JAMA Clinical Guidelines Synopsis

Corticosteroids for Sepsis, Acute Respiratory Distress Syndrome, or Community-Acquired Pneumonia

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GUIDELINE TITLE 2024 Focused Update: Guidelines on Use of Corticosteroids in Sepsis, Acute Respiratory Distress Syndrome, and Community-Acquired Pneumonia

RELEASE DATE January 2024

DEVELOPER AND FUNDING SOURCE Society of Critical Care Medicine (SCCM)

TARGET POPULATION Critical care and internal medicine physicians

SELECTED RECOMMENDATIONS

- Administer corticosteroids to adult patients with septic shock (conditional recommendation; low certainty of evidence) at a daily dose of less than 400 mg of hydrocortisone equivalent (strong recommendation; moderate certainty of evidence).
- Administer corticosteroids to adult hospitalized patients with acute respiratory distress syndrome (ARDS) (conditional recommendation; moderate certainty of evidence).
- Administer corticosteroids to adult patients hospitalized with severe bacterial community-acquired pneumonia (CAP) (strong recommendation; moderate certainty of evidence).

Summary of the Clinical Problem

Many acutely ill patients, including those hospitalized with severe pulmonary infections, have a dysregulated systemic inflammatory response, characterized by hypothalamic-pituitary-adrenal axis dysfunction, altered cortisol metabolism, and tissue corticosteroid resistance.[1] Given the growing body of evidence regarding corticosteroid use in critical illness, this guideline sought to provide updated recommendations on corticosteroid use for adults with sepsis, ARDS, and CAP.[2]

Characteristics of the Guideline Source

This guideline was developed and funded by the SCCM and also sponsored by the Endocrine Society. An international, interdisciplinary expert panel was selected by the SCCM Board of Regents. A comprehensive literature review identified 82 randomized clinical trials (RCTs) published prior to October 2022 to inform the guideline recommendations using the GRADE methodology. All panel members disclosed potential financial and nonfinancial conflicts of interest (Table).[2]

Evidence Base

Recommendations were based on 46 RCTs evaluating the effect on mortality or length of intensive care unit stay for adult patients with sepsis or septic shock treated with corticosteroids compared with placebo or standard of care. Among these studies, the most common corticosteroid dosing regimen in patients with septic shock was intravenous hydrocortisone, 200 mg/d (continuous infusion or divided every 6 hours), with or without enteral fludrocortisone, 50 µg/d for 7 days or until intensive care unit discharge. However, the dosage, type, and duration of corticosteroids were variable (even including tapering regimens) in these RCTs, and the studies aggregated in this panel's meta-analysis included participants with sepsis and septic shock, regardless of infection source.

The panel made (1) a conditional recommendation to administer corticosteroids to adult patients with septic shock and (2) a strong recommendation not to administer high-dose/short-duration corticosteroids (daily dose of >400 mg hydrocortisone equivalent for <3 days) for adult patients with septic shock.

To assess mortality in the intensive care unit and mortality at 14 to 30 days, the guideline evaluated 39 RCTs (9632 patients) that randomized patients with sepsis and septic shock to corticosteroid vs placebo or usual care and reported moderate certainty of evidence of a reduction in mortality with steroids (steroids, 27.4%, vs placebo or usual care, 29.7%; risk ratio [RR], 0.93; 95% CI, 0.88-0.98).[2] Based on 9 studies (6438 patients), corticosteroids may reduce 60-day to 1-year mortality vs placebo (35.2% vs 37.2%; RR, 0.94; 95% CI, 0.89-1.0; low certainty of evidence).[2] Also, compared with placebo or no corticosteroids, corticosteroid use was associated with higher rates of shock reversal (72.4% vs 62.7%; RR, 1.24; 95% CI, 1.11-1.38; high certainty of evidence) and greater reductions in organ dysfunction, defined as a lower Sequential Organ Failure Assessment score (mean difference, −1.41; 95% CI, −1.87 to −0.96 at 7 days; high certainty of evidence). Corticosteroid use may

Table. Guideline Rating[a]

Standard	Rating
Establish transparency	Good
Management of conflict of interest in the guideline development group	Fair
Guideline development group composition	Good
Clinical practice guideline–systematic review intersection	Good
Establishing evidence foundations and rating strength for each of the guideline recommendations	Fair
Articulation of recommendations	Fair
External review	Good
Updating	Fair
Implementation issues	Fair

[a] Cifu AS, Davis AM, Livingston EH. Introducing JAMA Clinical Guidelines Synopsis. *JAMA*. 2014;312(12):1208-1209.

