygen; PCR, polymerase chain reaction; RCT, randomized controlled trial; REM, remdesivir; SpO_2, oxygen saturation.

Timing of Initiation	Drug Dose/route/ frequency	Total duration (days)	Mortality	Organ failure-free days	Other Outcomes
8 days (DEX arm) vs. 9 days (usual care arm) Timing from MV not reported	DEX 6 mg IV daily	10 or until hospital discharge	28-d mortality 22.9% DEX vs. 25.7% placebo $p < 0.001$	Not reported	Time until hospital discharge Progression to MV RR, 0.79 (95% CI, 0.64–0.97) Removal of invasive MV in those receiving MV at randomization: RR, 1.47 (95% CI 1.20–1.78)
13.5 hrs from ICU admission	HCT IV 100 every 6 hours HCT IV 50 every 6 hours	7	28-d mortality fixed-dose 30%, shock dependent 26%, and placebo 33%, P = NS	Median organ support failure-free days 0 in all three groups, p = NS	Fixed-dose HCT reduced days free of vasopressor/ inotropes: OR 1.68 (1.03, 2.59) Fixed-dose HCT reduced progression to intubation, ECMO, or death of those not on MV or ECMO at baseline OR 3.02 (1.18, 6.56)
Majority >1 week; Not all patients had MV	HCT continuous infusion 200 mg x 7days, 100 mg x 4 days, and 50 mg x 3 days	14 or ICU discharge	All-cause mortality at 21 days 14.7% HCT vs. 27.4% placebo, $p = 0.06$	Not reported	Treatment failure at day 21 (death or persistent dependency on MV or high-flow oxygen therapy) 42.1% HCT vs. 50.7% placebo
9 days (DEX arm) vs. 10 days (standard-of-care arm); 1 day for both arms	DEX 20 mg IV daily x 5 days, and then 10 mg IV daily x5 days	10 or ICU discharge	All-cause mortality at 28 days 56.3% DEX vs. 61.5% placebo, $p = 0.85$	Ventilator-free days 6.6 DEX vs. 4 placebo $p = 0.04$	6-point ordinal scale at day 15 5 (3–6) DEX vs. 5 (5–6) placebo, $p = 0.07$ ICU-free days at 28 days 2.1 DEX vs. 2.0 placebo, $p = 0.5$; Mean SOFA score at 7 days 6.1 DEX vs. 7.5 placebo, $p = 0.004$
Median 3 days from MV, 13 days from illness onset to randomization	MP IV 0.5 mg/kg twice daily	5	28-day mortality MP 37.1% vs. 38.2% placebo, $p = 0.629$	Not reported	No difference in any outcomes between MP and placebo Need for intubation (19.4% vs. 16.8%, $p = 0.654$) Length of hospitalization (10 days vs. 9 days, $p = 0.296$)
Presumably upon hospital presentation, median presentation of symptom onset to admission = 8 days	DEX 20 mg IV daily x 5 days, then 10 mg IV daily x 5 days	10	28-day mortality: 64% DEX vs. 60% control, $p = 0.500$	Not reported	Need for invasive MV: 52% DEX vs. 44% control, $p = 0.389$ Weaning from O_2 support: Hospital LOS: 11 days (6–16) DEX vs. 6 (4–9), $p = 0.036$ Improvements in CT: 40% DEX vs. 12% control
Not reported	MP IV 2 mg/kg/ day tapered by 50% every 5 days vs. DEX 6mg IV daily	10	28-day mortality MP 18.6% vs. 37.5% DEX, $p = 0.07$	WHO ordinal scale at days 0, 5, and 10 improved in MP group, $p = 0.001$	Hospital LOS 7.43 ± 3.64 days MP vs. 10.52 ± 5.47 DEX MP reduced need for MV 18.2% vs. DEX 38.1%, $p = 0.04$

