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]

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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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Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19
A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

IMPORTANCE Effective therapies for patients with coronavirus disease 2019 (COVID-19) are needed, and clinical trial data have demonstrated that low-dose dexamethasone reduced mortality in hospitalized patients with COVID-19 who required respiratory support.

OBJECTIVE To estimate the association between administration of corticosteroids compared with usual care or placebo and 28-day all-cause mortality.

DESIGN, SETTING, AND PARTICIPANTS Prospective meta-analysis that pooled data from 7 randomized clinical trials that evaluated the efficacy of corticosteroids in 1703 critically ill patients with COVID-19. The trials were conducted in 12 countries from February 26, 2020, to June 9, 2020, and the date of final follow-up was July 6, 2020. Pooled data were aggregated from the individual trials, overall, and in predefined subgroups. Risk of bias was assessed using the Cochrane Risk of Bias Assessment Tool. Inconsistency among trial results was assessed using the I^2 statistic. The primary analysis was an inverse variance–weighted fixed-effect meta-analysis of overall mortality, with the association between the intervention and mortality quantified using odds ratios (ORs). Random-effects meta-analyses also were conducted (with the Paule-Mandel estimate of heterogeneity and the Hartung-Knapp adjustment) and an inverse variance–weighted fixed-effect analysis using risk ratios.

EXPOSURES Patients had been randomized to receive systemic dexamethasone, hydrocortisone, or methylprednisolone (678 patients) or to receive usual care or placebo (1025 patients).

MAIN OUTCOMES AND MEASURES The primary outcome measure was all-cause mortality at 28 days after randomization. A secondary outcome was investigator-defined serious adverse events.

RESULTS A total of 1703 patients (median age, 60 years [interquartile range, 52-68 years]; 488 [29%] women) were included in the analysis. Risk of bias was assessed as "low" for 6 of the 7 mortality results and as "some concerns" in 1 trial because of the randomization method. Five trials reported mortality at 28 days, 1 trial at 21 days, and 1 trial at 30 days. There were 222 deaths among the 678 patients randomized to corticosteroids and 425 deaths among the 1025 patients randomized to usual care or placebo (summary OR, 0.66 [95% CI, 0.53-0.82]; $P < .001$ based on a fixed-effect meta-analysis). There was little inconsistency between the trial results ($I^2 = 15.6\%$; $P = .31$ for heterogeneity) and the summary OR was 0.70 (95% CI, 0.48-1.01; $P = .053$) based on the random-effects meta-analysis. The fixed-effect summary OR for the association with mortality was 0.64 (95% CI, 0.50-0.82; $P < .001$) for dexamethasone compared with usual care or placebo (3 trials, 1282 patients, and 527 deaths), the OR was 0.69 (95% CI, 0.43-1.12; $P = .13$) for hydrocortisone (3 trials, 374 patients, and 94 deaths), and the OR was 0.91 (95% CI, 0.29-2.87; $P = .87$) for methylprednisolone (1 trial, 47 patients, and 26 deaths). Among the 6 trials that reported serious adverse events, 64 events occurred among 354 patients randomized to corticosteroids and 80 events occurred among 342 patients randomized to usual care or placebo.

CONCLUSIONS AND RELEVANCE In this prospective meta-analysis of clinical trials of critically ill patients with COVID-19, administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality.

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Group Information: The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group authors and collaborators are listed at the end of this article.

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The role of corticosteroids in treating severe infections has been an enduring controversy.[1-3] During the coronavirus disease 2019 (COVID-19) pandemic, rigorous data on the efficacy of corticosteroids have been limited.[4,5] The pandemic has been a potent stimulus for clinical research addressing this controversy.

As of July 24, 2020, 55 studies of corticosteroids for the treatment of COVID-19 have been registered on ClinicalTrials.gov. Recognizing the urgency of generating reliable data on the efficacy of corticosteroids to guide clinical management, the Clinical Characterization and Management Working Group of the World Health Organization (WHO) developed a protocol for a prospective meta-analysis[6] of ongoing randomized clinical trials.

While this initiative was in development, the UK-based Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial reported its findings from 6425 patients randomized to 6 mg/d of dexamethasone or usual care. Overall, dexamethasone resulted in an absolute reduction in mortality of 2.8% (22.9% vs 25.7% for usual care; age-adjusted rate ratio, 0.83 [95% CI, 0.75-0.93]). The benefit was greatest for patients who were receiving invasive mechanical ventilation at the time of randomization with mortality of 29.3% for dexamethasone vs 41.4% for usual care (rate ratio, 0.64 [95% CI, 0.51-0.81]).[7] The signal seen in this trial led most ongoing trials of corticosteroids to suspend recruitment.

The objective of this prospective meta-analysis of randomized trials was to estimate the association between administration of corticosteroids, compared with usual care or placebo, and 28-day all-cause mortality in hospitalized, critically ill patients with suspected or confirmed COVID-19.

Key Points

Question Is administration of systemic corticosteroids associated with reduced 28-day mortality in critically ill patients with coronavirus disease 2019 (COVID-19)?

Findings In this prospective meta-analysis of 7 randomized trials that included 1703 patients of whom 647 died, 28-day all-cause mortality was lower among patients who received corticosteroids compared with those who received usual care or placebo (summary odds ratio, 0.66).

Meaning Administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality in critically ill patients with COVID-19.

Methods

Identification of Trials

Trials were identified through a comprehensive systematic search of ClinicalTrials.gov, the Chinese Clinical Trial Registry, and the EU Clinical Trials Register, from December 31, 2019, to April 6, 2020. All recruiting clinical trials related to COVID-19 that examined the therapeutic efficacy of corticosteroids were identified.

The search terms used to identify studies for the meta-analysis were *COVID-19*, *corticosteroids*, and *steroids*. Thirteen clinical trials were identified using these search terms. Three additional records not identified in the registries were identified through experts from the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Three staff members at the W_2O Group conducted the initial search, the results of which were presented to the protocol writing group. The protocol writing group determined by consensus whether trials met the inclusion criteria.

Development of Prospective Meta-analysis

Senior investigators of all trials identified as potentially eligible were asked to participate in weekly calls starting on May 14, 2020, during which plans for the prospective meta-analysis and drafts of the protocol were developed and reviewed. The protocol was registered and made publicly available on the PROSPERO database (CRD42020197242) on July 6, 2020, and has been published.[8]

Based on information from the published protocols and prior communications with trial investigators, the trials that had randomly assigned critically ill patients to a group in whom corticosteroids were administered and to a group in whom corticosteroids were not administered were invited by the WHO chief scientist on behalf of the Clinical Characterization and Management Working Group of the WHO to participate in the prospective meta-analysis. The protocol for the prospective meta-analysis stipulated that no additional trials would be included after outcome data were shared, but that if results from further eligible trials became available before the results of the prospective meta-analysis were published, additional meta-analyses including these results would be conducted and reported. Additional potentially eligible trials were identified through contact with experts and when published in peer-reviewed journals.

All trials secured institutional review board approval, but approval was not required for the secondary data analysis reported here. Informed consent for participation in each trial was obtained and was consistent with local institutional review board requirements. There were minor variations in the definitions of critically ill used to specify each trial's eligibility criteria (**Table 1**).[9] The RECOVERY trial recruited both critically ill and non-critically ill hospitalized patients. Because it was not possible to distinguish whether patients had been critically ill but not receiving invasive mechanical ventilation at the time of randomization, data were requested only for the patients in the RECOVERY trial who received invasive mechanical ventilation. Data were pooled from patients recruited to the participating trials through June 9, 2020, because patient management after that date was likely to be affected by the release of results of the RECOVERY trial on June 16, 2020.

Outcomes

The primary outcome was all-cause mortality up to 30 days after randomization and was determined before any outcome data were available from any of the studies. Shorter-term mortality (eg, 21 days) was acceptable if longer-term mortality was not available. Five trials reported mortality at 28 days after randomization; therefore, the primary outcome is reported as 28-day all-cause mortality. The Community-Acquired Pneumonia: Evaluation of Corticosteroids in

Table 1. Characteristics of Included Trials

	DEXA-COVID 19	CoDEX	RECOVERY	CAPE COVID	COVID STEROID	REMAP-CAP	Steroids-SARI[a]
ClinicalTrials.gov identifier	NCT04325061	NCT04327401	NCT04381936	NCT02517489	NCT04348305	NCT02735707	NCT04244591
Planned sample size	200	350	NA	290	1000	NA[b]	80
Eligibility criteria	• Intubation • Mechanical ventilation • Moderate to severe ARDS per Berlin criteria[9] • Confirmed COVID-19	• Intubation • Mechanical ventilation • Moderate to severe ARDS per Berlin criteria[9] • Onset of ARDS <48 h before randomization • Probable or confirmed COVID-19	Criteria[c] used for this meta-analysis: Intubation Suspected or confirmed COVID-19	• Minimal severity • Admitted to ICU or intermediate care unit • Oxygen (≥6 L/min) • Probable or confirmed COVID-19	• Oxygen (≥10 L/min) • Confirmed COVID-19	• Admitted to ICU receiving high-flow nasal oxygen with Fio_2 ≥0.4 at ≥30 L/min, noninvasive or invasive ventilatory support, or receiving vasopressors • Probable or confirmed COVID-19	• Admitted to ICU with Pao_2:Fio_2 <200 mm Hg on positive pressure ventilation (invasive or noninvasive) or high-flow nasal canulae >45 L/min • Confirmed COVID-19
Corticosteroid							
Drug name	Dexamethasone	Dexamethasone	Dexamethasone	Hydrocortisone	Hydrocortisone	Hydrocortisone	Methylprednisolone
Dosage and administration	20 mg/d intravenously × 5 d and then 10 mg/d intravenously × 5 d	20 mg/d intravenously × 5 d and then 10 mg/d intravenously × 5 d	6 mg/d orally or intravenously	Continuous intravenous infusion × 8 d or 14 d (200 mg/d × 4 d or 7 d; 100 mg/d × 2 d or 4 d; 50 mg/d × 2 d or 3 d)	200 mg/d intravenously × 7 d (continuous or bolus dosing every 6 h)	50 mg intravenously every 6 h × 7 d[d]	40 mg intravenously every 12 h × 5 d
Dose classification	High	High	Low	Low	Low	Low	High
Control intervention	Usual care	Usual care	Usual care	Placebo	Placebo	Usual care	Usual care
Primary outcome	60-d mortality	Ventilator-free days	28-d mortality	21-d treatment failure (death or persistent requirement for mechanical ventilation or high-flow oxygen therapy)	Days alive without life support at 28 d	Composite of hospital mortality and ICU organ support–free days to 21 d	Lower lung injury score at 7 d and 14 d
Mortality outcome, d	28	28	28	21	28	28	30
Serious adverse event definitions	• Secondary infections of pneumonia, sepsis, or other similar • Pulmonary embolism	• Mortality • Infections • Insulin use	• Cause-specific mortality • Ventilation • Dialysis • Cardiac arrhythmia (in a subset) • Other that were believed to be related to study treatment	• Any • Excluded some listed in protocol • Excluded expected adverse events related to the patient's disease or comorbidity	• New episodes of septic shock (Sepsis-3 criteria) • Invasive fungal infection • Clinically important gastrointestinal bleeding • Anaphylaxis	• Per ICH good clinical practice guidelines (events not already captured as a trial end point; eg, mortality) • When the event may reasonably have occurred because of study participation	• Secondary bacterial infections • Barotrauma • Severe hyperglycemia • Gastrointestinal bleeding requiring transfusion • Acquired weakness
Location	Spain	Brazil	UK	France	Denmark	Australia, Canada, European Union, New Zealand, UK, US	China

