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Low-Dose Corticosteroids for Critically Ill Adults With Severe Pulmonary Infections
A Review

Romain Pirracchio, MD, MPH, PhD; Balasubramanian Venkatesh, MD; Matthieu Legrand, MD, PhD

IMPORTANCE Severe pulmonary infections, including COVID-19, community-acquired pneumonia, influenza, and *Pneumocystis* pneumonia, are a leading cause of death among adults worldwide. Pulmonary infections in critically ill patients may cause septic shock, acute respiratory distress syndrome, or both, which are associated with mortality rates ranging between 30% and 50%.

OBSERVATIONS Corticosteroids mitigate the immune response to infection and improve outcomes for patients with several types of severe pulmonary infections. Low-dose corticosteroids, defined as less than or equal to 400 mg hydrocortisone equivalent daily, can reduce mortality of patients with severe COVID-19, community-acquired pneumonia, and *Pneumocystis* pneumonia. A randomized clinical trial of 6425 patients hospitalized with COVID-19 who required supplemental oxygen or noninvasive or invasive mechanical ventilation reported that dexamethasone 6 mg daily for 10 days decreased 28-day mortality (23% vs 26%). A meta-analysis that included 7 randomized clinical trials of 1689 patients treated in the intensive care unit for severe bacterial community-acquired pneumonia reported that hydrocortisone equivalent less than or equal to 400 mg daily for 8 days or fewer was associated with lower 30-day mortality compared with placebo (10% vs 16%). In a meta-analysis of 6 randomized clinical trials, low-dose corticosteroids were associated with lower mortality rates compared with placebo for patients with HIV and moderate to severe *Pneumocystis* pneumonia (13% vs 25%). In a predefined subgroup analysis of a trial of low-dose steroid treatment for septic shock, patients with community-acquired pneumonia randomized to 7 days of intravenous hydrocortisone 50 mg every 6 hours and fludrocortisone 50 µg daily had decreased mortality compared with the placebo group (39% vs 51%). For patients with acute respiratory distress syndrome caused by various conditions, low-dose corticosteroids were associated with decreased in-hospital mortality (34% vs 45%) according to a meta-analysis of 8 studies that included 1091 patients. Adverse effects of low-dose corticosteroids may include hyperglycemia, gastrointestinal bleeding, neuropsychiatric disorders, muscle weakness, hypernatremia, and secondary infections.

CONCLUSIONS AND RELEVANCE Treatment with low-dose corticosteroids is associated with decreased mortality for patients with severe COVID-19 infection, severe community-acquired bacterial pneumonia, and moderate to severe *Pneumocystis* pneumonia (for patients with HIV). Low-dose corticosteroids may also benefit critically ill patients with respiratory infections who have septic shock, acute respiratory distress syndrome, or both.

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Supplemental content

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Author Affiliations: Department of Anesthesia and Perioperative Medicine, University of California San Francisco (Pirracchio, Legrand); Associate Editor, *JAMA* (Pirracchio); The George Institute for Global Health, University of New South Wales Sydney, Australia (Venkatesh); Gold Coast University Hospital, Southport, Queensland, Australia (Venkatesh).

Corresponding Author: Romain Pirracchio, MD, MPH, PhD, Department of Anesthesia and Perioperative Medicine, Zuckerberg San Francisco General Hospital and Trauma Center, University of California San Francisco, 1001 Potrero Ave, San Francisco, CA 94910 (romain.pirracchio@ucsf.edu).

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Pulmonary infections account for nearly 70% of patients admitted for sepsis in the intensive care unit (ICU).[1,2] Current management of severe pulmonary infections includes antimicrobials and respiratory support, if needed, with supplemental oxygen and mechanical ventilation.[3]

The local response to infection involves immune activation and local release of both proinflammatory and anti-inflammatory mediators.[4] In the lung, this release can damage the alveolar-capillary barrier, leading initially to interstitial and alveolar edema and then the development of pulmonary fibrosis.[5] During the first hours after severe infection, the host response results in activation of the hypothalamus-pituitary-adrenal axis by inflammatory cytokines[6] (**Figure 1**), which induces an increase in circulating free cortisol levels, the active endogenous form of glucocorticoids. Corticosteroids can mitigate the inflammatory response by inhibiting the expression of several proinflammatory genes, decreasing T-cell proliferation and cytokine production, impairing migration of immune cells through effects on adhesion molecules and chemokine signaling, and activating kinase pathways.[7] This phase is followed by a subacute phase lasting several days, with a decline in cortisol secretion.[6] For patients with prolonged sepsis (several days to weeks), decreased serum cortisol level may result in critical illness–related corticosteroid insufficiency, leading to persistent hypotension, which requires treatment with vasopressors, and to encephalopathy[8,9] (Figure 1).

Two randomized clinical trials (RCTs) conducted in the 1980s reported that use of high-dose corticosteroids was not beneficial for treatment of critically ill patients with septic shock. One of these studies, which randomized 59 patients to 2 boluses of methylprednisolone 30 mg/kg or dexamethasone 6 mg/kg administered a mean (SD) of 17.5 (5.4) hours after onset of septic shock, reported no improvement in overall survival vs placebo.[10] The second study[11] reported that, vs placebo, there was no improvement in overall mortality and increased deaths due to secondary infection for 382 patients who received methylprednisolone 30 mg/kg every 6 hours for 24 hours, started within 2 hours of diagnosis of septic shock.

More recent studies, however, suggest that lower doses of corticosteroids benefit patients with certain severe pulmonary infections.[12-14] This Review summarizes recent evidence on the use of low-dose corticosteroids, defined as less than 400 mg hydrocortisone equivalent daily,[15] for critically ill adults with pulmonary infections, including those with septic shock and acute respiratory distress syndrome (ARDS) (**Figure 2**). Critically ill patients were defined as those requiring ICU admission for vital organ support and monitoring.