TABLE 3 Risk of bias assessment

Trial	Domain 1 Risk of bias arising from randomization process	Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Domain 3: Missing outcome data	Domain 4: Risk of bias in measurement of the outcome	Domain 5: Risk of bias in selection of the reported result	Overall Risk of Bias
Non-COVID–19 ARDS Studies						
Bernard et al. *N Engl J Med* 1987[29]	Low	Low	Low	Low	Low	Low
Meduri et al. *JAMA* 1998[30]	Low	Low	Low	Low	Low	Low
Meduri et al. *CHEST* 2007[32]	Low	Low	Low	Low	Low	Low
ARDS Clinical Trials Network. *N Engl J Med* 2006[16]	Low	Low	Low	Low	Low	Low
Confalonieri et al. *Am J Respir Crit Care Med* 2005[31]	Low	Some Concerns[a]	Low	Low	Low	Some Concerns
Annane et al. *Crit Care Med* 2006[35]	Low	Low	Low	Low	Some Concerns[b]	Some Concerns
Tongyoo et al. *Crit Care* 2016[36]	Low	Low	Low	Low	Low	Low
DEXA-ARDS *Lancet Respir Med* 2020[38]	Low	Low	Low	Low	Some Concerns[e]	Some Concerns
COVID-19 ARDS Studies						
RECOVERY *N Engl J Med* 2020[42]	Low	Low	Low	Low	Low	Low
REMAP-CAP *JAMA* 2020[43]	Low	Some Concerns[a]	Low	Low	Low	Some Concerns
CAPE-COVID *JAMA* 2020[44]	Low	Low	Low	Low	Some Concerns[c]	Some Concerns
CoDEX *JAMA* 2020[45]	Low	Low	Low	Low	Low	Low
Metcovid *Clin Infect Dis* 2020[46]	Low	Low	Low	Low	Low	Low
Jamaati et al.[47]	Low	Some Concerns[f]	Low	Low	Low	Some Concerns
Ranjbar et al. *BMJ Inf Dise* 2020[20]	Low	Some Concerns[a]	Some Concerns[d]	Low	Low	High

[a]Some concerns: due to analysis excluding patients who exited the study, etc., and not intention-to-treat analysis.

[b]Some concerns: this was a post hoc analysis of an RCT due to the nature of not being pre-planned has some concerns for bias risk.

[c]Some concerns: mortality at day 21 was a post hoc outcome.

[d]Possible that missingness in outcome influenced by true value in patients who exited study due to adverse effects/ no information.

[e]Domain 5 assessed as some concerns as a result of trial being stopped prior to enough patients being enrolled to meet power; data were not analyzed in accordance with pre-specified analysis plan (domain 5.1). There were no multiple eligible outcome measurements (5.2) or analyses of the data (5.3).

[f]Unclear if analysis was intent to treat.

data were available for 99% of patients. There were 10 safety events reported in the corticosteroid arms, and one in the control arm; however, details were not reported, and secondary infection rates are likely underreported (Table 4). This trial was halted early following release of RECOVERY findings. Limitations of this study include the unblinded treatment arms and up to 15% of the no-HCT group received a corticosteroid. Strengths include an intent-to-treat analysis of outcomes, including a primary analysis of corticosteroid-only patients.

3.13 | CAPE-COVID *JAMA* 2020

The effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19 (CAPE-COVID) evaluated the effect of hydrocortisone (200 mg/day IV until day 7, 100 mg/day IV days 8–11, and then 50 mg/day IV days 12–14) in ICU patients with COVID-19 acute respiratory failure.[44] The primary outcome was treatment failure (death or persistent dependency on MV or high-flow oxygen therapy) at day 21 from randomization. Treatment failure occurred in 32/76 (42.1%) vs. 37/73 (50.7%) of those in the hydrocortisone group vs. the placebo group, respectively; difference of proportions, −8.6% [95.48% CI, −24.9% to 7.7%]; $p = 0.29$. Mortality rates were not statistically different between groups. At day 28, 58 patients had at least one nosocomial infection. This study was terminated early after publication of the RECOVERY trial and was underpowered for the primary outcome. Other limitations include >40% of patients enrolled in each group were receiving alternative experimental drugs for the treatment of COVID-19 (i.e., hydroxychloroquine and azithromycin). The trial is not generalizable as severity criteria for enrollment was based on respiratory function and the time to administration of treatment, and not representative of a pure ARDS population.