Abbreviations: ARDS, acute respiratory distress syndrome; CAPE COVID, Community-Acquired Pneumonia: Evaluation of Corticosteroids in Coronavirus Disease; CoDEX, COVID-19 Dexamethasone; COVID-19, coronavirus disease 2019; COVID STEROID, Hydrocortisone for COVID-19 and Severe Hypoxia; DEXA-COVID 19, Efficacy of Dexamethasone Treatment for Patients With ARDS Caused by COVID-19; Fio_2, fraction of inspired oxygen; ICU, intensive care unit; NA, not applicable; RECOVERY, Randomized Evaluation of COVID-19 Therapy; REMAP-CAP, Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia; Sepsis-3, Third International Consensus Definitions for Sepsis and Septic Shock; Steroids-SARI, Glucocorticoid Therapy for COVID-19 Critically Ill Patients With Severe Acute Respiratory Failure.

[a] Trial did not specify whether adverse events were serious or nonserious.

[b] No sample size was specified at the start of the trial.

[c] The RECOVERY trial also recruited hospitalized patients with suspected or confirmed COVID-19 who were not receiving invasive mechanical ventilation at randomization.

[d] Too few patients were randomized to the high-dose group to permit separate analyses.

Coronavirus Disease (CAPE COVID; NCT02517489) trial[10] reported mortality at 21 days and the Glucocorticoid Therapy for COVID-19 Critically Ill Patients With Severe Acute Respiratory Failure (Steroids-SARI; NCT04244591) trial reported mortality at 30 days.

The secondary outcome was serious adverse events. Details of the definitions and measurement of serious adverse events were collected in advance of the trials sharing outcome data.

Data Aggregation

Before sharing outcome data, trial investigators provided summary information on the characteristics of patients at the time of randomization and the numbers of patients lost to follow-up together with the age of each participant; these data were used to calculate the median age across trials. Trial investigators then provided summary tables showing the numbers of participants who did and did not experience each outcome according to intervention group, overall, and in the following patient subgroups based on status at randomization: (1) whether patients were receiving invasive mechanical ventilation, (2) whether patients were receiving vasoactive medication, (3) whether patients were aged 60 years or younger or were older than 60 years (the median across trials), (4) sex (male or female), and (5) whether patients had been symptomatic for 7 days or less or for more than 7 days. The fifth subgroup was specified post hoc based on results from the RECOVERY trial. All other subgroup analyses were prespecified before any outcome data became available.

Risk of Bias Assessment

For each trial, we assessed the risk of bias ("low risk," "some concerns," or "high risk" of bias) in the overall effect of corticosteroids on mortality and serious adverse events using version 2 of the Cochrane Risk of Bias Assessment Tool.[11] We also assessed risk of bias for the effect of assignment to the intervention. Risk of bias assessments were based on the trial protocols and flowcharts following the Consolidated Standards of Reporting Trials together with this information supplied by the investigators of each trial: (1) the methods used to generate the allocation sequence and conceal randomized allocation; (2) whether patients and health professionals were blinded to assigned intervention; (3) the methods used to ensure that patients received their allocated intervention and the extent of deviations from the assigned intervention; and (4) the methods used to measure mortality and serious adverse events. Risk of bias assessments were done independently by 4 of the investigators (A.G., J.P.T.H., M.H.M., and J.S.), with disagreements resolved through discussion. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[12] approach to assess the certainty of the evidence that corticosteroids reduce mortality in critically ill patients with COVID-19.

Data Analysis

We classified the trials according to the corticosteroid drug used in the intervention group and whether the trial used a low dose or a high dose of corticosteroids based on the following a priori-defined cutoffs: 15 mg/d of dexamethasone, 400 mg/d of hydrocortisone, and 1 mg/kg/d of methylprednisolone.[13] The primary analysis was an inverse variance–weighted fixed-effect meta-analysis of odds ratios (ORs) for overall mortality, which was repeated after excluding results from the RECOVERY trial. We also conducted random-effects meta-analyses (with the Paule-Mandel estimate of heterogeneity)[14,15] and an inverse variance–weighted fixed-effect analysis using risk ratios. We applied the Hartung-Knapp adjustment[16,17] to account for uncertainty in the estimation of between-study variance in the random-effects meta-analysis. This variance is imprecisely estimated when few studies are included and when some studies are small (both of which are the case with this meta-analysis), leading to 95% CIs that are much wider than for the fixed-effect analysis.

We quantified inconsistency in associations among the trials using the I^2 statistic and derived P values for heterogeneity using the Cochran Q statistic. We report precise P values. The protocol specified that a threshold for statistical significance would not be used. Odds ratios with 95% CIs were plotted for the association between corticosteroids, compared with usual care or placebo, and serious adverse events. Because the definitions of serious adverse events varied among the trials, a meta-analysis of this outcome was not conducted. Participants with missing outcome data were excluded from the analyses.

Evidence for differences in associations between the subgroups was quantified by ratios of ORs comparing associations in the subgroups and the corresponding P values for interaction. If the ratio of ORs is equal to 1, the estimated associations in the 2 subgroups are the same. The further the ratio of ORs is from 1, the greater is the difference between the estimated associations in the 2 subgroups. Comparisons between subgroups defined by trial characteristics were made using random-effects meta-regression and interpreted as exploratory because of the small number of trials and the potential for confounding by other characteristics. Comparisons between subgroups defined by patient characteristics were done by estimating the trial-specific ratios of ORs comparing associations between subgroups and then combining these in meta-analyses.[18]

A hybrid approach was adopted for the analysis relating to critically ill patients who were vs who were not receiving invasive mechanical ventilation at randomization because in some trials all patients were receiving invasive mechanical ventilation. For this analysis, we compared the overall associations among critically ill patients who were and who were not receiving invasive mechanical ventilation at randomization (including patients in the RECOVERY trial who received invasive mechanical ventilation) with the association among patients in the RECOVERY trial who required oxygen with or without noninvasive ventilation but were not receiving invasive mechanical ventilation at randomization.

To obtain illustrative estimates of absolute risks for the overall analysis and for different types of corticosteroids, we assumed a mortality risk without corticosteroids of 40% (approximately, the risk among all patients allocated to usual care or placebo) and applied the meta-analytic OR to obtain a mortality risk with corticosteroids. To obtain illustrative

estimates of absolute risks for different patient subgroups, we assumed a mortality risk equal to the observed risk across patients in that subgroup who were randomized to usual care or placebo, and applied the subgroup meta-analytic OR to obtain a mortality risk with corticosteroids in the subgroup.

Because the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP; NCT02735707) trial[19,20] assigned patients to both high-dose and low-dose corticosteroid interventions, we planned to use network meta-analysis to estimate associations between high-dose vs low-dose corticosteroids and mortality. However, too few patients in this trial were randomized to high-dose corticosteroids for such an analysis to be feasible.

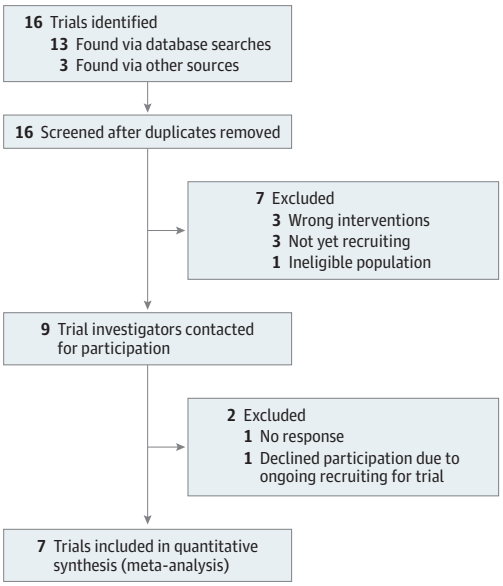
All analyses were conducted using Stata statistical software version 16 (StataCorp) and new Stata commands to conduct and graph the results of meta-analyses.

Results

Sixteen trials that were recruiting critically patients with COVID-19 and had randomized patients to receive corticosteroids vs usual care or placebo were identified (**Figure 1**). One trial (NCT04273321) did not respond to requests to participate in the prospective meta-analysis and by May 2020 it had recruited 86 patients. Another trial (NCT04344730) declined participation because randomization was ongoing and by June 2020 it had recruited 14 patients. Other trials were excluded because their investigators confirmed that they had not recruited any patients (ChiCTR2000029656, ChiCTR2000030481, and 2020-002191-12 [no longer registered]), because they recruited patients with mild or moderate disease (NCT04329650), or because randomization did not include a group without corticosteroid treatment (NCT04330586, 2020-001306-35, and NCT04251871).

Seven trials were included in the final meta-analysis (Table 1). Patients were recruited from Australia, Brazil, Canada, China, Denmark, France, Ireland, the Netherlands, New Zealand, Spain, the UK, and the US. Patients were recruited from February 26, 2020, to June 9, 2020, and the date of final follow-up was July 6, 2020. The corticosteroid groups included dexamethasone at low and high doses, low-dose hydrocortisone, and high-dose methylprednisolone. The Efficacy of Dexamethasone Treatment for Patients With ARDS Caused by COVID-19 (DEXA-COVID 19; NCT04325061) trial and the COVID-19 Dexamethasone (CoDEX; NCT04327401) trial[21] only enrolled patients receiving invasive mechanical ventilation. For the RECOVERY trial,[7] only patients who received invasive mechanical ventilation at randomization were included in the primary analysis. The REMAP-CAP trial[19,20] (NCT02735707) and the Steroids-SARI (NCT04244591) trial only enrolled patients admitted to an intensive care unit. The CAPE COVID trial[10] (NCT02517489) enrolled patients admitted to an intensive care unit or an intermediate care unit who were receiving a minimum of 6 L/min of supplemental oxygen. The Hydrocortisone for COVID-19 and Severe Hypoxia (COVID STEROID; NCT04348305) trial enrolled patients receiving a minimum of 10 L/min of supplemental oxygen. The definitions

Figure 1. Flow Diagram Showing the Identification of Eligible Trials and Participating Trials



of serious adverse events varied between the trials, and mainly focused on secondary infections and sepsis (Table 1).