Methods

PubMed, Embase, and Web of Science were searched for studies published from January 1, 1990, to January 30, 2024, without restriction on language for studies of systemic corticosteroids in adult patients with COVID-19 pneumonia, community-acquired pneumonia (CAP), ARDS, sepsis, and septic shock. Of 859 articles identified, 60 were included, consisting of 26 RCTs, 16 meta-analyses of RCTs, 3 secondary analyses of RCTs, 8 retrospective observational studies, and 7 practice guidelines and consensus statements (eAppendix in the Supplement). Studies of corticosteroids for acute exacerbations of chronic obstructive pulmonary disease or asthma and studies of treatment with topical corticosteroids were not included.

Discussion

COVID-19

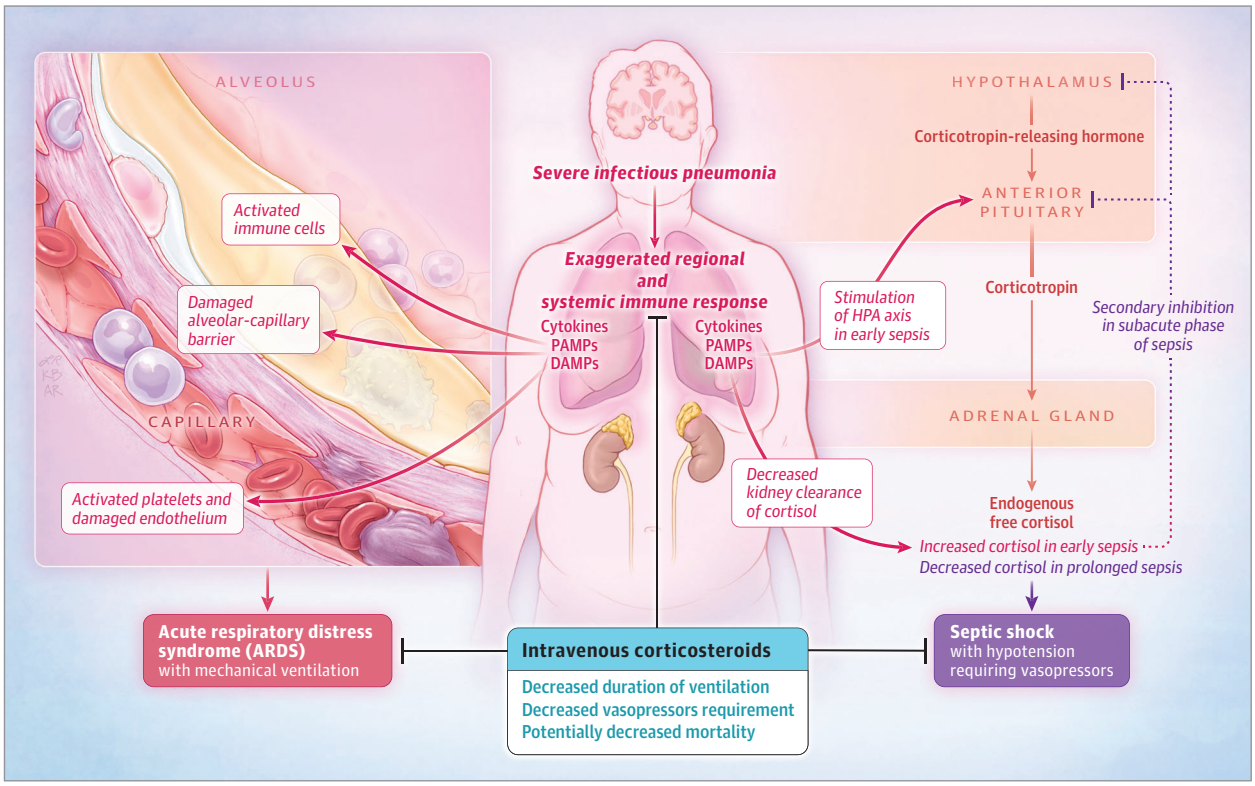
Patients hospitalized with COVID-19 who require supplemental oxygen to maintain oxygen saturation by pulse oximeter greater than 90% benefit from dexamethasone 6 mg daily for 10 days, based on evidence from 4 RCTs and a prospective meta-analysis by the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, which reported that patients with severe COVID-19 who were treated with corticosteroids had decreased mortality and an increase in mechanical ventilation–free days.[14,16-19] The RECOVERY trial[14] (n = 6425) randomized hospitalized patients with COVID-19 pneumonia to standard of care plus dexamethasone 6 mg daily for 10 days vs standard of care alone and reported a significant reduction in 28-day mortality for patients who were receiving mechanical ventilation (29% vs 41%; relative risk, 0.64; 95% CI, 0.51-0.81) or supplemental oxygen (23% vs 26%; relative risk, 0.82; 95% CI, 0.72-0.94). However, hospitalized patients with COVID-19 pneumonia who were not receiving supplemental oxygen had no decrease in mortality with corticosteroids compared with standard of care (18% vs 14%; relative risk, 1.19; 95% CI, 0.92-1.55). Therefore, outpatients with COVID-19 and hospitalized patients who do not require supplemental oxygen should not be treated with corticosteroids.[20]

Higher-Dose Corticosteroids for COVID-19

Use of corticosteroids at doses higher than 6 mg daily for patients hospitalized with COVID-19 pneumonia is associated with increased mortality for patients who require no oxygen or low levels of conventional oxygen, defined as low flow via face mask or nasal cannula. The RECOVERY follow-up trial[21] randomized adult patients with COVID-19 and hypoxia to dexamethasone 20 mg daily for 5 days, followed by 10 mg daily for 5 days or until hospital discharge vs usual care. In the usual care group, 87% of patients received dexamethasone 6 mg daily for 10 days. An interim analysis demonstrated that among the 1272 patients treated with conventional oxygen (defined as oxygen delivered through low-flow oxygen devices) or not requiring oxygen, high-dose dexamethasone resulted in a higher 28-day mortality rate compared with usual care (19% vs 12%; relative risk, 1.59; 95% CI, 1.20-2.10). In accordance with these findings, the data and safety monitoring board recommended continuing study enrollment only of patients with COVID-19 who required mechanical ventilation or extracorporeal membrane oxygenation. These study results are pending.[21,22]

