EDITORIAL

Corticosteroids in COVID-19 ARDS
Evidence and Hope During the Pandemic

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Corticosteroids, such as hydrocortisone and dexamethasone, have anti-inflammatory, antifibrotic, and vasoconstrictive effects, which intensivists have been trying to leverage for decades to improve outcomes in patients with acute respiratory distress syndrome (ARDS) and septic shock. In the first description of ARDS in 1967, Ashbaugh and colleagues noted that "corticosteroids appeared to have value in the treatment of patients with fat-embolism and possibly viral pneumonia."[1]

Related articles pages 1298, 1307, 1317, and 1330

Over the intervening decades, many clinical trials have tested the utility of corticosteroids in critically ill patients with pneumonia, septic shock, or ARDS. However, due to limited sample sizes, variable dosing strategies, and inconsistent findings, results remained inconclusive. Uptake of this therapeutic approach was modest in 2014, with only 18% of 2377 patients with ARDS in the LUNG SAFE study receiving corticosteroids.[2]

Over the past 3 years, accruing data from larger, well-conducted randomized clinical trials (RCTs) have suggested benefit of corticosteroids in ARDS and septic shock. The APROCCHSS trial enrolled 1241 patients with septic shock who received high-dose vasopressors for at least 6 hours and found that patients randomized to low-dose hydrocortisone plus fludrocortisone had lower 90-day mortality (43.0% vs 49.1%, $P = .03$).[3] The ADRENAL trial enrolled 3658 patients with septic shock who were receiving vasopressors for at least 4 hours and found that patients randomized to low-dose hydrocortisone infusion vs placebo had shorter duration of mechanical ventilation (6 vs 7 days, $P < .001$) and faster resolution of shock (3 vs 4 days, $P < .001$),[4] although 90-day mortality was not different. The DEXA-ARDS trial enrolled 277 patients with moderate to severe ARDS and found that patients randomized to high-dose dexamethasone compared with continued routine intensive care had lower 60-day all-cause mortality (21% vs 36%, $P = .005$) and more ventilator-free days (12 vs 7, $P < .001$).[5]

In meta-analyses that incorporated these recent RCTs, corticosteroid use was associated with more rapid resolution of shock and mechanical ventilation in septic shock and possible lower mortality in both septic shock and ARDS.[6,7] However, due to inconsistent findings across individual studies and lingering concern that important adverse effects such as secondary infection and delirium may be undermeasured and underreported in these clinical trials, many clinicians remained hesitant to prescribe corticosteroids for these conditions.

At the onset of the coronavirus disease 2019 (COVID-19) pandemic, guidance regarding corticosteroids was mixed. The Surviving Sepsis Campaign guidelines for COVID-19 published in March 2020 issued a weak recommendation to use corticosteroids in patients with COVID-19 and ARDS who required mechanical ventilation, but also indicated that some expert panel members preferred not to make a recommendation until further high-quality evidence was available.[8] Conversely, guidelines from the Infectious Diseases Society of America published in April 2020 issued a weak recommendation against corticosteroids, except for patients with COVID-19 and ARDS treated in the context of a clinical trial.[9]

While early observational data from China suggested a potential mortality benefit of corticosteroids in COVID-19,[10] previous studies of corticosteroids in other viral pneumonias, especially severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), found an association with delayed viral clearance, and reinforced concerns that corticosteroids may impair host response to SARS-CoV-2.[11,12] Furthermore, a meta-analysis of observational studies suggested increased mortality with corticosteroid treatment in influenza pneumonia.[7]

As the COVID-19 pandemic spread across the world, clinicians struggled to weigh the potential benefits of corticosteroids against the many potential harms associated with these drugs. Despite being overwhelmed with critically ill patients, multiple clinical trial groups around the world launched high-quality RCTs of corticosteroids for severe COVID-19. Additionally, recognizing the urgency of aggregating data from these trials to guide management, the World Health Organization (WHO) coordinated a prospective meta-analysis of these ongoing RCTs (PROSPERO CRD42020197242). The clinical trial groups agreed to share data, even prior to acceptance of their individual trial data for primary publication.

With a press release on June 16, 2020, reporting the results of the UK-based RECOVERY trial, the existing approach for treating and studying patients with COVID-19 underwent a major change. In this large open-label randomized trial enrolling 6425 patients (2104 randomized to receive dexamethasone and 4321 randomized to receive usual care), treatment with dexamethasone (6 mg/d for 10 days) reduced mortality by one-third in patients receiving mechanical ventilation (29.3% vs 41.4%, respectively; rate ratio, 0.64 [95% CI, 0.51-0.81]) and by one-fifth in patients receiving supplemental oxygen (23.3% vs 26.2%, respectively; 0.82 [95% CI, 0.72-0.94]) compared with usual care alone.[13] However, there was no benefit among patients not receiving respiratory support (1.19 [95% CI, 0.91-1.55]), and the possibility of harm could not be excluded.