A total of 1703 patients were randomized (678 to corticosteroids and 1025 to usual care or placebo) in the 7 trials, the median age was 60 years (interquartile range, 52-68 years), and 488 patients (29%) were women (**Table 2**). The larger number of patients randomized to usual care or placebo was due to randomization in the RECOVERY trial (contributed 1007 [59.1%] patients to this analysis) in which patients were assigned to corticosteroid or usual care in a ratio of 1:2. Most patients had severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection confirmed by polymerase chain reaction; and the proportions of patients with SARS-CoV-2 infection confirmed by polymerase chain reaction ranged from 78.7% to 100% across trials. In all trials, the majority of patients were male. The extent of concurrent treatment with antiviral agents or azithromycin varied substantially among the trials (Table 2).

There were minimal missing outcome data. Follow-up was complete for both mortality and serious adverse events for 4 of the 7 trials. In the RECOVERY trial (NCT04381936), 1 patient who received invasive mechanical ventilation (of 1007) in the corticosteroid group withdrew consent. In the CAPE COVID trial (NCT02517489), 1 patient (of 76) in the corticosteroid group withdrew consent. In the REMAP-CAP trial (NCT02735707), 5 patients (of 110) withdrew consent in the corticosteroid group and 6 patients (of 98) withdrew consent in the usual care group.

Association Between Corticosteroids and 28-Day All-Cause Mortality

Risk of bias was assessed as "low" for 6 of the 7 mortality results and as "some concerns" for the Steroids-SARI trial (NCT04244591; eTable 1 in the Supplement) because this trial used a fixed-randomization block size within centers and used text messages to implement randomization allocations.

Table 2. Characteristics of Patients Included in the Prospective Meta-analysis

	DEXA-COVID 19		CoDEX		RECOVERY		CAPE COVID		COVID STEROID		REMAP-CAP[a]		Steroids-SARI[b]	
	Steroid	No steroid	Steroid	No steroid	Steroid	No steroid	Steroid	No steroid	Steroid	No steroid	Steroid	No steroid	Steroid	No steroid
Patients randomized by June 9, 2020	7	12	128	128	324	683	76	73	15	14	105	92	24	23
Age, median (IQR), y	62 (48-68)	60 (52-69)	62 (50-70)	64 (57-73)	59 (52-66)	60 (52-68)	63 (52-71)	66 (54-73)	57 (52-75)	62 (55-71)	59 (53-68)	62 (50-72)	67 (61-74)	62 (54-68)
Female sex, No. (%)	3 (42.9)	3 (25)	47 (36.7)	44 (34.4)	91 (28.1)	182 (26.6)	22 (28.9)	23 (31.5)	2 (13.3)	4 (28.6)	30 (28.6)	25 (27.2)	7 (29)	5 (22)
PCR-confirmed SARS-CoV-2 infection, No. (%)	7 (100)	12 (100)	120 (93.8)	122 (95.3)	301 (92.9)	647 (94.7)	72 (94.7)	72 (98.6)	15 (100)	14 (100)	80 (76.2)	75 (81.5)	24 (100)	23 (100)
Treatments at randomization, No. (%)														
Mechanical ventilation	7 (100)	12 (100)	128 (100)	128 (100)	324 (100)	683 (100)	62 (81.6)	59 (80.8)	7 (46.7)	8 (57.1)	68 (64.8)	49 (53.3)	13 (54)	14 (61)
Vasoactive	3 (42.9)	7 (58.3)	83 (65.4)	88 (68.8)	Not recorded	Not recorded	18 (23.7)	13 (17.8)	5 (33.3)	5 (35.7)	46 (43.8)	27 (29.3)	14 (58)	18 (78)
Any antiviral[c]	6 (86)	10 (83)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	24 (100)	23 (100)
Remdesivir	Not recorded	Not recorded	0	0	1 (0.3)	0	1 (1.3)	0	0	4 (28.6)	1 (1.0)	0	Not recorded	Not recorded
Lopinavir or ritonavir	Not recorded	Not recorded	0	1 (0.8)	0	0	8 (10.5)	9 (12.3)	0	0	0	2 (2.2)	Not recorded	Not recorded
Favipravir	Not recorded	Not recorded	0	0	0	0	0	0	0	0	0	0	Not recorded	Not recorded
Hydroxychloroquine	7 (100)	12 (100)	30 (23.4)	22 (17.2)	0	0	29 (38.2)	32 (43.8)	1 (6.7)	0	5 (4.8)	2 (2.2)	0	0
Azithromycin	0	0	83 (64.8)	81 (63.3)	59 (18.2)	81 (11.9)	19 (25.0)	24 (32.9)	Not recorded	Not recorded	9 (8.6)	6 (6.5)	Not recorded	Not recorded
Convalescent plasma	0	0	Not recorded	Not recorded	0	0	0	0	0	2 (14.3)	0	0	Not recorded	Not recorded

Abbreviations: CAPE COVID, Community-Acquired Pneumonia: Evaluation of Corticosteroids in Coronavirus Disease; CoDEX, COVID-19 Dexamethasone; COVID STEROID, Hydrocortisone for COVID-19 and Severe Hypoxia; DEXA-COVID 19, Efficacy of Dexamethasone Treatment for Patients With ARDS Caused by COVID-19; IQR, interquartile range; NA, not applicable; PCR, polymerase chain reaction; RECOVERY, Randomized Evaluation of COVID-19 Therapy; REMAP-CAP, Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Steroids-SARI, Glucocorticoid Therapy for COVID-19 Critically Ill Patients With Severe Acute Respiratory Failure.

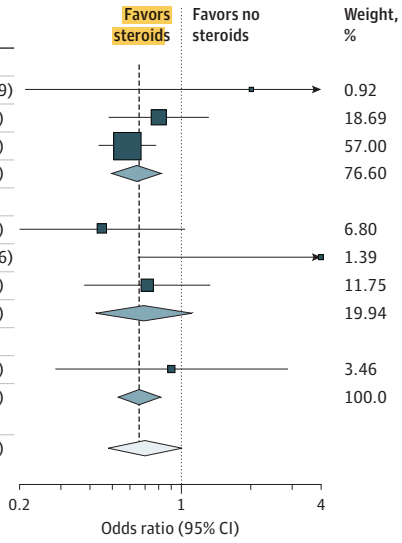
[a] Missing substantial data on antiviral use.

[b] Missing data on PCR results.

[c] Some of the trials did not provide information on individual antiviral drugs, which is indicated by "not recorded." The trials with NA is this row provided data on individual antiviral drugs in the rows below.

Figure 2. Association Between Corticosteroids and 28-Day All-Cause Mortality in Each Trial, Overall, and According to Corticosteroid Drug

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60
Hydrocortisone						
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)	6.80
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)	1.39
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)	11.75
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)	19.94
Methylprednisolone						
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)	3.46
Overall (fixed effect) $P = .31$ for heterogeneity; $I^2 = 15.6\%$			222/678	425/1025	0.66 (0.53-0.82)	100.0
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)	



The area of the data marker for each trial is proportional to its weight in the fixed-effect meta-analysis. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial result is for patients who were receiving invasive mechanical ventilation at randomization. CAPE COVID indicates Community-Acquired Pneumonia: Evaluation of Corticosteroids in Coronavirus Disease; CoDEX, COVID-19 Dexamethasone; COVID STEROID, Hydrocortisone for COVID-19 and Severe Hypoxia; DEXA-COVID 19, Efficacy of Dexamethasone Treatment for Patients With ARDS Caused by COVID-19; REMAP-CAP, Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia; Steroids-SARI, Glucocorticoid Therapy for COVID-19 Critically Ill Patients With Severe Acute Respiratory Failure.

[a] The random-effects analysis estimates both the average and variability of effects across studies. The 95% CI for the average effect (shown here) is wide because there is a small number of studies, some of which have very small sample size. The prespecified primary analysis was the fixed-effect analysis, which should be used to guide clinical interpretation of the results.

In the RECOVERY trial (NCT04381936), approximately 16% of patients in the control group received dexamethasone. This was regarded as reflecting usual practice,[22] and was not considered to introduce a risk of bias in the effect of assignment to the intervention. Furthermore, any such bias would be toward the null.

There were 222 deaths among 678 patients randomized to corticosteroids and 425 deaths among 1025 patients randomized to usual care or placebo. Based on a fixed-effect meta-analysis, the summary OR was 0.66 (95% CI, 0.53-0.82; $P < .001$) for all-cause mortality comparing corticosteroids with usual care or placebo (**Figure 2**). This corresponds to an absolute mortality risk of 32% with corticosteroids compared with an assumed mortality risk of 40% with usual care or placebo. There was little inconsistency between the trial results ($I^2 = 15.6\%$; $P = .31$ for heterogeneity), and the summary OR was 0.70 (95% CI, 0.48-1.01; $P = .053$) based on a random-effects meta-analysis.

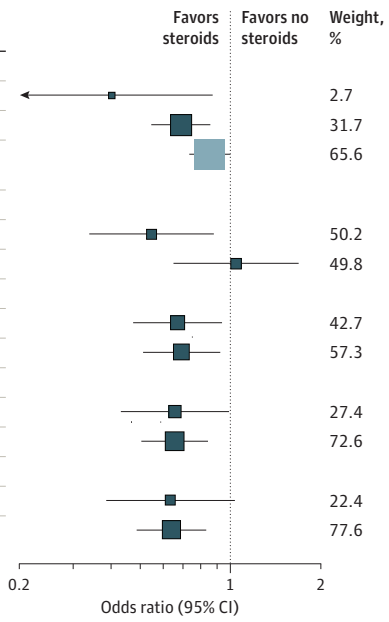
In the analysis that excluded patients recruited to the RECOVERY trial, the OR was 0.77 (95% CI, 0.56-1.07) for all-cause mortality comparing corticosteroids with usual care or placebo, which was consistent with the corresponding result based on patients in the RECOVERY trial who were receiving invasive mechanical ventilation at randomization (OR, 0.59 [95% CI, 0.44-0.78]). This latter OR was not adjusted for age and therefore differs from the age-adjusted rate ratio in the report of the RECOVERY trial.[7]

The overall inverse variance–weighted fixed-effect risk ratio was 0.80 (95% CI, 0.70-0.91) for all-cause mortality comparing corticosteroids with usual care or placebo. The GRADE assessment of the certainty of the evidence that corticosteroids reduce all-cause mortality in critically ill patients with COVID-19 was moderate due to minor concerns across (1) imprecision, (2) a small amount of heterogeneity, and (3) a small risk of reporting bias due to some trials not responding to the requests for data.