Several other studies of patients with COVID-19 and severe hypoxia have not shown a mortality benefit with use of higher-dose dexamethasone. The COVID STEROID 2 trial,[23] which randomized 1000 hospitalized adults with COVID-19 who required oxygen at greater than or equal to 10 L/min or mechanical ventilation to 12 vs 6 mg of intravenous dexamethasone, reported no difference in mortality rates at day 28 (27% vs 32%; adjusted relative risk, 0.86; 99% CI, 0.68-1.08) or at day 90 (32% vs 38%; adjusted relative risk, 0.87; 99% CI, 0.70-1.07). The COVIDICUS trial[24] also

Figure 1. Pathophysiology of Response to Pulmonary Infection



Progression of regional and systemic immune and inflammatory response to organ failure and septic shock after an infection in the lungs. The key mediators include pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), and cytokines, and the interaction with the hypothalamic-pituitary-adrenal (HPA) axis is shown. Exogenous glucocorticoids limit pulmonary inflammation minimizing progression or hastening the resolution of lung injury.

reported no difference in 60-day mortality (27% vs 26%; hazard ratio, 0.96; 95% CI, 0.69-1.33) among 546 ICU patients with COVID-19 and acute hypoxemic respiratory failure who were randomized to dexamethasone 6 mg once daily for 10 days or dexamethasone 20 mg once daily for 5 days, and then 10 mg once daily for 5 days.

However, a meta-analysis that included 20 studies of 10 155 patients with severe or critical COVID pneumonia (defined as tachypnea >30/min, oxygen saturation <90% on room air, or ARDS) concluded that dexamethasone 12 mg daily for 10 days was associated with reduced mortality compared with 6 mg daily for 10 days (absolute risk difference, −14 per 1000; 95% CI, −26 to −2).[25] Therefore, according to this study, patients requiring supplemental oxygen at greater than or equal to 10 L/min, noninvasive ventilation, or invasive mechanical ventilation may benefit from treatment with higher-dose dexamethasone.[26]

Community-Acquired Bacterial Pneumonia

Patients with severe CAP may benefit from a short course of low-dose corticosteroids, defined as a hydrocortisone equivalent of 200 mg daily for 5 to 7 days, started within the first 24 hours of the onset of any severity criterion during hospitalization or ICU admission (**Table 1**).[15,41] A trial from 2011 and 2 trials from 2015 reported that hospitalized patients with CAP who were randomized to a low-dose corticosteroid regimen initiated between 12 and 36 hours after hospital admission had lower rates of treatment failure, defined as an absence of clinical or radiologic improvement, clinical deterioration, or death,[27,28] and decreased hospital length of stay.[29]

A 2017 Cochrane meta-analysis of 17 studies that included 2264 patients reported that low-dose corticosteroids were associated with lower rates of all-cause mortality in adults with severe CAP (Pneumonia Severity Index score ≥4 or equivalent). Most included trials used corticosteroid doses equivalent to 160 to 200 mg hydrocortisone equivalent per day, initiated between 12 and 36 hours after hospital admission for 5 to 10 days (absolute risk of death, 131 per 1000 vs 76 per 1000; relative risk, 0.58; 95% CI, 0.40-0.84; moderate level of evidence).[42] However, an individual patient data meta-analysis[43] that included 6 studies of 1506 patients did not report a reduction in 30-day mortality with use of low-dose corticosteroids typically initiated within 36 hours of admission (adjusted odds ratio [OR], 0.75; 95% CI, 0.46-1.21), but reported a significant reduction in the length of hospital stay (−1.15 days; 95% CI, −1.75 to −0.55). According to these data, the 2019 Infectious Diseases Society of America/American Thoracic Society guidelines recommended against corticosteroids.[44]

Two recent trials of low-dose corticosteroids for treatment of severe CAP are the ESCAPe trial,[30] published in 2022, and the CAPE COD trial,[13] published in 2023. The ESCAPe trial[30] randomized 586 ICU patients with CAP and 1 major or 3 minor modified Infectious Diseases Society of America/American Thoracic Society criteria for

Figure 2. Summary of Clinical Indications of Low-Dose Corticosteroids for Severe Pulmonary Infections per Guidelines