By this point in the pandemic, publication to preprint servers in advance of peer review was common, but this press release provided a new degree of anxiety. Without access to full trial details, clinicians were uncertain whether to begin using dexamethasone in patients hospitalized with COVID-19, and if they used it, how they should implement it in practice. Clinical trialists also faced difficult questions. Should the control group of trials be changed to include dexamethasone? Would clinicians lack equipoise to enroll patients? Was it unethical to keep enrolling patients with COVID-19 in other placebo-controlled trials of corticosteroids? Or were the RECOVERY data rigorous enough to halt other RCTs of corticosteroids in the treatment of COVID-19?

The answer to all of these questions turned out to be yes. Practice guidelines were updated to include strong recommendations for use of corticosteroids in patients receiving mechanical ventilation; clinical equipoise and practice changed accordingly; and enrollment into other corticosteroid trials in critically ill patients with COVID-19 was halted.

This issue of *JAMA* includes 3 multicenter RCTs that assessed corticosteroid therapy in critically ill patients with COVID-19, as well as the WHO-sponsored prospective meta-analysis. All 3 trials halted enrollment in June 2020 after the RECOVERY press release. The meta-analysis included patients recruited through June 9, 2020, reasoning that the clinical management for patients enrolled afterward was likely influenced by the RECOVERY results.

The REMAP-CAP trial, an existing multicenter, multinational adaptive platform trial for pneumonia, randomized 403 patients with severe COVID-19 (in the intensive care unit [ICU] and receiving respiratory or cardiovascular organ support) to 1 of 3 open-label groups: fixed low-dose hydrocortisone, shock-dependent hydrocortisone, or no hydrocortisone.[14] The primary study outcome was days patients remained alive and free of organ support to day 21. The median organ-support-free days was 0 for each study group, reflecting the prolonged critical illness experienced by many patients with COVID-19. The bayesian model found that fixed-dose hydrocortisone (93% probability), as well as shock-dependent hydrocortisone (80% probability), were both likely superior to no hydrocortisone, but data were insufficient to confirm a single optimal regimen.[14] In addition, the probabilities did not meet the prespecified probabilities to define success.

The CoDEX trial randomized 299 patients in 41 ICUs in Brazil with moderate or severe ARDS and COVID-19 to open-label high-dose dexamethasone (20 mg/d for 5 days, then 10 mg/d for 5 days) vs usual care alone.[15] The primary outcome was ventilator-free days through day 28, which were greater in patients randomized to dexamethasone (6.6 vs 4.0, $P = .04$).[15] Two-thirds of patients (66.9%) were receiving vasopressors at the time of randomization, and 35% of the patients randomized to usual care received at least 1 dose of corticosteroids, potentially reducing the effect size between the study groups. While 28-day mortality was not significantly different between patients randomized to corticosteroids vs usual care (56.3% vs 61.5%, $P = .83$), stopping the study early when RECOVERY results were announced resulted in a sample size that was underpowered to adequately evaluate the effect of corticosteroids on mortality.

In the only blinded, placebo-controlled trial of the 3, CAPE COVID randomized 149 patients in 9 ICUs in France with severe respiratory disease from COVID-19 to low-dose hydrocortisone (200 mg/d infusion, tapered per protocol) vs placebo.[16] The primary outcome of 21-day treatment failure, defined as death or ongoing respiratory support with mechanical ventilation or high-flow oxygen, occurred in 42.1% of patients randomized to hydrocortisone vs 50.7% of those randomized to placebo ($P = .29$).[16]

The prospective meta-analysis from the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group pooled data from 7 trials (RECOVERY, REMAP-CAP, CoDEX, CAPE COVID, and 3 additional trials) totaling 1703 patients (678 had been randomized to corticosteroids and 1025 to usual care or placebo), of which 59% were from the RECOVERY trial.[17] The 28-day mortality was lower in patients randomized to corticosteroids: 222 deaths among 678 patients randomized to corticosteroids compared with 425 deaths among 1025 patients randomized to usual care or placebo (summary odds ratio, 0.66 [95% CI, 0.53,-0.82]; $P < .001$), with little heterogeneity across studies.[17] The association between administration of corticosteroids and reduced mortality was similar for dexamethasone and hydrocortisone, suggesting the benefit is a general class effect of glucocorticoids and not specific to any particular corticosteroid; was similar with lower- vs higher-dose corticosteroid regimens, although these estimates were imprecise, leaving the question of dose less definitively answered; and was similar among patients with fewer vs greater than 7 days of symptoms at randomization, although all patients were hospitalized with COVID-19 critical illness.