3.14 | CoDEX *JAMA* 2020

The COVID-19-associated ARDS treated with DEXamethasone (CoDEX) trial randomized patients to dexamethasone (20 mg IV daily days 2–5, 10 mg IV daily days 6–10, or until ICU discharge) or standard of care and assessed the primary outcome of MV-free days at 28 days.[45] Patients randomized to the dexamethasone group had a mean 6.6 MV-free days (95% CI, 5.0–8.2) during the first 28 days vs. 4.0 MV-free days (95% CI, 2.9–5.4) in the standard care group (difference, 2.26; 95% CI, 0.2–4.38; $p = 0.04$). There was no significant difference in the prespecified secondary outcomes of all-cause mortality at 28 days, ICU-free days during the first 28 days, MV duration at 28 days, or the 6-point ordinal scale at 15 days. While all patients had moderate-to-severe ARDS in this trial, a limitation is the low proning rate of 22%. Strengths of the trial include the multicenter design, and collection of detailed adverse effects and physiologic data.

3.15 | Metcovid *Clin Infect Dis* 2020

The Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid) was a double-blind, randomized trial of hospitalized adult patients with suspected COVID-19 and randomized patients to receive methylprednisolone 0.5 mg/kg IV twice daily for 5 days to assess the primary outcome of 28-day mortality.[46] There was no difference in 28-day mortality between methylprednisolone and placebo (37.1% vs. 38.2%, $p = 0.629$), need for intubation (19.4% vs. 16.8%, $p = 0.654$), or hospital LOS (10 days vs. 9 days, $p = 0.296$). Additionally, there was no difference in the need for insulin therapy, positive blood cultures, or sepsis. In a post hoc subgroup analysis of MV patients, there was no difference in 28-day mortality between methylprednisolone and placebo (80.3% vs. 85.1%, $p = 0.266$). In a post hoc subgroup analysis of patients >60 years old, 28-day mortality was lower in the methylprednisolone group (46.6% vs. 61.9%, $p = 0.039$). These patients also had higher median C-reactive protein values than those <60 years old (81.3 mg/L vs. 74.7 mg/L, $p = 0.0028$). Limitations of this trial include the single-center design, and delayed corticosteroid administration (3 days from MV and 13 days from illness onset). Additionally, the study included patients who may not have had COVID-19 (only 81.3% confirmed with SARS-CoV-2 polymerase chain reaction) with no separate outcome analysis on the confirmed COVID-19 cohort. Importantly, the primary outcome was not limited to a MV/ARDS population (analyses in MV were post hoc), and only 36.2% required ICU admission. Overall, there were no differences in the incidence of bacteremia/sepsis; however, all patients received antibiotics (ceftriaxone + macrolide).

3.16 | Jamaati et al. *Eur J Pharmacol* 2021

In their unblinded RCT, Jamaati and colleagues randomized 50 patients to receive dexamethasone 20 mg for 5 days, followed by 10 mg for 5 days vs. the control group in patients with mild-to-moderate ARDS.[47] Patients presented to the hospital a median of 8 days after symptom onset with randomization presumably on admission. The primary outcomes of invasive ventilation and 28-day mortality rate were studied with no difference in 28-day mortality (64% dexamethasone vs. 60% control, $p = 0.500$). MV was needed in 13 (52%) of the dexamethasone group and 11 (44%) of the control, $p = 0.389$. Patients with chronic kidney disease, chronic liver disease, and those presenting with hyperglycemia were excluded in addition to its small sample size, limiting the generalizability of these findings. Additionally, it is unknown what effect other therapies (lopinavir/ritonavir 400/100 mg twice daily) may have had with no other studies included in our review using this concomitant therapy.

3.17 | Ranjbar et al. *BMC Infect Dis* 2021

A recent triple-blinded RCT compared methylprednisolone vs. dexamethasone for COVID-19.[20] Eighty-six patients were randomized 1:1 to 10 days of tapering methylprednisolone 2mg/

TABLE 4 Adverse effects in non-COVID-19 and COVID-19 ARDS studies.