For all-cause mortality comparing corticosteroids vs usual care or placebo, the fixed-effect summary OR was 0.64 (95% CI, 0.50-0.82; $P < .001$) for trials of dexamethasone (3 trials, 1282 patients, and 527 deaths; corresponding absolute risk of 30% for dexamethasone vs an assumed risk of 40% for usual care or placebo) and the OR was 0.69 (95% CI, 0.43-1.12; $P = .13$) for trials of hydrocortisone (3 trials, 374 patients, and 94 deaths; corresponding absolute risk of 32% for hydrocortisone vs an assumed risk of 40% for usual care or placebo). Using meta-regression to compare the associations for hydrocortisone and dexamethasone, the ratio of ORs was 1.06 (95% CI, 0.37-2.99). From the random-effects meta-analyses, the OR was 0.65 (95% CI, 0.36-1.17) for dexamethasone and the OR was 0.87 (95% CI, 0.072-10.5) for hydrocortisone; the wide 95% CIs reflect the imprecisely estimated between-trial variance because each analysis included only 3 trials. Only 1 trial (NCT04244591), which enrolled 47 patients of whom 26 died, evaluated methylprednisolone and the OR was 0.91 (95% CI, 0.29, 2.87;

Figure 3. Association Between Corticosteroids and 28-Day All-Cause Mortality Within Subgroups Defined by Patient Characteristics at the Time of Randomization

Subgroup	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Invasive mechanical ventilation (IMV)				
No (I^2 = 0%)	14/70	28/74	0.41 (0.19-0.88)	2.7
Yes (I^2 = 44.1%)	208/608	397/951	0.69 (0.55-0.86)	31.7
Oxygen treatment without IMV (RECOVERY)	298/1279	682/2604	0.86 (0.73-1.00)	65.6
Taking vasoactive medication				
No (I^2 = 0%)	51/184	68/184	0.55 (0.34-0.88)	50.2
Yes (I^2 = 0%)	76/169	74/158	1.05 (0.65-1.69)	49.8
Age, y				
≤60 (I^2 = 0%)	72/338	141/483	0.67 (0.48-0.94)	42.7
>60 (I^2 = 49.7%)	150/339	284/541	0.69 (0.51-0.93)	57.3
Sex				
Female (I^2 = 0%)	60/202	106/286	0.66 (0.43-0.99)	27.4
Male (I^2 = 14.7%)	162/476	319/739	0.66 (0.51-0.84)	72.6
Symptomatic, d				
≤7 (I^2 = 69.1%)	51/130	99/211	0.63 (0.39-1.04)	22.4
>7 (I^2 = 0%)	139/418	293/693	0.64 (0.49-0.83)	77.6



The area of the data markers is proportional to their weight in the meta-analysis. The estimated odds ratios were derived using fixed-effect meta-analyses across all trials for which data on the specified subgroup were available. The results for patients in the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial who required oxygen with or without noninvasive ventilation but were not receiving invasive mechanical ventilation at randomization is shown in a light blue box because these data were not otherwise included in this prospective meta-analysis.

P = .87) for the association between methylprednisolone and all-cause mortality.

In trials that administered low doses of corticosteroids, the overall fixed-effect OR was 0.61 (95% CI, 0.48-0.78; *P* < .001) and the corresponding absolute risk was 29% for low-dose corticosteroids vs an assumed risk of 40% for usual care or placebo. In trials that administered high doses of corticosteroids, the fixed-effect OR was 0.83 (95% CI, 0.53-1.29; *P* = .46) and the corresponding absolute risk was 36% for high-dose corticosteroids vs an assumed risk of 40% for usual care or placebo. The ratio of ORs was 1.38 (95% CI, 0.69-2.79; *P* = .29). For trials that administered low-dose corticosteroids, the random-effects OR was 0.80 (95% CI, 0.063-10.32; *P* = .75). For trials that administered high-dose corticosteroids, the fixed-effect and random-effects estimates were identical (I^2 = 0%).

We identified 1 additional trial, the Methylprednisolone in the Treatment of Patients With Signs of Severe Acute Respiratory Syndrome in Covid-19 (Metcovid; NCT04343729),[23] when it was published on August 12, 2020 (eTables 2 and 3 in the Supplement); this trial had been registered after the searches of trial registries had been conducted. In this trial, 416 hospitalized patients with suspected SARS-CoV-2 infection were randomized to receive high-dose methylprednisolone or placebo. The risk of bias in the effect of assignment to intervention on 28-day mortality was assessed as "low" (eTable 4 in the Supplement). In an additional meta-analysis that included patients (71 in the steroid group and 70 in the no steroid group) from the Metcovid trial who were receiving invasive mechanical ventilation at randomization (based on an intention-to-treat analysis), the fixed-effect OR was 0.66 (95% CI, 0.54-0.82; *P* < .001) for the association between corticosteroids and 28-day mortality (eFigure 6 in the Supplement). There was little inconsistency among the trials (random-effects OR, 0.67 [95% CI, 0.51-0.87]; *P* = .009 and I^2 = 2.4%). For the association between methylprednisolone and 28-day mortality, the fixed-effect OR was 0.80 (95% CI, 0.40-1.63; *P* = .54).

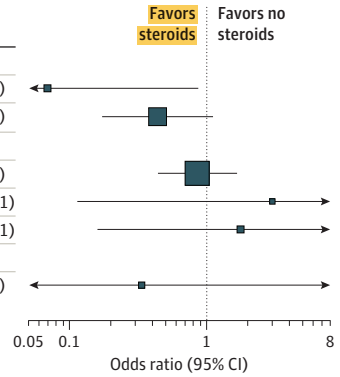
Association Between Corticosteroids and 28-Day All-Cause Mortality Within Subgroups

The estimated associations between corticosteroids vs usual care or placebo and mortality in the subgroups defined by patient characteristics at randomization appear in **Figure 3**. Among critically ill patients, many more were receiving invasive mechanical ventilation at randomization (1459 patients and 604 deaths) than were not (144 patients and 42 deaths). The overall fixed-effect OR was 0.69 (95% CI, 0.55-0.86) among patients who were receiving invasive mechanical ventilation at randomization (corresponding to an absolute risk of 30% for corticosteroids vs 38% for usual care or placebo) and the OR was 0.41 (95% CI, 0.19-0.88) among patients who were not receiving invasive mechanical ventilation at randomization (corresponding to an absolute risk of 23% for corticosteroids vs 42% for usual care or placebo). For comparison, the OR was 0.86 (95% CI, 0.73-1.00) among 3883 patients in the RECOVERY trial who required oxygen with or without noninvasive ventilation but were not receiving invasive mechanical ventilation at randomization.[7]

Among the 4 trials that recruited critically ill patients who were and were not receiving invasive mechanical ventilation at randomization, the association between corticosteroids and lower mortality was less marked in patients receiving invasive mechanical ventilation (ratio of ORs, 4.34 [95% CI, 1.46-12.91]; *P* = .008 based on within-trial estimates combined

Figure 4. Association Between Corticosteroids and Serious Adverse Events in Each Trial

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of events/total No. of patients: Steroids	No. of events/total No. of patients: No steroids	Odds ratio (95% CI)
Dexamethasone					
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	3/7	11/12	0.07 (0.01-0.86)
CoDEX	NCT04327401	High: 20 mg/d intravenously	7/128	15/128	0.44 (0.17-1.11)
Hydrocortisone					
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	28/75	30/73	0.85 (0.44-1.65)
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	1/15	0/14	3.00 (0.11-79.91)
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	2/105	1/92	1.77 (0.16-19.81)
Methylprednisolone					
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	23/24	23/23	0.33 (0.01-8.61)



The area of the data markers is proportional to the inverse of the variance of the estimated odds ratio. CAPE COVID indicates Community-Acquired Pneumonia: Evaluation of Corticosteroids in Coronavirus Disease; CoDEX, COVID-19 Dexamethasone; COVID STEROID, Hydrocortisone for COVID-19 and Severe Hypoxia; DEXA-COVID 19, Efficacy of Dexamethasone Treatment for Patients With ARDS Caused by COVID-19; REMAP-CAP, Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia; Steroids-SARI, Glucocorticoid Therapy for COVID-19 Critically Ill Patients With Severe Acute Respiratory Failure. The Steroids-SARI trial recorded adverse events but did not categorize them as serious or nonserious.

across trials; eFigure 1 in the Supplement); however, only 401 patients (120 deaths) contributed to this comparison.

Among 695 patients from 6 trials for whom data were available, 327 (47.0%) were receiving vasoactive agents for blood pressure support at randomization. For the association between corticosteroids and mortality, the OR was 1.05 (95% CI, 0.65-1.69) among patients who were receiving vasoactive agents at randomization (an absolute risk of 48% for corticosteroids vs 47% for usual care or placebo) and the OR was 0.55 (95% CI, 0.34-0.88) among patients who were not receiving vasoactive agents at randomization (an absolute risk of 24% for corticosteroids vs 37% for usual care or placebo). The ratio of ORs was 1.90 (95% CI, 0.97-3.73, P = .06; eFigure 2 in the Supplement).

All trials contributed data according to age group and sex. For the association between corticosteroids and mortality, the OR was 0.69 (95% CI, 0.51-0.93) among 880 patients older than 60 years, the OR was 0.67 (95% CI, 0.48-0.94) among 821 patients aged 60 years or younger (ratio of ORs, 1.02 [95% CI, 0.63-1.65], P = .94; eFigure 3 in the Supplement), the OR was 0.66 (95% CI, 0.51-0.84) among 1215 men, and the OR was 0.66 (95% CI, 0.43-0.99) among 488 women (ratio of ORs, 1.07 [95% CI, 0.58-1.98], P = .84; eFigure 4 in the Supplement). For the association between corticosteroids and mortality based on data from 4 trials, the OR was 0.64 (95% CI, 0.49-0.83) among 1111 patients who were symptomatic for more than 7 days prior to randomization and the OR was 0.63 (95% CI, 0.39-1.04) among 341 patients who were symptomatic for 7 days or less prior to randomization (ratio of ORs, 1.07 [95% CI, 0.40-2.81], P = .90; eFigure 5 in the Supplement).

Serious Adverse Events

The RECOVERY trial did not record serious adverse events. The Steroids-SARI trial (NCT04244591) recorded adverse events but did not categorize them as serious or nonserious adverse events. Risk of bias was assessed as "low" in 2 of the 6 available trial results for serious adverse events (eTable 1 in the Supplement). In these trials, the study personnel were blinded to the intervention group. The other 4 trials had unblinded outcome assessment, and the risk of bias was assessed as "some concerns" based on subjectivity implying that classification of serious adverse events could differ between intervention groups.

The associations between corticosteroids vs usual care or placebo and serious adverse events in each trial appear in **Figure 4**. Among the 6 trials that reported serious adverse events, 64 events occurred among 354 patients randomized to corticosteroids and 80 events occurred among 342 patients randomized to usual care or placebo. Adverse events varied across trials but there was no suggestion that the risk of serious adverse events was higher in patients assigned to corticosteroids except for the 2 smallest trials, in which the total number of serious adverse events was 1 and 3.