POPULATION	CURRENT GUIDELINE RECOMMENDATIONS	TREATMENT REGIMEN AND ADDITIONAL REMARKS	
Outpatients with COVID-19 Hospitalized patients who do not require supplemental oxygen	NIH COVID-19 Treatment Guidelines Strongly recommended against *Moderate evidence*	NA	In the RECOVERY trial, no survival benefit was observed with dexamethasone. In an observational cohort study, use of dexamethasone was associated with higher mortality in hospitalized patients with COVID-19 who did not require supplemental oxygen.
Hospitalized patients with COVID-19 who require conventional oxygen	Strongly recommended *Moderate evidence*	Dexamethasone 6 mg once daily for up to 10 d (dosing for critically ill patients was not addressed by the guidelines)	*Conventional oxygen* refers to oxygen supplementation that is not HFNC oxygen, NIV, MV, or ECMO. Use of dexamethasone 6 mg/d for 10 d or until hospital discharge signficantly reduced mortality in the RECOVERY trial.
Hospitalized patients with COVID-19 who require HFNC oxygen, noninvasive ventilation, or invasive mechanical ventilation	Strongly recommended *High evidence*		Dexamethasone was shown to reduce mortality in critically ill patients with COVID-19 in a meta-analysis of 7 randomized clinical trials.
Severe CAP, defined as patient with CAP requiring ICU admission	ERS/ESICM/ESCMID/ALAT 2023 Conditional use *Low evidence*	Multiple regimen accepted (eg, hydrocortisone 200 mg/d within the first 24 h of onset of severe CAP, or IV methylprednisolone equivalent at 40-80 mg/d for 4-7 d)	ICU admission is a subjective and institution-dependent criterion. Guideline recommended low-dose corticosteroids for patients with severe CAP and septic shock but did not provide a recommendation for patients without shock. Hydrocortisone 200 mg/d may be preferred over methylprednisolone 40 mg/d. Guideline was released before publication of the ESCAPe and CAPE COD trials.
Severe CAP, defined as either 1 major criterion or ≥3 minor criteria of the ATS/IDSA CAP severity criteria	ATS/IDSA 2019 Guideline not up to date *Moderate evidence*		Guideline recommends against use of corticosteroids but was released before publication of the ESCAPe and CAPE COD trials and may not apply to severe CAP without shock. Guideline suggested that corticosteroids can be considered for patients with CAP and refractory septic shock.
Severe CAP, no consensus on the definition of severe CAP	SCCM 2024 Strongly recommended *Moderate evidence*		Proposed severity criteria included ATS/IDSA 2007 criteria used in CAPE COD trial, and risk stratification scores.
Influenza pneumonia	ATS/IDSA 2019 Conditionally recommended against *Low evidence*	NA	Evidence is based on only observational studies.
Pneumocystis pneumonia in patients with HIV	HIV Medicine Association of IDSA 2019 Strongly recommended *High evidence*	Oral prednisone 40 mg twice daily days 1-5, 40 mg once daily days 6-10, 20 mg once daily days 11-21	Moderate to severe *Pneumocystis* pneumonia, defined as room air Pao_2 <70 mm Hg or alveolar-arterial gradient >35 mm Hg.
Septic shock	Surviving Sepsis Campaign 2021 Conditional use *Moderate evidence*	IV hydrocortisone 200 mg/d for 5-7 d	200 mg IV hydrocortisone given 50 mg every 6 h or as a continuous infusion. Steroids to be started for patients requiring norepinephrine or epinephrine ≥0.25 µg/kg/min for at least 4 h.
Septic shock	SCCM 2024 Conditional use *Low evidence*	IV hydrocortisone 200 mg/d with or without enteral fludrocortisone 50 µg/d for 7 d or until ICU discharge	Steroids should be started for all patients requiring vasopressors, regardless of vasopressor dose.
ARDS (Pao_2:Fio_2 ≤300)	ATS 2023 Conditional use *Moderate evidence*	No recommended regimen; align with regimen used for underlying cause or concurrent condition	Corticosteroids may decrease mortality, reduce the duration of mechanical ventilation, and reduce the length of hospital stay. Initiation of corticosteroid treatment >2 wk after the onset of ARDS may be associated with harm.
ARDS (Pao_2:Fio_2 <200 and within 14 d of onset)	SCCM 2024 Conditional use *Moderate evidence*	IV dexamethasone 20 mg/d for 5 d; then 10 mg/d for 5 d until extubation for early ARDS (within 24 h)	Patients with course of corticosteroid >7 d may have higher rates of survival than those who received a shorter course.

ALAT indicates Latin American Thoracic Association; ARDS, acute respiratory distress syndrome; ATS/IDSA, American Thoracic Society/Infectious Diseases Society of America; CAP, community-acquired pneumonia; ECMO, extracorporeal membrane oxygenation; ERS, European Respiratory Society; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; ESICM, European Society of Intensive Care Medicine; Fio_2, fraction of inspired oxygen; HFNC, high-flow nasal cannula; ICU, intensive care unit; IV, intravenous; MV, mechanical ventilation; NA, not applicable; NIH, National Institutes of Health; NIV, noninvasive ventilation; and SCCM, Society of Critical Care Medicine.

severe pneumonia[45] to intravenous methylprednisolone 40 mg/d, which was tapered during 20 days, vs placebo. This trial reported no significant difference in 60-day mortality among patients randomized to methylprednisolone (16%) vs placebo (18%) (adjusted OR, 0.90; 95% CI, 0.57-1.40). However, this study was stopped due to low recruitment, with only 586 patients enrolled out of a target of 1420, and thus may have been underpowered to detect the desired absolute difference of 7% mortality.

Table 1. Adverse Effects of Low-Dose Corticosteroids Reported in Randomized Trials in COVID-19, CAP, ARDS, and Septic Shock

Population and setting	Adverse event	NNH[a]
COVID-19, severe CAP, ARDS[12-14,18,23,24,27-35]	Gastrointestinal bleeding	100-1000
COVID-19, severe CAP, ARDS[12-14,18,21,24,27,29-32,34,36-38]	Hyperglycemia	5-2000
COVID-19, severe CAP[14,27,28,30,32,35]	Psychiatric disorders or delirium	63-2000
COVID-19, severe CAP, sepsis[12,13,16,17,23,24,27-35,37-39]	Superinfections	13-440
COVID-19, severe CAP, sepsis[12,16,24,30,32,33,36,40]	Neuromyopathy	14-625
Sepsis[32,34,36]	Hypernatremia	9-1000

Abbreviations: ARDS, acute respiratory distress syndrome; CAP, community-acquired pneumonia; NNH, number needed to harm.

[a] The NNH is calculated according to published data using the following formula: NNH = 1/ARI, where the absolute risk increase (ARI) equals the intervention event rate minus the control event rate, and the event is the adverse event of interest. References used to calculate the NNH are provided in eTable 2 in the Supplement.

In contrast, the CAPE COD trial[13] reported a mortality benefit, vs placebo, for patients with severe CAP who were randomized to a continuous infusion of 200 mg hydrocortisone for days 4 to 7, with tapering for a total of 8 or 14 days. This study was stopped by the data and safety monitoring board after second interim analysis and enrolled 800 critically ill patients with CAP who required invasive or noninvasive mechanical ventilation with a positive end-expiratory pressure level greater than or equal to 5 cm of water; oxygen via high-flow nasal cannula with a ratio of Pao_2 to the fraction of inspired oxygen (Fio_2) less than 300, with Fio_2 greater than or equal to 50%; nonrebreather oxygen mask with an estimated Pao_2:Fio_2 ratio less than 300; or a Pulmonary Severity Index score greater than 130.[46] Corticosteroids were initiated within 24 hours after the onset of meeting any of these severity criteria. Compared with patients in the placebo group, those in the corticosteroid group had a significant reduction in both 28-day mortality (6% vs 12%; absolute difference, −5.6 percentage points; 95% CI, −9.6 to −1.7) and 90-day mortality (9% vs 15%; absolute difference, −5.4 percentage points; 95% CI, −9.9 to −0.8).