Trial	ICU-AW	Hyperglycemia	Infection	Other
ARDS Studies				
Bernard et al. *N Engl J Med* 1987[29]	Not reported	Higher glucose in MP vs. placebo, $p < 0.01$	Similar incidence: 16% MP vs. 10% placebo, $p = 0.60$	No idiosyncratic reactions and no differences in blood hemoglobin levels
Meduri et al. *JAMA* 1998[30]	Not reported	Similar rates of new hyperglycemia (>250 mg/dL) 31% MP vs. 50% placebo	Similar rate of new infection: 75% MP vs. 75% placebo	Reduction of hemoglobin >0.20: 6% MP vs. 50% placebo, $p = 0.03$
Meduri et al. *CHEST* 2007[32]	Similar neuromuscular weakness: 6.4% MP vs. 3.6% placebo, $p = 1.0$	Similar hyperglycemia requiring insulin: 71.4% MP vs. 64.3%, $p = 0.50$	Lower rate of new infection 40/63 MP vs. 40/28 placebo, $p = 0.0002$	Pneumothorax: 7.9% MP vs. 21.4% placebo, $p = 0.09$
ARDS Clinical Trials Network. *N Engl J Med* 2006[16]	Increased serious AEs associated with myopathy or neuropathy: 9 MP vs. 0 placebo, $p = 0.001$	Mean serum glucose level higher days 1, 2, and 4 in MP vs. placebo Similar glucose level on day 7: 158.7±64.4 MP vs. 144.0±61.8 placebo	Similar no. of serious infections/no. of patients: 25/20 MP vs. 43/30 placebo, $p = 0.14$	Not reported
Confalonieri et al. *Am J Respir Crit Care Med* 2005[31]	Similar polyneuropathy of critical illness: 0% HCT vs. 13% placebo, $p = 0.23$	Not reported	Similar nosocomial infection 0% HCT vs. 18% placebo, $p = 0.11$	Delayed septic shock: 0% HCT vs. 52% placebo, $p < 0.001$ Major complications: 26% HCT vs. 78% placebo, $p < 0.001$
Annane et al. *Crit Care Med* 2006[35]	Not reported	Not reported	No difference in superinfection between responder and non-responder groups in steroids vs. placebo groups	No difference in GI bleeding between responder and non-responder groups in steroid vs. placebo groups No difference in psychiatric effects between responder and non-responder groups in steroid vs. placebo groups
Tongyoo et al. *Crit Care* 2016[36]	Not reported	Higher rate of hyperglycemia: 80.6% HCT vs. 67.7% placebo, $p = 0.04$	Similar rates of nosocomial infection: 17.3% HCT vs. 19.2% placebo, $p = 0.74$	Similar rate of GI bleeding: 3.1% HCT vs. 4% placebo, $p = 1.00$
DEXA-ARDS *Lancet Respir Med* 2020[38]	Not reported	No difference in hyperglycemia in the ICU: $p = 0.33$	No difference in new infection in the ICU: $p = 0.75$	No difference in barotrauma
COVID−19 Studies				
RECOVERY *N Engl J Med* 2020[42]	Not reported	2 patients with hyperglycemia	Not reported	1 patient with GI bleed 1 patient with psychosis
REMAP-CAP *JAMA* 2020[43]	1 patient with severe neuromyopathy in fixed HCT group, investigators thought possibly related to study group assignment	Not reported	1 patient with fungemia in fixed HCT group, investigators thought possibly related to study group assignment	No significant difference in serious AEs in steroid arms 9 (4 fixed dose and 5 shock dependent) vs. 1 in control

(Continues)

TABLE 4 (Continued)

Trial	ICU-AW	Hyperglycemia	Infection	Other
CAPE-COVID *JAMA* 2020[44]	Not reported	Not reported	No difference in nosocomial infections: 37.3% HCT vs. 41.1% placebo; HR, 0.81 (0.49 to 1.35)	No serious AEs attributed to study treatment
CoDEX *JAMA* 2020[45]	Not reported	No significant difference in need for insulin for hyperglycemia: 31.1% DEX vs. 28.4% standard care	No difference in new infections until day 28: 21.9% DEX vs. 29.1% standard care	Similar no. of patients with serious AEs: 5 patients DEX vs. 9 standard care
Metcovid *Clin Infect Dis* 2020[46]	Not reported	No difference in need for insulin therapy: 59.5% MP vs. 49.4% placebo, $p = 0.059$	No difference in positive blood cultures day 7: 8.3% MP vs. 8.0% placebo, $p = 0.923$	No difference in sepsis: 38.1% MP vs. 38.7% placebo, $p = 0.911$
Jamaati et al. *Eur J Pharmacol* 2021[47]	Not reported	Not reported	Not reported	Not reported
Ranjbar et al. *BMJ Inf Dise* 2020[20]	Not reported	Not reported	Not reported	Not reported

Abbreviations: AEs, Adverse events; DEX, dexamethasone; GI, gastrointestinal; HCT, hydrocortisone; ICU-AW, Intensive care unit–acquired weakness; MP, methylprednisolone; No., number.