Discussion

In this prospective meta-analysis of 7 randomized clinical trials that included 1703 critically ill patients with COVID-19 recruited from countries on 5 continents, administration of corticosteroids was associated with lower all-cause mortality at 28 days after randomization. There was no suggestion of an increased risk of serious of adverse events. The ORs for the association between corticosteroids and mortality were similar for dexamethasone and hydrocortisone. The comparison of the association between low-dose corticosteroids and mortality and the association between high-dose corticosteroids and mortality was imprecisely estimated.

Corticosteroids were associated with lower mortality among critically ill patients who were and were not receiving invasive mechanical ventilation at randomization, as well as

in patients from the RECOVERY trial who required oxygen with or without noninvasive ventilation but were not receiving invasive mechanical ventilation at randomization. These results were consistent with the subgroup analysis suggesting that the association between corticosteroids and lower mortality was stronger in patients who were not receiving vasoactive medication at randomization than in those who were receiving vasoactive medication at randomization. The ORs for the association between corticosteroids and mortality appeared similar for older and younger individuals, men and women, and for longer and shorter durations of symptoms before randomization.

This analysis was expedited because of the release of results from the RECOVERY trial, which found that the absolute risk of death was reduced by 12.1% among those assigned to low-dose dexamethasone who were receiving invasive mechanical ventilation at randomization. Most ongoing trials of corticosteroids in critically ill patients with COVID-19 suspended enrollment after these results became publicly available because equipoise for withholding corticosteroids was no longer present. These trial results from diverse clinical and geographic settings suggest that in the absence of compelling contraindications, a corticosteroid regimen should be a component of standard care for critically ill patients with COVID-19.

The optimal dose and duration of treatment could not be assessed in this analysis, but there was no evidence suggesting that a higher dose of corticosteroids was associated with greater benefit than a lower dose of corticosteroids. Inclusion of data from the Metcovid trial did not materially change the results other than reducing the inconsistency among the trials. Data from the Metcovid trial were not included in the primary meta-analysis because this trial was registered after the searches of the trial registries were conducted.

All subgroup analyses other than that comparing longer with shorter duration of symptoms at randomization were prespecified. Although the benefit associated with corticosteroids appeared greater in critically ill patients who were not receiving invasive mechanical ventilation at randomization, this comparison was based on only 4 trials and 144 patients who were not receiving invasive mechanical ventilation at randomization, of whom 42 died. Corticosteroids were associated with lower mortality in critically ill patients who were and were not receiving invasive mechanical ventilation at randomization, as well as in patients in the RECOVERY trial who required oxygen with or without noninvasive ventilation but were not receiving invasive mechanical ventilation at randomization.[7] It was not possible to classify this latter group according to whether they were critically ill at the time of randomization. These patients represented a spectrum of illness from patients receiving supplemental oxygen by nasal prongs to those receiving noninvasive ventilatory support in the form of high-flow oxygen or positive pressure by mask. Nonetheless, the substantial risk of death in these patients (682/2604 [26.1%] in the control group) is consistent with mortality in critically ill patients with COVID-19.[24,25]

The findings from this prospective meta-analysis provide evidence that treatment with corticosteroids is associated with reduced mortality for critically ill patients with COVID-19. The findings contrast with outcomes reported for the administration of corticosteroids among patients with influenza, for whom mortality and hospital-acquired infections may be increased by the administration of corticosteroids.[26] In the current study, potential corticosteroid-induced complications could not be analyzed reliably because of limitations of the available data (serious adverse events were reported by only 6 of the 7 trials, and their definitions and methods of assessment varied among trials). However, serious adverse events were generally less likely in patients randomized to corticosteroids than to usual care or placebo.

This prospective meta-analysis was based on a relatively large number of critically ill patients with COVID-19 from geographically diverse sites who were randomized to receive corticosteroids or to receive usual care or placebo. The protocol and analysis plan, including specification of subgroup analyses, was registered and made publicly available on the PROSPERO database prior to data analysis or receipt of outcome data. The protocol also has been published along with a structured abstract.[8] Provision of pooled data in prespecified subgroups facilitated rapid analysis and dissemination because a need for multiple data-sharing agreements was avoided. As is standard in meta-analyses, patients were compared only with other patients randomized in the same trial. Therefore, observed associations support a causal relationship between the administration of corticosteroids, compared with usual care or placebo, and reduced mortality.

Limitations

This study has several limitations. First, the prospective nature of this meta-analysis implies that there is little risk of selective reporting or of publication bias,[6] but it is possible that lack of participation by some investigators of ongoing trials was based on their knowledge of their trial results. Nonetheless, the number of patients randomized in eligible trials who did not participate is likely to be smaller than the number of patients included in this meta-analysis.

Second, all but 1 of the included trials was assessed as "low risk" of bias for the effect of assignment to the intervention. The trial for which the risk of bias was assessed as "some concerns" (Steroids-SARI; NCT04244591) was relatively small (47 patients and 26 deaths) and contributed only 3.5% of the weight in the primary meta-analysis. It was the only trial that assessed the effect of methylprednisolone.

Third, there were only limited missing outcome data, but in many trials, follow-up was censored when participants were discharged from the hospital. We are aware of no reason that the effect of corticosteroids on postdischarge 28-day mortality would differ from that on predischarge mortality, but it will be important to report on longer-term mortality, including postdischarge mortality, in future analyses.

Fourth, the definitions and reporting of serious adverse events were not consistent across the trials and therefore a meta-analysis for this secondary end point was not conducted.

Fifth, the trials only recruited adults, and the effect of corticosteroids on children remains unclear. Similarly, the trials were mainly conducted in high-income settings.

Sixth, 1 trial reported mortality at 21 days and 1 trial reported mortality at 30 days after randomization, potentially leading to inconsistency between trial results.

Seventh, the RECOVERY trial contributed 57% of the weight in the primary meta-analysis of 28-day all-cause mortality, although there was little inconsistency between the effects of corticosteroids on 28-day mortality estimated by the different trials.

Conclusions

In this prospective meta-analysis of clinical trials of critically ill patients with COVID-19, administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality.

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Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19

The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial

The Writing Committee for the REMAP-CAP Investigators

IMPORTANCE Evidence regarding corticosteroid use for severe coronavirus disease 2019 (COVID-19) is limited.

OBJECTIVE To determine whether hydrocortisone improves outcome for patients with severe COVID-19.

DESIGN, SETTING, AND PARTICIPANTS An ongoing adaptive platform trial testing multiple interventions within multiple therapeutic domains, for example, antiviral agents, corticosteroids, or immunoglobulin. Between March 9 and June 17, 2020, 614 adult patients with suspected or confirmed COVID-19 were enrolled and randomized within at least 1 domain following admission to an intensive care unit (ICU) for respiratory or cardiovascular organ support at 121 sites in 8 countries. Of these, 403 were randomized to open-label interventions within the corticosteroid domain. The domain was halted after results from another trial were released. Follow-up ended August 12, 2020.

INTERVENTIONS The corticosteroid domain randomized participants to a fixed 7-day course of intravenous hydrocortisone (50 mg or 100 mg every 6 hours) (n = 143), a shock-dependent course (50 mg every 6 hours when shock was clinically evident) (n = 152), or no hydrocortisone (n = 108).

MAIN OUTCOMES AND MEASURES The primary end point was organ support–free days (days alive and free of ICU-based respiratory or cardiovascular support) within 21 days, where patients who died were assigned −1 day. The primary analysis was a bayesian cumulative logistic model that included all patients enrolled with severe COVID-19, adjusting for age, sex, site, region, time, assignment to interventions within other domains, and domain and intervention eligibility. Superiority was defined as the posterior probability of an odds ratio greater than 1 (threshold for trial conclusion of superiority >99%).

RESULTS After excluding 19 participants who withdrew consent, there were 384 patients (mean age, 60 years; 29% female) randomized to the fixed-dose (n = 137), shock-dependent (n = 146), and no (n = 101) hydrocortisone groups; 379 (99%) completed the study and were included in the analysis. The mean age for the 3 groups ranged between 59.5 and 60.4 years; most patients were male (range, 70.6%-71.5%); mean body mass index ranged between 29.7 and 30.9; and patients receiving mechanical ventilation ranged between 50.0% and 63.5%. For the fixed-dose, shock-dependent, and no hydrocortisone groups, respectively, the median organ support–free days were 0 (IQR, −1 to 15), 0 (IQR, −1 to 13), and 0 (−1 to 11) days (composed of 30%, 26%, and 33% mortality rates and 11.5, 9.5, and 6 median organ support–free days among survivors). The median adjusted odds ratio and bayesian probability of superiority were 1.43 (95% credible interval, 0.91-2.27) and 93% for fixed-dose hydrocortisone, respectively, and were 1.22 (95% credible interval, 0.76-1.94) and 80% for shock-dependent hydrocortisone compared with no hydrocortisone. Serious adverse events were reported in 4 (3%), 5 (3%), and 1 (1%) patients in the fixed-dose, shock-dependent, and no hydrocortisone groups, respectively.

CONCLUSIONS AND RELEVANCE Among patients with severe COVID-19, treatment with a 7-day fixed-dose course of hydrocortisone or shock-dependent dosing of hydrocortisone, compared with no hydrocortisone, resulted in 93% and 80% probabilities of superiority with regard to the odds of improvement in organ support–free days within 21 days. However, the trial was stopped early and no treatment strategy met prespecified criteria for statistical superiority, precluding definitive conclusions.

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Supplemental content

Group Information: The members of the writing committee appear at the end of this article. The members of the REMAP-CAP Investigators appear in Supplement 2.

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Coronavirus disease 2019 (COVID-19) is an acute respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). First identified in Wuhan, China, in December 2019, more than 20 million COVID-19 cases and 750 000 deaths had been reported worldwide by August 2020.[1] Though many therapies are being evaluated, strong evidence of benefit is lacking.[2] One class of agents that has received considerable attention is corticosteroids. Corticosteroids were reported to be beneficial in several conditions analogous to COVID-19, including sepsis, pneumonia, and acute respiratory distress syndrome (ARDS).[3-5] However, other trials in these conditions, as well as in influenza and coronavirus respiratory syndromes, showed no benefit or possible harm.[3,6,7] Consequently, advice for COVID-19 has been mixed.[8] The China National Health Commission suggested hydrocortisone is appropriate[9]; the Surviving Sepsis Campaign recommended against corticosteroid use in the absence of ARDS, but suggested possible benefit in those with ARDS[10]; while the World Health Organization (WHO) initially recommended no corticosteroid treatment.[11] In practice, corticosteroids have been given variably to patients with COVID-19, and observational studies suggest both benefit and harm.[12-14] To reduce this uncertainty, several research groups launched randomized clinical trials (RCTs).