A 2023 meta-analysis of 7 randomized clinical studies of patients with severe CAP (n = 1689) that included the ESCAPe and CAPE COD trials reported a reduction in 30-day mortality with use of low-dose corticosteroids (hydrocortisone equivalent ≤400 mg daily for ≤8 days vs placebo; 10% vs 16%; relative risk, 0.61; 95% CI, 0.44-0.85; 7 RCTs).[47] On the basis of this recent meta-analysis and the CAPE COD trial, low-dose corticosteroids are recommended for hospitalized patients with severe CAP. To our knowledge, there are no published RCTs about use of corticosteroids for hospital- or ventilator-acquired pneumonia.

Non–COVID-19 Viral Pneumonia

Although non–COVID-19 viral infections account for 20% to 30% of CAP, few studies have been published on the use of corticosteroids for treatment of adults with these viral infections.[48,49]

Influenza Pneumonia

To our knowledge, there are no RCTs assessing use of corticosteroids for treatment of influenza pneumonia, so current evidence is based on observational studies. A Cochrane meta-analysis of 21 observational studies of 9536 patients with influenza pneumonia who required hospital admission reported a higher mortality for patients receiving corticosteroids vs control patients (absolute risk of death at 30 days after admission, 209 per 1000 vs 70 per 1000; OR, 3.90; 95% CI, 2.31-6.60).[50] Another meta-analysis[51] of 15 observational studies that included 6427 patients with influenza pneumonia and ARDS reported an association between corticosteroids and increased hospital mortality (27% vs 14%; OR, 2.30; 95% CI, 1.68-3.16). However, this association was no longer significant in the subgroup of 5 studies (5595 patients) that reported adjusted estimates (mortality, 25% vs 13%; adjusted OR, 1.31; 95% CI, 0.95-1.80). Other observational studies have showed either no association between use of corticosteroids and mortality[52] or increased mortality with high-dose corticosteroids (adjusted hazard ratio, 3.05; 95% CI, 1.28-7.25).[53] Therefore, low-dose corticosteroids are not currently recommended for critically ill patients with influenza pneumonia.[44]

Respiratory Syncytial Virus

To our knowledge, no clinical trials have evaluated the effect of corticosteroids in hospitalized adults with respiratory syncytial virus infection. In an observational study of 50 hospitalized adults with respiratory syncytial virus, 33 (66%) received systemic corticosteroids. Most patients received 4 to 10 mg of dexamethasone or 40 to 60 mg of methylprednisolone every 6 hours for 1 to 2 days, followed by an oral prednisone taper, for a mean (SD) duration of 11 (7.3) days. Corticosteroid use was not associated with a decrease in peak viral load or duration of respiratory syncytial virus shedding.[54] Therefore, low-dose corticosteroids are not recommended for critically ill patients hospitalized with respiratory syncytial virus.

SARS and Middle East Respiratory Syndrome

To our knowledge, there are no RCTs evaluating the effect of corticosteroids on patients with SARS or Middle East respiratory syndrome. The largest retrospective cohort study of patients with Middle East respiratory syndrome (n = 309) reported that corticosteroid use was not associated with decreased 90-day mortality (adjusted OR, 0.75; 95% CI, 0.52-1.07), but was associated with longer time to Middle East respiratory syndrome coronavirus RNA clearance (adjusted hazard ratio, 0.35; 95% CI, 0.17-0.72).[55] An observational study of 401 patients with SARS reported a reduction in hospital mortality in the subgroup of patients requiring ICU admission who were treated with corticosteroids (hazard ratio, 0.37; 95% CI, 0.14-1.00).[56] A retrospective observational study of 72 patients with presumed SARS who were treated with ribavirin and steroids reported that although fewer patients treated with high-dose methylprednisolone (>500 mg/d) required supplemental oxygen (24% vs 53%) compared with those treated with lower doses (<500 mg/d), there were no significant mortality differences between the groups (5.8% vs

Table 2. Randomized Clinical Trials of Low-Dose Corticosteroids for Severe Pulmonary Infections in COVID-19 and Community-Acquired Pneumonia