kg/day or dexamethasone 6 mg daily to assess the primary outcome of 28-day mortality. Mortality at 28 days was 37.5% in the dexamethasone arm, vs. 18.6% in the methylprednisolone arm, $p = 0.076$. The WHO ordinal scale was assessed at baseline, day 5, and day 10, by repeated measures ANOVA and was significantly improved in the methylprednisolone group, $p = 0.001$. Hospital LOS among survivors was reduced in the methylprednisolone arm 7.43 ± 3.64 days vs. 10.52 ± 5.47 days in dexamethasone arm, $p = 0.015$. It is unclear how many patients in this trial had ARDS, and baseline PaO_2/FiO_2 was not available. Strengths include the blinded design and dosing strategy of methylprednisolone. The lack of a placebo group limits the overall interpretation of this study, as does the lack of detail regarding the cohorts, including severity of lung dysfunction at baseline, concomitant COVID-19 treatments, and lack of adverse drug event reporting. However, the high baseline mortality rate appears to be similar to other COVID-19 ARDS trials, suggesting this trial treated patients with a high severity of illness.

A common theme among the COVID-19 ARDS studies is a lack of an intent-to-treat analysis on patients with confirmed SARS-CoV-2 infection, and in those who received the study drug, along with open label design. Most of the studies were also stopped prematurely due to the early publication of RECOVERY trial findings, leading to failure to reach statistical power. Many of the trials were conducted during the initial surge of the COVID-19 pandemic and the results may not reflect the risks or benefits within the framework of the current standard of care for these patients. Only one trial compared different corticosteroid regimens, yet this trial is the smallest and has the most profound limitations.

3.18 | Adverse effects

As corticosteroids become more widely used for ARDS, consideration for adverse drug events is warranted. Short-term corticosteroid use is associated with hyperglycemia, behavioral disturbances, or cutaneous effects.[48] Long-term corticosteroid use may lead to weight gain, osteoporosis, and ocular and cardiovascular effects.[49] Critically ill patients may have increased risk of developing bacterial or fungal infections or stress-related mucosal damage. In general, corticosteroid regimens should be limited to the lowest dose over the shortest duration to limit these reactions.[50] Here, we describe short-term adverse drug events associated with corticosteroid use in COVID-19 ARDS and report adverse effects from the included studies in Table 4.

3.18.1 | Intensive care unit–acquired weakness

Intensive care unit–acquired weakness (ICU-AW) is new-onset generalized muscle weakness developing during ICU admission presenting in various forms, including critical illness polyneuropathy (CIP) and critical illness myopathy (CIM). ICU-AW may lead to prolonged

MV, prolonged ICU, and hospital LOS, and mortality.[51,52] The incidence of ICU-AW is reported to be 40%, with increased incidence in those with MV (65%), ARDS (60%), or sepsis (67%) and remains high at hospital discharge (36%), contributing to long-term disability among survivors.[52-55] Corticosteroids are thought to contribute to ICU-AW through the breakdown of myosin and impairment of muscle membrane excitability.[51] A systematic review/meta-analysis found corticosteroid use was associated with increased odds of ICU-AW (OR 1.84; 95% CI 1.26–2.67; $p = 0.002$).[56] Those who received corticosteroids had higher overall incidence of ICU-AW compared to the control group (43% vs. 34%); however, these results may have been influenced by concurrent sepsis or use of MV.

Previous studies describing the additive risk for ICU-AW with concomitant use of corticosteroids and NMB must be interpreted with caution. Such studies evaluated corticosteroid doses higher than those used for ARDS in current practice.[57] These studies also evaluated aminosteroidal NMB rather than benzylisoquinoline NMB for prolonged durations.[58] More recent studies evaluating the combined effects of corticosteroids and NMB on ICU-AW have failed to show additive risk.[57,59]

3.18.2 | Hyperglycemia

Viral diseases such as SARS and COVID-19 are associated with multiorgan dysfunction. Of particular concern are the effects seen on the pancreatic islet cells and resultant hyperglycemia. Acute hyperglycemia occurs in as many as 50% of hospitalized COVID-19 patients.[60] SARS-CoV-2 uses the angiotensin converting enzyme 2 (ACE-2) receptor to enter host cells.[61] An increase in ACE-2 receptors in the islet cells is associated with an increase in death, leading to an acute insulin-dependent diabetes mellitus state.