In March 2020, investigators for the REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia) Study began randomizing patients with COVID-19 to alternative dosing strategies of the corticosteroid, hydrocortisone. Enrollment was halted on June 17, following the announcement by the RECOVERY Collaborative Group that dexamethasone reduced mortality compared with standard of care in patients with COVID-19 receiving either invasive mechanical ventilation or supplemental oxygen.[15] This report describes the effects of hydrocortisone, in doses of similar glucocorticoid equivalency to that used in RECOVERY, in severely ill patients with COVID-19 enrolled in REMAP-CAP.

Key Points

Question Does intravenous hydrocortisone, administered either as a 7-day fixed-dose course or restricted to when shock is clinically evident, improve 21-day organ support–free days (a composite end point of in-hospital mortality and the duration of intensive care unit–based respiratory or cardiovascular support) in patients with severe coronavirus disease 2019 (COVID-19)?

Findings In this bayesian randomized clinical trial that included 403 patients and was stopped early after results from another trial were released, treatment with a 7-day fixed-dose course of hydrocortisone or shock-dependent dosing of hydrocortisone, compared with no hydrocortisone, resulted in 93% and 80% probabilities of superiority, respectively, with regard to the odds of improvement in organ support–free days within 21 days.

Meaning Although suggestive of benefit for hydrocortisone in patients with severe COVID-19, the trial was stopped early and no treatment strategy met prespecified criteria for statistical superiority, precluding definitive conclusions.

Methods

Study Design

REMAP-CAP is an ongoing, international, multicenter, open-label trial that combines features of an adaptive platform trial with a pragmatic point-of-care trial to determine best treatment strategies for patients with severe pneumonia in both pandemic and nonpandemic settings. A detailed description of the trial design is provided elsewhere.[16] The trial uses a novel design, a randomized embedded multifactorial adaptive platform (REMAP).[17] The design has 5 key features: randomization, allowing causal inference; embedding of study procedures into routine care processes, facilitating enrollment, trial efficiency, and generalizability; a multifactorial statistical model comparing multiple interventions across multiple patient subgroups; response-adaptive randomization with preferential assignment to those interventions that appear most favorable after interim analyses; and a platform structured to permit continuous, potentially perpetual, enrollment.

The trial randomizes patients to multiple interventions within multiple domains, evaluating effectiveness within different patient strata. The term *domain* refers to a common therapeutic area (eg, antiviral therapy or immunoglobulin therapy) within which several interventions or intervention dosing strategies can be randomly assigned (including a control, such as no antiviral, as appropriate). All trial procedures are governed by a master, or "core," protocol and a series of appendices that describe aspects specific to each therapeutic domain, to adaptations during a pandemic, and to region-specific trial governance and conduct. The trial's core protocol, relevant protocol appendices, and statistical analysis plans (SAPs) are provided in Supplement 1. The trial is overseen by an international trial steering committee (ITSC), which is blinded to treatment assignment and outcome, and an unblinded independent data and safety monitoring board (Supplement 1). The study was approved by the relevant ethics committees at all participating sites and is conducted in accordance with Good Clinical Practice guidelines and the principles described in the Declaration of Helsinki.

The REMAP-CAP investigators introduced several design adaptations for COVID-19 (see Pandemic Appendix, January 31, 2020, and subsequent updates, in Supplement 1). Specifically, all patients hospitalized with suspected or proven COVID-19 were assigned to the COVID-19 patient stratum. They were further classified as clinically moderately or severely ill, and, depending on their moderate or severe state, were eligible for randomized assignment to alternative interventions within several COVID-19–specific domains, including antiviral, corticosteroid, targeted immune modulation, immunoglobulin, and therapeutic anticoagulation domains. The corticosteroid domain was eligible only to patients in the severe state. During the study period, the trial enrolled participants with severe COVID-19 at 121 clinical sites in Australia, Canada, France, Ireland, the Netherlands, New Zealand, the United Kingdom, and the United States. Written or verbal informed

consent,in accordance with local legislation, was obtained for all patients or from their surrogates.

Achieving a racially and ethnically diverse sample was a goal of the trial because of evidence of disparities in outcome and treatment effectiveness in pandemic and nonpandemic pneumonia. Participants (or their surrogates) self-reported their race/ethnicity via fixed categories appropriate to their region.

Participants

Patients aged 18 years or older with presumed or confirmed SARS-CoV-2 infection who were admitted to an intensive care unit (ICU) for provision of respiratory or cardiovascular organ support were classified as severe and eligible for enrollment in the COVID-19 corticosteroid domain. An ICU could include an area of the hospital repurposed to function as an ICU for surge capacity management. Respiratory organ support was defined as invasive or noninvasive mechanical ventilation or high-flow nasal cannula if the flow rate was 30 L/min or greater and fraction of inspired oxygen of 0.4 or greater. Cardiovascular organ support was defined as the intravenous infusion of any vasopressor or inotrope. Exclusion criteria included presumption that death is imminent with lack of commitment to full support and participation in the trial in the prior 90 days. Additional exclusion criteria for the corticosteroid domain included known hypersensitivity to hydrocortisone, systemic corticosteroid use, and more than 36 hours elapsed since ICU admission. Further details regarding eligibility are listed in the corticosteroid domain–specific appendix in Supplement 1 and in eAppendix 1 in Supplement 2.

Treatment Allocation

The COVID-19 corticosteroid domain contained fixed-dose and shock-dependent hydrocortisone interventions and a standard of care with no hydrocortisone (or other corticosteroid) use. Investigators at each participating site selected a priori 2 or more study group assignments to which patients could be randomized, based on local equipoise (see eAppendix 2 in Supplement 2 for the breakout by site of which sites selected which combinations). Participants were randomized to each locally available group using balanced assignment. Participants were randomly assigned via a computer software program to each locally available group using proportional assignment (eg, 1:1 if 2 groups available and 1:1:1 if 3 groups available).

Procedures

The study used an open-label design, in which the clinical team was provided instructions for hydrocortisone prescriptions. Hydrocortisone was supplied by each site's pharmacy. Other aspects of care were provided as per each site's standard of care. Data were collected on baseline characteristics, corticosteroid use, adverse events, and outcomes by site investigators via a combination of interactive web-based response technology and electronic health record abstraction with built-in validation and logic checks. Although clinical staff were aware of their individual patient's treatment assignment, neither they nor the ITSC were provided any information about aggregate patient outcomes.

Interventions

Participants were randomized to receive a fixed dose of intravenous hydrocortisone, 50 mg, every 6 hours for 7 days; intravenous hydrocortisone, 50 mg, every 6 hours while in shock for up to 28 days; or no hydrocortisone. A second fixed-dose regimen of 100 mg every 6 hours for 7 days was being incorporated across sites when the study was halted, such that only 2 patients were assigned to that group. The rationale underlying the shock-dependent dosing strategy was that restricting hydrocortisone to the period when the patient had overt shock would maximize the risk-benefit ratio. Shock was defined as the requirement for intravenous vasopressor infusion for the treatment of shock presumed due to COVID-19 and not due to untreated hypovolemia or secondary consequences of other therapies (eg, sedation agents). Hydrocortisone was discontinued in the shock-dependent group once shock was considered to have resolved or vasopressors had been discontinued for 24 hours. In all groups, systemic corticosteroid therapy was permitted if a new clinical indication developed for which corticosteroids are an established treatment such as postextubation stridor, bronchospasm, or anaphylaxis.

In addition to assignment to interventions in the corticosteroid domain, participants could be randomly assigned to other interventions within other therapeutic domains, depending on whether the site was active for that domain, patient eligibility, and consent (see Supplement 1 and https://www.remapcap.org for more details).

Outcomes

The primary outcome was respiratory and cardiovascular organ support–free days up to day 21, an ordinal end point with death within the hospital as the worst outcome (labeled -1), then the length of time free of both respiratory and cardiovascular organ support, such that the best outcome would be 21 organ support–free days. Organ support was defined using the same criteria as those for study entry. This outcome was used in a recent registration trial in septic shock approved by the Food and Drug Administration (although up to 28 days), with a 1.5-day difference (7.5%-15% relative difference) considered to be the minimal clinically important difference.[18]

Secondary outcomes were in-hospital mortality, ICU and hospital length of stay, respiratory support–free days, cardiovascular organ support–free days, a composite outcome of progression to invasive mechanical ventilation, extracorporeal membrane oxygenation (ECMO) or death among those not ventilated at baseline, and the WHO ordinal scale (range, 0-8, where 0 = no illness, 1-7 = increasing level of care, and 8 = death) assessed at day 14.[19,20] This scale was used in a recent COVID-19 RCT of remdesivir, where an odds ratio of 1.32 was considered clinically important, although few data support that assumption.[20]

Study Power and Sample Size

The trial was designed with no maximum sample size, given the uncertainty of the pandemic. Sample size calculations for the primary outcome were calculated using trial simulations

of the adaptive design rules. If both hydrocortisone groups had effect sizes (odds ratios) of 1.75 compared with the no hydrocortisone group, there would be 90% power to determine whether either group was superior to the no hydrocortisone group with a sample size of 500 patients. If the effect was 1.5, there would be 90% power with a sample size of 1000 patients.

Statistical Analysis

The SAP for the COVID-19 corticosteroid domain was written by blinded steering committee members, posted online (https://www.remapcap.org/) before data lock and analysis, and appears in Supplement 1). The primary analysis was generated from a bayesian cumulative logistic model, which estimated posterior probability distributions of the 21-day organ support-free days (primary outcome) based on the evidence accumulated in the trial in terms of the observed primary outcome and assumed prior knowledge in the form of a prior distribution. Data from the United Kingdom national clinical audit on all COVID-19 ICU admissions (provided by Intensive Care National Audit & Research Centre, London, United Kingdom) were used to inform prior distributions, necessary for bayesian analyses, including initial estimates of the effect of age on outcome. Prior distributions for treatment effects were neutral.

The primary model adjusted for location (site, nested within country), age (categorized into 6 groups), sex, and time period (2-week epochs). The model estimated treatment effects for each intervention within each domain and prespecified treatment-by-treatment interactions across domains. The primary analysis was conducted on all randomized patients who met severe COVID-19 criteria as of June 17, 2020, and not just those randomized within the corticosteroid domain. This approach allowed maximal incorporation of all information, providing the most robust estimation of the coefficients of all included covariates. Not all patients were eligible for all domains nor for all interventions within each domain (depending on site participation, baseline entry criteria, and patient or surrogate preference). Therefore, the model included covariate terms reflecting each patient's intervention and domain eligibility, such that the estimate of an intervention's effectiveness relative to any other intervention within that domain was generated from those patients who might have been randomized to either.