Study	Population, setting, and inclusion	Comparison	Outcome and main results	NNT or NNH[a]
Horby et al,[14] RECOVERY, 2021	Patients hospitalized with suspected or laboratory-confirmed SARS-CoV-2 at 176 UK hospitals	Dexamethasone 6 mg daily vs placebo	Mortality at day 28 was 22.9% in the steroids group vs 25.7% in the usual care group (rate ratio, 0.83; 95% CI, 0.75-0.93; *P* < .001)	NNT = 36 to prevent 1 death at 28 d
Angus et al,[16] REMAP-CAP, 2020	Adults with clinically suspected or laboratory-confirmed SARS-CoV-2 with respiratory failure or cardiovascular organ support admitted to 121 ICUs in 8 countries	Hydrocortisone (50 or 100 mg every 6 h) vs no hydrocortisone	Median respiratory and cardiovascular organ support-free days at 21 d was 0 d (IQR, -1 to 15 d) in the steroids group and 0 d (IQR, -1 to 11 d) vs the usual care group	NNT = 22 to prevent 1 in-hospital death
Dequin et al,[17] CAPE COVID, 2020	Adults with COVID-19 and severe acute respiratory failure admitted to 28 ICUs in France	Hydrocortisone 200 mg/d vs placebo	Treatment failure at day 21, defined as death or persistent dependency on mechanical ventilation or high-flow oxygen therapy, occurred in 42.1% in the steroids group vs 50.7% in the placebo group (difference of proportions, −8.6% [95.48% CI, −24.9% to 7.7%]; *P* = .29)	NNT = 12 to prevent 1 treatment failure
Tomazini et al,[18] CoDEX trial, 2020	Adults with ARDS due to COVID-19 in 41 ICUs in Brazil	Dexamethasone 10 mg daily vs standard of care	Mean ventilator-free days during the first 28 d was 6.6 d (95% CI, 5.0-8.2) in the steroids group vs 4.0 d (95% CI, 2.9-5.4) in the standard care group (difference, 2.26; 95% CI, 0.2-4.38; *P* = .04)	NNT = 19 to prevent 1 death at 28 d
Jeronimo et al,[37] 2021	Adult patients with suspected or proven COVID-19 with hypoxemia in 1 center in Brazil	Methylprednisolone 0.5 mg/kg for 5 d vs placebo	Mortality at day 28 was 37.1% in the steroids group vs 38.2% in the placebo group (*P* = .63)	NNT = 93 to prevent 1 death at 28 d
COVID STEROID 2,[23] 2021	Adult patients with COVID-19 and severe hypoxemia in 26 hospitals in Europe and India	Dexamethasone 12 mg/d for 10 d vs 6 mg/d	Median No. of days alive without life support (invasive mechanical ventilation, circulatory support, or kidney replacement therapy) at 28 d was 22.0 d (IQR, 6.0-28.0 d) in the 12-mg group and 20.5 d (IQR, 4.0-28.0 d) in the 6-mg group (adjusted mean difference, 1.3 d; 95% CI, 0-2.6; *P* = .07).	NNT = 19 to prevent 1 death at 28 d
RECOVERY,[21] 2023	Adults hospitalized with COVID and hypoxemia in the UK, South and Southeast Asia, and Africa	Dexamethasone 20 mg once daily for 5 d followed by 10 mg dexamethasone once daily for 5 d vs usual care	Mortality at day 28 was 19% in the high-dose group vs 12% in usual care (rate ratio, 1.59; 95% CI, 1.20-2.10; *P* = .001)	NNH = 16 to cause 1 adverse event
Bouadma et al,[24] COVIDICUS, 2022	Adults in the ICU with COVID-19 and severe AHRF in 9 ICUs in France	Dexamethasone 20 mg/d for 5 d and then 10 mg/d for 5 d vs 6 mg/d for 10 d	Mortality at day 60 was 25.9% in the high-dose group vs 26.8% in the low-dose group (absolute risk difference, −0.8% [95% CI, −8.3% to 6.5%]; HR, 0.96 [95% CI, 0.69-1.33]; *P* = .79)	NNT = 113 to prevent 1 death at 60 d
Bozzette et al,[39] 1990	251 Patients with HIV-related *Pneumocystis* pneumonia in 5 centers in California	Prednisone (40 mg twice a day for 5 d, followed by 40 mg daily for 5 d, followed by 20 mg daily for the duration of anti-*Pneumocystis* therapy vs standard treatment; n = 128)	Respiratory failure on day 21 occurred in 13% in the steroids group and 28% in the standard-treatment groups (*P* = .004)	NNT = 6 to prevent 1 respiratory failure
Confalonieri et al,[33] 2005	46 Patients with severe community-acquired pneumonia in 6 ICUs in Italy	Hydrocortisone (200-mg IV bolus, followed by continuous infusion at 10 mg/h for 7 d) vs placebo (n = 24); trial suspended after interim analysis	Multiple Organ Dysfunction Syndrome score was 0.3 ± 0.5 in the steroids group vs 1.0 ± 0.9 in the placebo group (*P* = .003). Delayed septic shock by day 8 occurred in 0% in the steroids group and 70% in the placebo group (*P* = .001).	NNT = 3 to prevent 1 death at 28 d
Meijvis et al,[29] 2011	304 Patients with community-acquired pneumonia in 2 emergency departments in the Netherlands	Dexamethasone 5-mg IV bolus daily for 3 d vs placebo	Median length of hospital stay was 6.5 d (IQR, 5.0-9.0 d) in the steroids group vs 7.5 d (IQR, 5.3-11.5 d) in the placebo group (*P* = .048)	NNT = 90 to prevent 1 death at 30 d
Blum et al,[27] 2015	785 Patients with community-acquired pneumonia in 7 emergency departments in Switzerland	Prednisone 50 mg daily for 7 d vs placebo	Median time to clinical stability was 3.0 d (IQR, 2.5-3.4 d) in the steroids group vs 4.4 d (IQR, 4.0-5.0 d) in the placebo group (HR, 1.33; 95% CI, 1.15-1.50; *P* < .001)	NNH = 129 to cause 1 death at 30 d

(continued)

Table 2. Randomized Clinical Trials of Low-Dose Corticosteroids for Severe Pulmonary Infections in COVID-19 and Community-Acquired Pneumonia (continued)

Study	Population, setting, and inclusion	Comparison	Outcome and main results	NNT or NNH[a]
Torres et al,[28] 2015	120 Patients with severe community-acquired pneumonia and C-reactive protein level ≥150 mg/L in 3 Spanish hospitals	Methylprednisolone 0.5 mg/kg IV every 12 h for 5 d vs placebo	Treatment failure occurred in 13% in the steroids group vs 31% in the placebo group (P = .02)	NNT = 6 to prevent 1 treatment failure
Meduri et al,[30] 2022	584 Patients with severe community-acquired pneumonia or health care-associated pneumonia in 42 Veterans Affairs medical centers in the United States	Methylprednisolone 40 mg/d IV for 7 d, followed by tapering until day 20 vs placebo	Mortality at day 60 was 16% in the steroids group vs 18% in the control group (absolute risk difference, 2% [95% CI, 8%-5%]; OR, 0.89 [95% CI, 0.58-1.38]; P = .61)	NNT = 50 to prevent 1 death at 60 d
Dequin et al,[13] 2023	795 Patients with severe community-acquired pneumonia in 31 centers in France	Hydrocortisone 200 mg/d for 8 to 14 d vs placebo	Mortality at day 28 was 6.2% in the steroids group vs 11.9% in the placebo group (absolute difference, −5.6 percentage points; 95% CI, −9.6 to −1.7; P = .006)	NNT = 18 to prevent 1 death at 28 d

Abbreviations: AHRF, acute hypoxemic respiratory failure; ARDS, acute respiratory distress syndrome; HR, hazard ratio; ICU, intensive care unit; IV, intravenous; NNH, number needed to harm; NNT, number needed to treat; OR, odds ratio.