be associated with reduced length of stay in the intensive care unit (mean difference, 0.60 days fewer; 95% CI, −1.48 to 0.27 days more) and in the hospital (mean difference, 0.74 days fewer; 95% CI, −2.06 to 0.57 days more). Adverse effects associated with steroid use with at least moderate certainty of evidence were hyperglycemia (33.1% vs 29.1%; RR, 1.13; 95% CI, 1.08-1.18) and hypernatremia (5.9% vs 4.0%; RR, 1.64; 95% CI, 1.32-2.03).[2]

A planned subgroup analysis compared corticosteroid use for more than 3 days vs 3 days or less with placebo or no corticosteroid use (25 studies used fixed steroid doses <400 mg/d, 12 used weight-based dosing, and 1 did not report the dose) on 28-day mortality due to sepsis and septic shock; a corticosteroid duration of more than3 days was associated with a mild benefit in mortality (RR, 0.92; 95% CI, 0.87-0.98), whereas a duration of 3 days or less did not show reduced mortality (RR, 0.90; 95% CI, 0.59-1.37).[2]

The strong recommendation not to administer high-dose corticosteroids (>400 mg/d of hydrocortisone equivalent) for short durations (<3 days) was based on contemporaneous and historical trials suggesting a potential elevated risk of hyperglycemia and secondary infections from short high-dose courses of steroids without significant improvements in mortality in patients with septic shock.[2]

Based on 16 RCTs (2740 patients) of 28-day mortality in critically ill adults with ARDS, the guideline issued a conditional recommendation (moderate certainty) for administration of corticosteroids (mortality with corticosteroids, 35.8%, vs mortality without corticosteroids, 44.6%; RR, 0.82; 95% CI, 0.72-0.95).[2] A longer course of corticosteroids (>7 days) in those with ARDS was associated with higher rates of survival than a shorter course (≥7 days) (P = .04 for subgroup interaction; moderate credibility). Steroid dosing regimens varied across studies from 40 mg/d to 2 mg/kg/d of intravenous methylprednisolone equivalents, with durations of 7 to 30 days.[2] Corticosteroid use was associated with fewer days of mechanical ventilation and shorter hospital length of stay (both with low certainty of evidence).

The guideline also provided an important update about use of corticosteroids in adults with bacterial CAP based on 18 RCTs of 4567 patients comparing hospital mortality for adults with suspected or probable CAP, including those with severe and less severe disease. Definitions of severe CAP varied among studies and included the American Thoracic Society/Infectious Diseases Society of America criteria,[3] the Pulmonary Severity Index score group IV or V, and other clinical criteria associated with severe CAP, such as septic shock, mechanical ventilation, hypoxemia, and confusion. Based on 12 RCTs of 2133 patients with severe bacterial CAP, the guideline provided a strong recommendation for use of corticosteroids in adults hospitalized with severe bacterial CAP (10.4% mortality with corticosteroids vs 17.2% in controls; RR, 0.62; 95% CI, 0.45-0.85). Corticosteroids probably also reduce the need for invasive mechanical ventilation (corticosteroids, 5.1%, vs usual care, 8.9%; RR, 0.56; 95% CI, 0.42-0.74) in adults hospitalized with severe and less severe CAP.[2] In 7 RCTs of 2434 patients with less severe CAP, there was no difference in mortality (corticosteroids, 8.6%, vs usual care, 8.1%; RR, 1.08; 95% CI, 0.83-1.42).

Discussion

Compared with the 2017 guidelines,[4] the 2024 update provides (1) a conditional recommendation for broader use of corticosteroids in septic shock (not isolated to septic shock unresponsive to both fluid and moderate- to high-dose vasopressor therapy), (2) a conditional recommendation for use of corticosteroids in patients with ARDS of all degrees of severity (no longer focused on solely early moderate to severe ARDS), and (3) a strong recommendation for use of corticosteroids in patients with severe CAP (in contrast to the prior conditional recommendation in hospitalized patients with CAP).

Areas for Future Research

Upcoming data from ongoing trials such as HYDRO-SHIP (NCT05354778), a multicenter RCT investigating hydrocortisone use in critically ill patients with nosocomial pneumonia, may inform corticosteroid use in severe hospital-acquired pneumonia. Additionally, a phase 3 trial, COLOSSEUM (NCT03745664), is evaluating whether corticosteroid use in patients hospitalized with CAP reduces myocardial injury, as assessed by serum high-sensitivity cardiac troponin T. Additional research is required to (1) better define critical illness–related corticosteroid insufficiency, including greater understanding of its relevance in managing the various phenotypes and genotypes of sepsis and critical illness and (2) evaluate optimal doses and durations of corticosteroids when used in sepsis, ARDS, and CAP.

ARTICLE INFORMATION

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