Corticosteroid-induced hyperglycemia is reported to be as high as 50% among those with no history of diabetes.[62] Tamez-Pérez and colleagues describe several mechanisms for hyperglycemia: (1) interference in signaling cascades in muscle or adipose tissue, leading to an insulin-resistant state; (2) antagonism of insulin metabolic effects through induction of enzymes promoting gluconeogenesis, lipolysis, proteolysis, and nuclear peroxisome proliferator-activated receptor α; (3) enhancement of counterregulatory hormones (e.g., glucagon); (4) altered pancreatic beta cell function leading to reductions in insulin synthesis and secretion.[63] These mechanisms have been associated with a 30–50% reduction in insulin-stimulated glucose uptake and a 70% reduction in insulin-stimulated glycogen synthesis. The degree of hyperglycemia is thought to be dose dependent with intermediate-acting steroids (e.g., methylprednisolone) thought to have a shorter duration of hyperglycemia compared to long-acting steroids (e.g., dexamethasone).[64]

3.18.3 | Infection

Corticosteroid administration brings forth a double-edged sword of concern in the COVID-19 pandemic. Corticosteroids induce an immunosuppressed state through sequestration of $CD4^+$ T cells and inhibition of cytokine transcription.[65] Chronic use has been associated with reduction in natural killer cells and complement pathway activation.[66] Additionally, reduced reactive oxygen species production and increased pro-inflammatory cytokine release (e.g., IL-6 and tumor necrosis factor-α) combined with an increase in apoptosis leading to fewer T and B cells may increase the risk of infection.

Among those with COVID-19, the risk of secondary infection from corticosteroid use may be as high as 25% for bacterial and 12.7% for fungal infections.[67] A systematic review and meta-analysis with over 6,000 patients found that patients with influenza treated with corticosteroids were more likely to develop secondary bacterial or fungal infections compared to those not receiving steroids (RR 2.0, 95% CI 1.0 to 3.8; $p = 0.04$).[55] The incidence of bacterial co-infection in COVID-19 patients may be as high as 28%, although co-infection and secondary infection are difficult to differentiate.[68] Interestingly, the recent COVID-19 corticosteroid trials have not reported a high incidence of secondary infections compared to placebo (Table 4). Of particular concern with corticosteroid use is the potential for fungal or opportunistic infections. Fungal infections in SARS had an incidence of 33% in severe disease and fungal infection-associated mortality in 73.7% of cases.[69] The risk for fungal infections should not be minimized, with the rate of presumed invasive pulmonary aspergillosis reported as high as 19.4% among COVID-19 admitted patients.[70] One patient in the REMAP study developed fungemia that the authors associated with hydrocortisone; otherwise fungemia was not reported in the other included trials.[43] In addition to fungal disease, infection due to strongyloidiasis is also of concern.[71,72]

3.18.4 | Central nervous system

Central nervous system effects include behavioral, psychiatric, and cognitive effects. Behavioral effects associated with corticosteroid therapy include sleep disturbances and "steroid euphoria." Sleep disorders (restlessness and insomnia) occur in up to 73% of patients on corticosteroids.[6] Approximately 20% of patients treated with corticosteroids develop psychiatric disorders, including depression (40.5%), mania (27.8%), psychosis (13.9%), and delirium (10.1%).[73,74] Cognitive effects (difficulty concentrating, memory loss, and delirium) are generally dose and time dependent and remission occurs with drug withdrawal or decreased doses.[73] The mechanism leading to this effect is thought to be due to endogenous corticosteroid binding to receptors in the prefrontal cortex, hippocampus, and basolateral amygdala modulating the hunger, sleep–wake cycle, memory, and learning.[75] Thus, modifying the release of dopamine and serotonin, and affecting the processing of emotional information and memory.

Patients with COVID-19 can experience memory loss, cognitive decline, anxiety, and depression after recovery from acute illness.[76] Corticosteroid use in these patients may further predispose them to these effects. Factors associated with psychosis among patients with SARS include a higher total dose of corticosteroids compared to

those without (10,975 mg vs. 6,780 mg hydrocortisone equivalent) lending credibility to this concern.[77]

3.18.5 | Viral shedding

Recognizing potential for already prolonged viral shedding in COVID-19, concerns for further prolongation with corticosteroid use must be considered. Li and colleagues evaluated 206 COVID-19 patients for the proposed dose–response effect of corticosteroid dose on COVID-19 viral shedding finding high-dose (80 mg/day prednisone; aHR, 0.67 [95% CI, 0.46–0.96]; $p = 0.031$), not low-dose (40 mg/day prednisone; aHR, 0.72 [95% CI, 0.48–1.08]; $p = 0.11$) corticosteroids were associated with delayed viral shedding.[60] Whether prolonged viral shedding correlates with a longer duration of symptoms remains unclear.

