Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Do Systemic Corticosteroids Reduce Mortality in Critically Ill Adult Patients With COVID-19?

TAKE-HOME MESSAGE

Corticosteroids are associated with reduced rates of all-cause mortality in critically ill adult patients receiving respiratory support who have suspected or confirmed coronavirus disease 2019 (COVID-19).

METHODS

DATA SOURCES

Meta-analysis authors performed a search of ClinicalTrials.gov, the Chinese Clinical Trial Registry, and the European Union Clinical Trials Register for registered studies from December 31, 2019, to April 6, 2020. The authors included studies that evaluated systemic corticosteroids for the treatment of suspected or confirmed COVID-19 in hospitalized, critically ill adult patients.

STUDY SELECTION

The authors screened all randomized controlled trials that compared systemic corticosteroids with placebo or usual care in critically ill adult patients with COVID-19 with a primary outcome of mortality. All patients across the selected studies received respiratory support with either oxygen supplementation or mechanical ventilation. Authors of the identified trials were directly recruited to assist in the meta-analysis and provided all data directly.

EBEM Commentators
Michael J. Yoo, MD
Brit Long, MD
Department of Emergency Medicine
San Antonio Uniformed Services Health Education Consortium
Fort Sam Houston, TX
Michael Gottlieb, MD
Department of Emergency Medicine
Rush University Medical Center
Chicago, IL

This review does not reflect the views or opinions of the US government, Department of Defense or its components, US Army, US Air Force, or SAUSHEC EM Residency Program.

Jestin N. Carlson, MD, MS, Alan Jones, MD, and Michael Gottlieb, MD, serve as editors of the SRS series.

Editor's Note: This is a clinical synopsis, a regular feature of the *Annals'* Systematic Review Snapshot (SRS) series. The source for this systematic review snapshot is: **Sterne JAC, Murthy S, et al; WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA*.** https://doi.org/10.1001/jama.2020.17023.

Results

Odds ratio of mortality in patients given corticosteroids versus control.

	No. of Deaths/Total Patients (%)		
Intervention	Steroids	Control	OR (95% CI)
Overall	222/678 (32.7)	425/1,025 (41.5)	0.66 (0.53–0.82)

OR, Odds ratio; *CI*, confidence interval.

The meta-analysis included 7 randomized studies comprising 1,703 patients.[2] Individual study sample sizes ranged from 19 to 1,007 patients. Two studies evaluated high-dose dexamethasone (20 mg per day), 1 study evaluated low-dose dexamethasone (6 mg per day), 3 studies evaluated low-dose hydrocortisone (200 mg per day), and 1 study evaluated high-dose methylprednisolone (80 mg per day). Patients with COVID-19 who were receiving respiratory

DATA EXTRACTION AND SYNTHESIS

The primary outcome was 28-day all-cause mortality. The secondary outcome was investigator-defined serious adverse events. The data were analyzed with an odds ratio derived with inverse variance–weighted fixed effects and random effects with 95% confidence intervals. Furthermore, the authors assessed heterogeneity with the I^2 statistic and the Cochrane Q statistic. Risk of bias was determined by the Cochrane Risk of Bias Assessment Tool.[1]

support and systemic corticosteroids had reduced 28-day all-cause mortality compared with controls (Table). The authors performed a subgroup analysis evaluating the benefits of corticosteroids with respect to invasive mechanical ventilation, oxygen treatment, vasoactive medications, age, sex, and days of symptoms. They identified a benefit in all groups except those receiving vasoactive medications. For the secondary outcome, the authors reported a total of 64 adverse events (18.1%) in patients receiving corticosteroids and 80 (23.4%) in those receiving placebo or usual care.

Commentary

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2, first identified in Wuhan, China, in 2019.[3] As of October 2020, approximately 33.7 million cases have been identified across 188 countries, with more than 1 million deaths.[4] Illness severity in individuals with COVID-19 varies widely; however, preliminary data demonstrate that the presence of one or more underlying chronic diseases, such as diabetes or cardiovascular disease, is associated with ICU admission.[5,6] In the most severe presentations, patients develop substantial hypoxia and signs and symptoms that may meet the Berlin criteria for acute respiratory distress syndrome.[7] Although the pathophysiology of severe COVID-19 manifestations is still under investigation, critically ill patients with the disease appear to have immune system dysregulation and higher levels of proinflammatory cytokines.[7]

The utility of systemic corticosteroids has been previously studied in patients with non–COVID-19 causes of acute respiratory distress syndrome.[8] Specifically, the Society of Critical Care Medicine and the European Society of Intensive Care Medicine recommend the administration of corticosteroids in patients with early and moderate to severe acute respiratory distress syndrome.[8] However, the true benefit of corticosteroids in non–COVID-19 causes of acute respiratory distress syndrome is controversial, with insufficient evidence to support their routine use.[9] Researchers theorize that in patients with acute respiratory distress syndrome, corticosteroids may reduce serum levels of proinflammatory cytokines, total ventilator days, and inhospital mortality.[8] With severe presentations of COVID-19 appearing to be a specific phenotype of acute respiratory distress syndrome, several investigators have evaluated the benefit of systemic corticosteroids in critically ill patients with COVID-19. The results of this meta-analysis suggest that systemic corticosteroids reduce 28-day all-cause mortality in critically ill adult patients with COVID-19.[2]

However, this meta-analysis has several limitations. First, the process regarding final authority and handling of discrepancies in article selection was not clearly defined. Additionally, the definition of critical illness was not entirely clear, and further research is needed to better delineate which patients are most likely to benefit from corticosteroids administration. Only patients receiving supplemental oxygen appear to benefit from corticosteroids. There was significant heterogeneity between studies regarding patient populations, time of onset, and type and dose of the corticosteroid. Future studies are needed to determine the optimal dose, timing, and route of corticosteroid administration. Outcome data were more limited for patients who left the hospital before 28 days, which may have underestimated the longer-term effect. For the primary endpoint, The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial evaluating dexamethasone provided the majority of the data (57%),[2,10] likely because of the early suspension of other studies after the release of the RECOVERY trial data.[2] Adverse event definitions and reporting varied between studies, limiting the ability to meta-analyze this outcome. Finally, this meta-analysis included only adult patients, and the benefits of systemic corticosteroids in critically ill children remain unknown.

Dr. Jones was the supervising editor on this article. Dr. Gottlieb did not participate in the editorial review or decision to publish this article.

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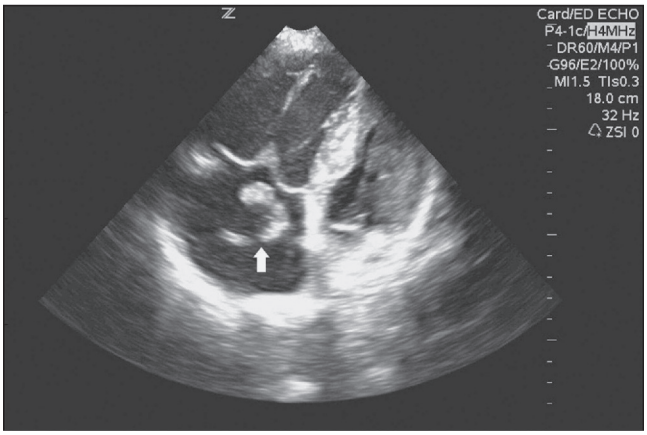

"Elderly Female With Syncope" by Byrne, Czuczman, and Hwang, July 2011, Volume 58, #1, pp. 105, 115.