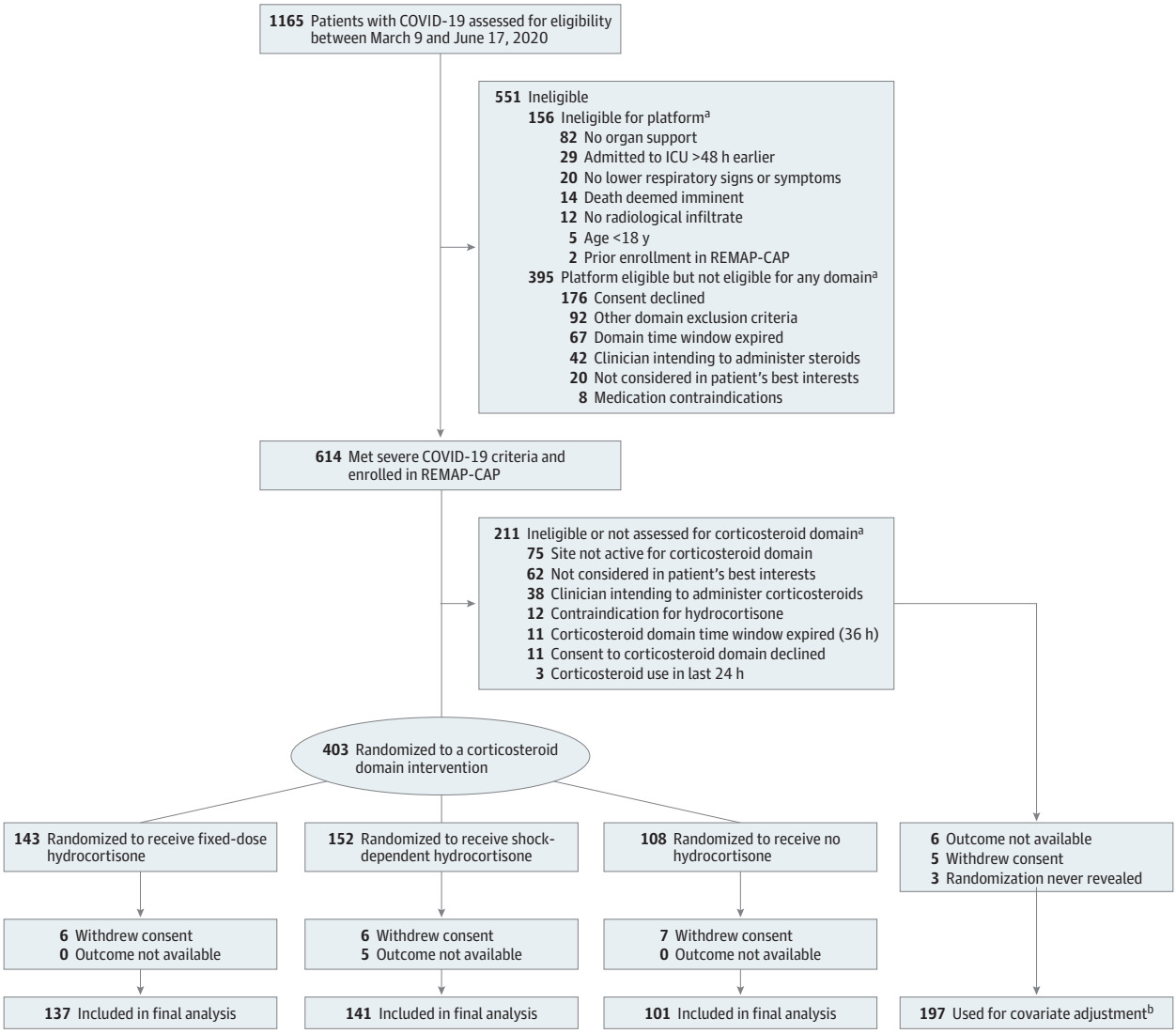
Because the primary model included information about assignment to interventions within domains whose evaluation is ongoing, it was run by the fully unblinded statistical analysis committee (Supplement 1), which conducts all protocol-specified trial update analyses and reports those results to the data and safety monitoring board. For the primary analysis, the 2 fixed-dose hydrocortisone groups were combined, such that there were 3 groups: fixed-dose, shock-dependent, and no hydrocortisone. The cumulative log odds for the primary end point was modeled such that a parameter greater than 0 reflects an increase in the cumulative odds for the organ support-free day outcome, which implies benefit. The model assumed proportional effects across the ordinal organ support-free days scale. This assumption was assessed by inspection of the distribution for clinically important deviations. Patients missing the primary end point (n = 5) were ignored; there was no imputation of missing primary (or secondary) end point values. A patient who survived to hospital discharge was assumed to be free of organ support through 21 days (last status carried forward).

The model was fit using a Markov Chain Monte Carlo algorithm that drew iteratively (10 000 draws) from the joint posterior distribution, allowing calculation of odds ratios with their 95% credible intervals (CrIs) and the probability that each corticosteroid domain intervention (including the no hydrocortisone group) was optimal, that either hydrocortisone group was superior to no hydrocortisone, and that the fixed-dose and shock-dependent hydrocortisone groups were equivalent. An odds ratio greater than 1 represents more survival and more days free from ICU organ support. Although this analysis was conducted in response to the disclosure of the RECOVERY trial results, it was also the first interim analysis of the COVID-19 patient cohort, which had preexisting internal statistical triggers for trial conclusions and disclosure of results (99% probability of superiority or inferiority, defined as odds ratio >1 and <1, respectively, and 90% probability for equivalence, defined as an odds ratio between 1/1.2 and 1.2).

Analysis of the primary outcome was then repeated in a second model using only data from those patients enrolled in the corticosteroid domain with no adjustment for assignment to interventions in other domains. Although using less information, this analysis is more typical for an RCT. Further secondary analyses explored the effects of excluding patients who were ruled out for COVID-19 (defined as documented negative test results for SARS-CoV-2 infection and no positive test results), of excluding adjustment for site and time epoch, and of combining the fixed-dose and shock-dependent hydrocortisone groups.

Identical analyses were conducted to estimate the effect on mortality, except the outcome was dichotomous (alive or dead at hospital discharge). There were also 7 secondary outcome analyses (all using the corticosteroid domain cohort): time to death, respiratory support-free days, cardiovascular organ support-free days, length of ICU stay, length of hospital stay, the WHO ordinal scale at 14 days, and progression to invasive mechanical ventilation, ECMO, or death in those not receiving invasive mechanical ventilation at enrollment. The time-to-death and length-of-stay outcomes were time-to-event analyses with results expressed as hazard ratios. The proportional hazards assumption was assessed by testing whether scaled Schoenfeld residuals and time were independent ($P > .05$) for each covariate. All 3 models met the assumption. The primary safety analysis compared the proportion of patients who developed 1 or more serious adverse events across groups. All analyses were prespecified and are listed in section 15 of the COVID-19 Corticosteroid Domain SAP (pp 391-431) in Supplement 1. Data management and summaries were created using R version 3.5.2, and the primary analysis was computed in R version 4.0.0 using the rstan package version 2.19.3 (R Foundation). Additional data

Figure 1. Screening, Randomization, and Follow-up of Participants in the REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial



COVID-19 indicates coronavirus disease 2019; ICU, intensive care unit; and REMAP-CAP, Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia.

[a] Patients could meet more than 1 ineligibility criterion.

[b] The primary analysis of alternative interventions within the corticosteroid domain is estimated from a model that adjusts for patient factors and for assignment to interventions in other domains. To obtain the most reliable estimation of the effect of these patient factors and of other interventions on the primary outcome, all patients enrolled in the severe COVID-19 cohort (for whom there is consent and follow-up) are included. Importantly, however, the model also factors eligibility for the corticosteroid domain and its interventions, such that the final estimate of a corticosteroid domain intervention's effectiveness relative to any other within that domain is generated from those patients that might have been randomized to either.

management and analysis were performed in R, SQL 2016, SPSS version 26 (IBM), and Stata version 14.2 (StataCorp).

Study Termination

Following a press release from the RECOVERY trial on June 16, 2020, and in response to discussions held across the participating sites, the blinded international trial steering committee decided on June 17, 2020, to stop enrollment of patients with COVID-19 in the corticosteroid domain due to a loss of equipoise. No data from the trial were reviewed prior to the decision.

Results

Participants

Between March 9 and June 17, of 1165 screened patients, 614 met criteria for severe COVID-19, were enrolled in REMAP-CAP, and were randomized within at least 1 therapeutic domain (**Figure 1**). Patients were recruited at 121 sites, of whom 113 (93%) were open for the corticosteroid domain, though 24 sites (21%) only permitted randomization to fixed-dose or shock-dependent hydrocortisone groups

(eAppendix 2 in Supplement 2). Among the 614 patients with severe COVID-19, 403 were enrolled in the corticosteroid domain and randomly assigned to the fixed-dose (n = 143), shock-dependent (n = 152), and no (n = 108) hydrocortisone groups. There were 24 participants (of whom 19 were in the corticosteroid domain) for whom either they or the local ethics board requested withdrawal of all data.

The baseline characteristics of the corticosteroid study groups whose data were available (n = 384) were similar across groups and typical of patients requiring ICU care for COVID-19 (**Table 1** and eAppendix 2 in Supplement 2). For an additional 11 patients, of whom 5 were in the corticosteroid domain, follow-up data were unavailable. Thus, the final cohort available for outcome analysis comprised 576 participants in the REMAP-CAP severe COVID-19 cohort (whose data are used for covariate adjustment in the primary analysis), of whom 379 were randomized within the corticosteroid domain (after removing 5 patients in the shock-dependent hydrocortisone group whose outcomes were not available). The mean age for the 3 groups ranged between 59.5 and 60.4 years; most patients were male (range, 70.6%-71.5%); body mass index ranged between 29.7 and 30.9; and patients receiving mechanical ventilation ranged between 50.0% and 63.5% (Table 1).

Intervention Fidelity

Information on corticosteroid dosing during the first week (defined as study day 1 through day 8) was available for 376 participants (99%) in the corticosteroid domain. Among those assigned to the fixed-dose hydrocortisone group, 97% (n = 130/134) received at least 1 dose of hydrocortisone, an additional 1.5% (2/134) received an alternative systemic corticosteroid, and only 2 (1.5%) received no corticosteroid. The first dose of hydrocortisone was given before midnight of the first study day in 95% of patients (124/130) and the median duration of hydrocortisone therapy was 7 days (interquartile range [IQR], 6-8). Among those assigned to shock-dependent dosing, 43% (62/143) received at least 1 dose of hydrocortisone (and 49% [70/143] received any systemic corticosteroid, including hydrocortisone). Among those treated, the median study day on which hydrocortisone was commenced was study day 1 (IQR, 1-4), and the median duration was 3 days (IQR, 1-4) of hydrocortisone and 3 days (IQR, 2-4) of any systemic corticosteroid. Among those assigned to the no hydrocortisone group, 15% (15/99) received a systemic corticosteroid (6 of whom received hydrocortisone). For those receiving a corticosteroid, the median duration was 2 days (IQR, 2-6).