[a] The NNT and NNH are calculated according to published data using the following formula: NNT (NNH) = 1/ARR, where the absolute risk reduction (ARR) equals the control event rate minus the intervention event rate. The event is mortality when calculation of the NNT was not possible for the primary end point (ie, for continuous end points).

5.4%).[57] Therefore, low-dose corticosteroids are not recommended for critically ill patients hospitalized with SARS or Middle East respiratory syndrome, pending further studies.

Pneumocystis jirovecii Pneumonia

Low-dose corticosteroids have been reported to improve outcomes in adults with HIV and moderate to severe *Pneumocystis* pneumonia, defined as an arterial oxygen partial pressure less than 70 mm Hg or an alveolar-arterial gradient greater than 35 mm Hg on room air.[58] A meta-analysis that included 6 RCTs with 489 patients who had *P jirovecii* pneumonia and HIV reported a lower 1-month mortality with adjunctive corticosteroids (13%) vs placebo (25%) (relative risk, 0.56; 95% CI, 0.32-0.98)[59] (**Table 2**). To our knowledge, there are no RCTs investigating use of low-dose corticosteroids for patients with *Pneumocystis* pneumonia without HIV infection. In a meta-analysis of 16 observational studies of *Pneumocystis* pneumonia in patients who did not have HIV (2518 patients), low-dose corticosteroids were associated with increased mortality (26% vs 25%; OR, 1.37; 95% CI, 1.07-1.75),[60] but among those with severe acute respiratory failure (arterial oxygen partial pressure <60 mm Hg), corticosteroids were associated with decreased mortality (30% vs 47%; OR, 0.63; 95% CI, 0.41-0.95).[60] Therefore, low-dose corticosteroids are recommended for patients with moderate to severe *P jirovecii* pneumonia and HIV, and may be considered for patients with *Pneumocystis* pneumonia without HIV who have severe hypoxemia.

Septic Shock

Pneumonia accounts for nearly 70% of cases of sepsis and septic shock,[61] which is associated with a mortality rate of 30% to 50%.[62,63] The 2021 Surviving Sepsis Campaign guidelines provided a weak recommendation for use of hydrocortisone for patients with septic shock who had ongoing vasopressor requirements.[64] The 2024 focused update of the guidelines from the Society of Critical Care Medicine[15] recommended that patients with septic shock receive intravenous hydrocortisone 200 mg/d (via continuous infusion or every 6 hours) with or without fludrocortisone 50 µg enterally daily for 7 days or until ICU discharge.

To our knowledge, randomized clinical trials have not investigated the role of low-dose corticosteroids exclusively for patients with pulmonary infection–associated septic shock. In a 2023 meta-analysis of patients with severe CAP,[47] 5 trials (n = 1525) included patients with septic shock at enrollment. In this subgroup, low-dose corticosteroids were associated with a reduction in 30-day all-cause mortality (risk ratio, 0.61; 95% CI, 0.42-0.90).

The APROCCHSS trial randomized 1240 patients with septic shock (59% had a pulmonary source of sepsis)[12,65] to a 7-day course of intravenous hydrocortisone 50 mg every 6 hours and enteral fludrocortisone 50 µg daily vs placebo. This trial reported a mortality reduction with steroids vs placebo (43% vs 49%; relative risk, 0.88; 95% CI, 0.78-0.99) (eTable 1 in the Supplement). A prespecified subgroup analysis of the APROCCHSS trial showed a mortality reduction in the group with septic shock due to CAP (39% vs 51%; OR, 0.60; 95% CI, 0.43-0.83).[65,66] Therefore, low-dose corticosteroids are conditionally recommended for patients with septic shock due to CAP.

ARDS

Pneumonia and sepsis are the primary causes of ARDS.[67] The 2024 update of the ARDS guidelines[15,67,68] provided a conditional recommendation for use of low-dose corticosteroids for patients with ARDS (moderate certainty of evidence). To our knowledge, no RCT has focused specifically on patients with ARDS due to pulmonary infection.

A 2020 meta-analysis of 8 RCTs (1091 patients)[69] of patients with ARDS due to various conditions, with pulmonary source ranging from 40% to 100%, reported a decrease in hospital mortality (34% vs 45%; relative risk, 0.79; 95% CI, 0.64-0.98) and an increase in ventilator-free days at day 28 (mean difference, 4.06 days; 95% CI, 2.66-5.45) with corticosteroids (4 studies used low-dose corticosteroids and 4 studies used >400 mg hydrocortisone equivalent per day) vs placebo.

In the study by Tongyoo et al,[31] 51% of patients had ARDS from pneumonia. Mortality at 28 days was 23% in the low-dose corticosteroid group vs 26% in the placebo group (relative risk, 0.88; 95% CI, 0.44-1.77). In APROCCHSS,[12] among patients with CAP who had ARDS (n = 347), low-dose corticosteroids were associated with

Box. Commonly Asked Questions

Which patients with COVID-19 should be treated with low-dose corticosteroids?

Hospitalized patients with COVID-19 who require supplemental oxygen to keep oxygen saturation by pulse oximeter greater than 90% should be treated with dexamethasone 6 mg per day for 10 days. This steroid regimen has been associated with decreased mortality and increased ventilator-free days in randomized clinical trials.

Do low-dose corticosteroids reduce mortality of patients with severe pulmonary infections other than COVID-19?

Hospitalized patients with severe community-acquired pneumonia had reduced mortality when treated with low-dose corticosteroids (200 mg hydrocortisone equivalent for 5-7 days). Low-dose corticosteroids (prednisone 40 mg twice daily tapered during 21 days) were also associated with decreased mortality of patients with HIV and moderate to severe *Pneumocystis* pneumonia.

What are potential adverse effects of low-dose corticosteroids?