Corticosteroids also appear to be associated with benefit among critically ill patients with COVID-19 whether they are receiving mechanical ventilation or oxygen without mechanical ventilation. Although the meta-analysis suggests the benefit may be higher in those not receiving mechanical ventilation, imprecision in this result is high due to enrollment of relatively few patients not mechanically ventilated in most of the trials and the inclusion of all patients receiving oxygen from the RECOVERY trial in this comparison (due to ambiguity over which patients enrolled in RECOVERY were truly critically ill). Although the meta-analysis suggests corticosteroids might not be associated with improved mortality in critically ill patients with COVID-19 and shock, this result is prone to bias by both off-protocol corticosteroid use in the usual care group as well as exclusion of patients already receiving corticosteroids at screening. Overall, the meta-analysis indicates that administration of steroids is clearly associated with benefit among critically ill patients with COVID-19, although the exact threshold at which an individual patient should be prescribed corticosteroids remains unclear.

The efforts of the clinical trial groups for the launch and conduct of high-quality trials in the midst of a pandemic should be acknowledged as an important accomplishment. The agreement among the trialists to share unpublished

data with WHO is an example of how science can advance and is critical in the midst of what is likely to be numerous underpowered RCTs.[18] The trials required established research infrastructure, dedicated study teams, and clinical equipoise that was often absent during the pandemic.[19] Corticosteroids are inexpensive, readily available, and based on these data, are associated with reduced mortality in critically ill patients with COVID-19.

The findings not only guide management of patients with severe COVID-19, but also contribute to the evidence base informing treatment of ARDS among patients without COVID-19. Some clinicians may question why corticosteroids demonstrated benefit in patients with ARDS related to COVID-19, after decades of uncertainty and mixed findings for use of steroids in patients with ARDS. However, the pooled estimates of treatment effect in ARDS in patients with COVID-19 are similar to pooled estimates from recent trials in ARDS in patients without COVID-19,[7] suggesting benefit may be similar regardless of ARDS etiology.

The COVID-19 pandemic may be seen as a tipping point in the long saga of corticosteroid use in critical illness, representing the point at which sufficient data were accrued to issue a strong recommendation to treat patients with ARDS with corticosteroids. However, it will not be the end of the saga. The traditional approach once taught that the findings of clinical trials should be applied to all patients who meet inclusion for the trial. However, it is now recognized that there is substantial heterogeneity of treatment effect across patients, such that the treatment approach can likely be refined beyond the simplistic "treat all who meet trial inclusions".[20] For example, patients with milder acute illness but comorbidities that increase risk for medication-related adverse effects such as delirium and secondary infection may be less likely to benefit from corticosteroids.

The publication of these 3 randomized trials of corticosteroids and the prospective meta-analysis in this issue of *JAMA* represents an important step forward in the treatment of patients with COVID-19. While the RECOVERY results were embraced because they provided hope in the treatment of this catastrophic disease, numerous study limitations prevented complete confidence in using corticosteroids in hospitalized patients with COVID-19. These trials and the meta-analysis have strengthened confidence, further defined the benefit, and shifted usual care of COVID-19–related ARDS to include corticosteroids.

However, many clinically important questions remain. Do the benefit and optimal dosing of corticosteroids differ between different ARDS subphenotypes? Should corticosteroid administration be individualized, with initiation, dosing, and duration guided by clinical response or biomarkers, such as C-reactive protein? Does inflammation rebound after cessation of corticosteroids in some patients and would tapering them improve outcomes? What are the true incidence and optimal management of adverse effects, given that most of the randomized trials are open-label pragmatic designs with minimal reporting of adverse effects? Should less severely ill or nonhospitalized patients be treated with corticosteroids? What is the threshold of illness severity at which corticosteroids are now indicated? Do corticosteroids delay clearance of SARS-CoV-2, especially in less ill patients not hospitalized, and if so, does this affect clinical outcomes? Should remdesivir or other potentially active therapeutics be administered with corticosteroids? While much work remains on the exact details of implementation into clinical practice, the consistent findings of benefit in these studies provide definitive data that corticosteroids should be first-line treatment for critically ill patients with COVID-19.

The COVID-19 pandemic has brought fear and a sea of change to the world. These studies provide evidence and some hope that an effective, inexpensive, and safe treatment has been identified. Hope because corticosteroids provide a widely available treatment for the most severely ill patients with COVID-19. But also hope from the science, by demonstration of the ability of networks to quickly launch and complete randomized trials, even during an unprecedented clinical burden; from the willingness of networks to collaborate and join forces to conduct important clinical trials more rapidly; and from the high level of coordination and data sharing facilitated by organizations like WHO to more definitively and efficiently answer important clinical questions in the treatment of COVID-19. With these efforts and with rigorous evidence comes hope. Despite the widespread morbidity and mortality, and societal disruption caused by this pandemic, the work and collaboration of these networks provide hope for advancing science and humanity through this pandemic and beyond.

ARTICLE INFORMATION

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