4 | DISCUSSION

Given the mixed findings from trials evaluating the use of corticosteroids in ARDS, and variability of regimens, the decision of whether, when, and how to initiate corticosteroids for ARDS should be patient specific. Prior to the DEXA-ARDS trial, previous guidelines evaluating the use of corticosteroids in non-COVID-19 ARDS stated the evidence was insufficient while other guidelines recommend corticosteroid use for early management of non-COVID-19-ARDS and warn of potential harm when starting methylprednisolone greater than 14 days from symptom onset.[16,19,78] Corticosteroids may have a positive disease-modifying effect and benefits of therapy may outweigh the risk of adverse effects. However, in critically ill patients with COVID-19 ARDS, benefits of corticosteroids have been clearly reported, and therefore use is recommended in this subset of patients.[79-81] The studies included in our review found mortality benefit in 6/15 (40%) studies with benefit being seen at varying time points (ICU survival, hospital, and 28 and 60 days) in the COVID-19 and non-COVID-19 studies. One non-COVID-19 ARDS trial found an increased risk of mortality at both 60 and 180 days in patients receiving methylprednisolone greater than 14 days after the onset of ARDS.[16] Interestingly, studies showing 28-day mortality benefit in COVID-19 were the largest trial (RECOVERY), and a post hoc analysis of patients >60 years old in the Metcovid trial. These findings align with a meta-analysis finding all-cause mortality benefit with the use of corticosteroids for COVID-19 ARDS.[80] The two non-COVID-19 trials assessing LIS improvements found significant improvements with corticosteroid use.[30,32] The four non-COVID-19 ARDS trials assessing MV-free days found a significant increase in MV-free days compared to placebo.[16,31,32,35] The increase in MV-free days has been previously supported in a meta-analysis of RCTs using corticosteroids for ARDS patients.[81]This systematic review included data from RCTs and assessment of bias was completed with the RoB 2.0 tool strengthening our review. Additionally, the majority of included studies were multicenter and many were blinded. Furthermore, we included both COVID-19 and non-COVID-19 ARDS RCTs. A limitation of included studies is heterogeneity in terms of corticosteroid agent, dosing, and duration. Time to initiation of corticosteroids from symptom onset varied, more in the non-COVID-19 ARDS RCTs (4 within 30 h, 3 at >7 days) compared to COVID-19 RCTs, where corticosteroids were often started >7 days after symptom onset. Comparison of specific adverse effects varied between the included RCTs with some trials not including this data, limiting our ability to evaluate this information. Additionally, not all trials reported number of patients with ARDS in addition to there being variations in diagnosis of ARDS. Lastly, therapies received in addition to corticosteroids greatly varied in the COVID-19 ARDS studies, with few patients overall receiving remdesivir, anti-IL6, azithromycin, hydroxychloroquine, lopinavir/ritonavir, or convalescent plasma.

The preferred corticosteroid for ARDS remains to be determined, however, glucocorticoid activity appears to have superior effects on lung inflammation. Data thus far suggest dexamethasone or methylprednisolone be used for the treatment of non-COVID and COVID-19 ARDS. The non-COVID-19 ARDS historical and contemporary data provide the strongest evidence for methylprednisolone and dexamethasone. Mortality data for COVID-19 ARDS are the strongest with the use of dexamethasone in the RECOVERY trial; however, a small RCT found greater benefit with methylprednisolone over dexamethasone.[20,42] Perhaps this variability exists because the optimal regimen has not yet been studied in large, prospective, blinded, RCTs. Additionally, enrichment strategies using ARDS subphenotypes should be considered in future trials. Such data may better determine corticosteroid benefit for the right patient, using the right drug, and at right dose.[82]

5 | CONCLUSION

Corticosteroids have been shown to improve mortality and MV-free days in both COVID-19 and non-COVID-19 ARDS, with evidence suggesting their use in these settings.[39,77-80] Vigilant monitoring to promote the safe and effective use of corticosteroid dosing, duration, and drug selection is necessary.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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