Low-dose corticosteroids may be associated with hyperglycemia, gastrointestinal bleeding, neuropsychiatric disorders, muscle weakness, hypernatremia, and development of secondary infections.

a reduction in the 90-day mortality rate compared with placebo (45% vs 58%).[66] In the ESCAPe trial,[30] the subgroup of patients with CAP and ARDS (11%) had a 60-day mortality of 15% with low-dose corticosteroids vs 36% with placebo (OR, 0.32; 95% CI, 0.09-1.13). Therefore, low-dose corticosteroids are conditionally recommended for patients with ARDS due to CAP.

Adverse Effects and Complications of Corticosteroid Treatment

Short courses of corticosteroids may have adverse effects, including hyperglycemia, hypernatremia, secondary infections, gastrointestinal bleeding, hypertension, neuromyopathy, and neuropsychiatric complications such as delirium (Table 1; eTable 3 in the Supplement).[27-40] Several RCTs of corticosteroids vs placebo for patients with CAP reported that use of corticosteroids was associated with higher rates of hyperglycemia, defined as nonfasting glucose level greater than 198 mg/dL (44% vs 23%),[29] more hyperglycemic episodes needing new insulin treatment (19% vs 11%),[27] and higher insulin requirement.[10] However, an individual patient data meta-analysis of 7017 patients with septic shock found no association between corticosteroids and the risk of hyperglycemia (34% vs 32%; relative risk, 1.05; 95% CI, 0.98-1.12).[70] Increased risk of hypernatremia, defined as a serum sodium concentration greater than 145 mEq/L, was found in a meta-analysis of 6 trials (5033 patients) of patients with septic shock who were treated with corticosteroids (7%) vs placebo (3%) (relative risk, 2.01; 95% CI, 1.56-2.60).[70]

The risk of secondary infections associated with corticosteroids depends on the dose of corticosteroids and the timing of assessment of secondary infections. A meta-analysis of 10 trials that included 6970 patients with septic shock reported no association between low-dose corticosteroids and risk of superinfection during the ICU stay (19% vs 20%; relative risk, 1.04; 95% CI, 0.95-1.15).[70] A meta-analysis of 4 studies of 1000 patients with severe CAP[47] also reported no association between low-dose corticosteroids and risk of secondary health care–associated infections in the ICU (8% vs 10%; relative risk, 0.89; 95% CI, 0.60-1.32). However, a 180-day follow-up of 727 patients enrolled in the STEP trial (corticosteroids for CAP) demonstrated a higher risk of recurrent pneumonia (8% vs 3%; OR, 2.57; 95% CI, 1.29-5.12) and secondary infections such as dermatologic, urogenital, pulmonary, intestinal, and endocardium/foreign body infections (17% vs 10%; OR, 1.94, 95% CI, 1.25-3.03) with corticosteroids.[71] A meta-analysis of 9 studies reported a significantly lower risk of nosocomial infections in 2311 patients with COVID-19 treated with dexamethasone 12 vs 6 mg daily (absolute risk difference, −16.7 per 1000; 95% CI, −25 to −5.4; very low certainty).[25] However, data from retrospective studies and case series suggested that patients with COVID-19 treated with high doses of corticosteroids were at increased risk of nocardiosis,[72] mucormycosis, and pulmonary aspergillosis.[73-76]

Low-dose corticosteroids can cause gastrointestinal bleeding. A meta-analysis of 80 trials (36 407 patients) comparing systemic corticosteroids administered for more than 24 hours with placebo or no treatment for critically ill adults found a pooled incidence of clinically important gastrointestinal bleeding of 2.3% in the corticosteroid group vs 1.8% in the control group (relative risk, 1.26; 95% CI, 1.01-1.57).[77] However, meta-analyses of patients with CAP[47] (7 studies, 1689 patients) and septic shock[70] (7 studies, 5929 patients) did not find an association between corticosteroids and gastrointestinal bleeding.

Evidence about corticosteroid use and myopathy is inconclusive. An RCT of 586 patients with severe CAP did not report higher incidence of muscle weakness in the group treated with corticosteroids vs placebo (0.003% vs 0.003%).[30] Two large trials of patients with septic shock (ADRENAL and APROCCHSS) also did not find a higher incidence of neuromuscular weakness with corticosteroid use. However, a patient-level meta-analysis that included 2647 patients with septic shock reported more muscle weakness with low-dose corticosteroids (28% vs 16%; relative risk, 1.73; 95% CI, 1.49-1.99).[70]

Neuropsychiatric complications such as insomnia, irritability, mania, psychosis, and delirium were not increased with use of corticosteroids in a 2019 Cochrane meta-analysis[78] of patients with septic shock (61 studies, 12 192 patients), in a 2017 Cochrane review of patients with CAP[42] (17 studies, 2264 patients), or in the ESCAPe[30] and CAPE COD[13] trials. However, neuropsychiatric complications may be underreported and are often not evaluated in critical care trials. Other potential complications such as delayed wound healing are unlikely with low-dose, short-course corticosteroids.[79] There was no significant difference in impaired wound healing in a 2016 RCT[32] of hydrocortisone 200 mg daily for 5 days, followed by tapering until day 11, vs placebo for 353 patients with severe sepsis (2.7% vs 1.6%).

Limitations

This Review has several limitations. First, relevant articles may not have been included. Second, some severe and less common respiratory infections, such as varicella pneumonia and cytomegalovirus-related pneumonia in immunocompromised patients, were not discussed. Third, quality of included articles was not formally assessed. Fourth, there was heterogeneity in results across clinical trials, suggesting that differences in clinical setting and patient selection may influence effects of corticosteroids.

Conclusion

Treatment with low-dose corticosteroids, defined as less than or equal to 400 mg hydrocortisone equivalent daily, is associated with decreased mortality for patients with severe COVID-19 infection, severe community-acquired bacterial pneumonia, and moderate to severe *Pneumocystis* pneumonia (for patients with HIV) (**Box**). Low-dose corticosteroids may also benefit critically ill patients with respiratory infections who have septic shock, ARDS, or both.

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