Primary Outcome

Primary outcomes are presented in **Table 2** and **Figure 2**. The median organ support-free days were 0 (IQR, -1 to 15), 0 (IQR, -1 to 13), and 0 (IQR, -1 to 11) for the fixed-dose, shock-dependent, and no hydrocortisone groups. Relative to the no hydrocortisone group, the median adjusted odds ratios from the primary model were 1.43 (95% CrI, 0.91-2.27) and 1.22 (95% CrI, 0.76-1.94) for the fixed-dose and shock-dependent groups, respectively, yielding 93% and 80% probabilities of superiority. There were no clinically relevant deviations from the assumption of proportional effects across the organ support-free days scale, with the 2 treatment groups having observed benefit across the entire range (Figure 2B). In the prespecified secondary analysis of the primary outcome using only data from participants in the corticosteroid domain and not adjusting for intervention assignment in other domains, the median adjusted odds ratios were 1.45 (95% CrI, 0.93-2.30) and 1.24 (95% CrI, 0.80-1.95) for the fixed-dose and shock-dependent groups, respectively, yielding 95% and 83% probabilities of superiority. Estimates when excluding those who were ruled out for COVID-19, when dropping site and time from the model, and when combining the fixed-dose and shock-dependent groups are shown in eTables 1 and 2 in Supplement 2.

In-Hospital Mortality and Other Secondary Outcomes

The mortality analyses and secondary outcomes are presented in **Table 3**. The in-hospital mortality rates were 30% (n = 41/137), 26% (n = 37/141), and 33% (n = 33/99) in the fixed-dose, shock-dependent, and no hydrocortisone groups, respectively. Relative to the no hydrocortisone group, the median adjusted odds ratios from the primary model were 1.03 (95% CrI, 0.53-1.95) and 1.10 (95% CrI, 0.58-2.11) (where a value >1 represents benefit) for the fixed-dose and shock-dependent hydrocortisone groups, respectively, yielding 54% and 62% bayesian posterior probabilities of superiority. Results from secondary analyses of in-hospital mortality using only data from the corticosteroid domain are presented in eTables 2 and 3 in Supplement 2. Other secondary outcome analyses are presented in Table 3. Full model results of all outcome analyses are provided in eAppendices 3 and 4 in Supplement 2.

Adverse Events

Serious adverse event rates are presented in Table 3 and eAppendix 4 in Supplement 2. There were 10 patients (2.6%) who incurred a serious adverse event (none incurred >1), 9 of whom were in the fixed-dose (n = 4) and shock-dependent (n = 5) hydrocortisone groups. Two events (severe neuromyopathy and fungemia) occurred in the fixed-dose hydrocortisone group and were considered by the site investigator as possibly related to study group assignment. The other events, none of which were considered related, were single cases of pneumonia, pulmonary embolism, elevated serum troponin, postoperative hemorrhage, intracranial hemorrhage, thrombocytopenia, ventricular tachycardia, and hypoglycemia.

Discussion

The principal findings from this study were a 93% probability of benefit of a fixed-duration dosing of hydrocortisone and an 80% probability of benefit of a shock-dependent dosing of hydrocortisone, compared with no hydrocortisone, with regard to the odds of improvement in organ support-free days within 21 days. However, the study was stopped early, the probability of benefit with hydrocortisone did not meet

Table 1. Participant Characteristics at Baseline

Characteristic	No./total No. (%) of participants[a]		
	Fixed-dose hydrocortisone (n = 137)[b]	Shock-dependent hydrocortisone (n = 146)	No hydrocortisone (n = 101)
Age, mean (SD), y	60.4 (11.6)	59.5 (12.7)	59.9 (14.6)
Sex			
Male	98 (71.5)	103 (70.6)	72 (71.3)
Female	39 (28.5)	43 (29.5)	29 (28.7)
Body mass index[c]			
No.	135	141	100
Mean (SD)	30.9 (7.3)	30.7 (7.4)	29.7 (7.5)
Race/ethnicity[d]			
White	79/111 (71.2)	80/105 (76.2)	45/79 (57.0)
Asian	18/111 (16.2)	11/105 (10.5)	22/79 (27.9)
Black	4/111 (3.6)	7/105 (6.7)	4/79 (5.1)
Mixed	4/111 (3.6)	0/105	2/79 (2.5)
Other[d]	6/111 (5.4)	7/105 (6.7)	6/79 (7.6)
Confirmed SARS-CoV-2 infection[e]	109/134 (81.3)	87/125 (69.6)	79/100 (79.0)
Preexisting conditions			
Diabetes	50/129 (38.8)	39/144 (27.1)	30/98 (30.6)
Respiratory disease	27/127 (21.3)	28/144 (19.4)	20/98 (20.4)
Asthma/COPD	21/137 (15.3)	25/144 (17.4)	16/100 (16.0)
Other	7/127 (5.5)	4/144 (2.8)	4/95 (4.2)
Kidney disease	13/128 (10.2)	11/127 (8.7)	8/92 (8.7)
Severe cardiovascular disease	9/136 (6.6)	13/140 (9.3)	6/99 (6.1)
Immunosuppressive disease	7/127 (5.5)	9/144 (6.3)	2/95 (2.1)
Chronic immunosuppressive therapy	8/137 (5.8)	7/142 (4.9)	6/100 (6.0)
Time to enrollment, median (IQR)			
From hospital admission, d	1.2 (0.8-2.6)	1.0 (0.7-2.8)	1.1 (0.7-2.0)
From ICU admission, h	15.1 (7.5-19.8)	12.3 (5.4-18.8)	13.5 (8.1-17.5)
Acute respiratory support			
None/supplemental oxygen only	0	1 (0.7)	0
High-flow nasal cannula	17 (12.4)	23 (15.8)	16 (15.8)
Noninvasive ventilation only	33 (24.1)	49 (33.6)	32 (31.7)
Invasive mechanical ventilation	87 (63.5)	73 (50.0)	53 (52.5)
ECMO	1/137 (0.7)	0/143	2/99 (2.0)
Vasopressor support	56 (40.9)	47 (32.2)	30 (29.7)
APACHE II score, median (IQR)[f]			
No.	123	130	94
Median (IQR)	18 (10-23)	17 (12-24)	15 (12-21)
Glasgow Coma Scale score, mean (SD)[g]			
No.	131	133	98
Mean (SD)	13 (4)	13 (4)	14 (3)

(continued)

Table 1. Participant Characteristics at Baseline (continued)

Characteristic	No./total No. (%) of participants[a]		
	Fixed-dose hydrocortisone (n = 137)[b]	Shock-dependent hydrocortisone (n = 146)	No hydrocortisone (n = 101)
Acute physiology and laboratory values[h]			
Pao_2/Fio_2			
No.	130	142	96
Mean (SD)	149 (83)	137 (74)	138 (78)
Creatinine, mg/dL			
No.	136	143	98
Median (IQR)	0.9 (0.7-1.2)	0.9 (0.7-1.3)	0.8 (0.6-1.2)
Lactate, mmol/L			
No.	124	124	88
Median (IQR)	1.2 (0.9-1.5)	1.1 (0.9-1.6)	1.1 (0.8-1.5)
Platelet count, $\times 10^9$/L			
No.	135	143	98
Mean (SD)	254 (117)	259 (112)	259 (112)
Bilirubin, mg/dL			
No.	129	134	93
Median (IQR)	0.1 (0.1-0.2)	0.1 (0.1-0.2)	0.1 (0.1-0.2)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; Fio_2, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; Pao_2, partial pressure of arterial oxygen; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

SI conversion factors: To convert bilirubin to µmol/L, multiply by 17.104; creatinine to µmol/L, multiply by 88.4; lactate to mg/dL, divide by 0.111.

[a] Unless otherwise indicated. Percentages may not sum to 100 because of rounding.

[b] Fixed dose combines patients assigned to 50 mg (n = 135) or 100 mg (n = 2) intravenous hydrocortisone every 6 hours for 7 days.

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Data collection not approved in Canada and continental Europe. "Other" includes "declined" and "multiple."

[e] Infection confirmed by respiratory tract polymerase chain reaction test.

[f] Range: 0-71, with higher scores indicating greater severity of illness.

[g] Range: 3-15, with higher scores indicating greater consciousness, using values closest to randomization but prior to use of sedative agents.

[h] Value closest to randomization within prior 8 hours. For creatinine, lactate, platelet count, and bilirubin, if the prerandomization value was missing, the closest value within 2 hours after randomization was used.

the prespecified statistical trigger for a trial conclusion of superiority, and no strategy was determined to be optimal.

REMAP-CAP is designed to test numerous interventions for pandemic and nonpandemic pneumonia over time. The design has internal statistical triggers for stopping particular study questions, but external factors, such as lack of equipoise following new evidence, can also trigger termination of a portion of the trial. This analysis was prompted by the loss of equipoise following announcement that dexamethasone reduced mortality in the RECOVERY trial.[18] Coincidentally, this analysis was also the first interim analysis of the severe COVID-19 cohort: had any internal threshold been triggered, the results would have been released regardless of RECOVERY. However, had RECOVERY not prompted cessation, the internal action would simply be to generate updated randomization proportions and continue enrollment.

Given the findings from contemporaneous trials, the findings might generally be considered supportive of corticosteroid use in this patient population.[15,21] For example, the benefit reported in RECOVERY was in patients similar to those enrolled in this trial using a corticosteroid, dexamethasone, with a similar glucocorticoid effect to that of the fixed-dose hydrocortisone course in this trial. As such, it seems reasonable that either dexamethasone or hydrocortisone might be beneficial. In turn, it is plausible that the primary benefit is exerted through glucocorticoid, rather than mineralocorticoid effects, given dexamethasone's lack of mineralocorticoid activity. Systemic corticosteroids have well-described adverse effects. In this open-label trial, serious adverse events were rare, precluding statistical inference. However, they were reported more commonly in the 2 hydrocortisone groups.

The findings regarding the shock-dependent hydrocortisone group are less clear, with an 80% probability of benefit. In this group, physicians only administered hydrocortisone when the patient was in shock. Thus, if corticosteroids are beneficial for COVID-19 through mechanisms other than mitigation of shock, this group was effectively undertreated, and one would anticipate less average benefit. In contrast, if the benefits of corticosteroids largely accrue to those in shock, avoidance of unnecessary corticosteroid therapy in those not in shock might improve the safety profile of corticosteroid therapy. This question remains unresolved.

Strengths of the study include the pragmatic and international design, rendering findings likely generalizable at least to other resource-rich settings around the world. In addition, all analyses were specified prior to unblinding results, results were robust to sensitivity analyses, and findings of multiple secondary outcomes demonstrated similar probabilities of benefit of hydrocortisone. An advantage of using a bayesian approach is that any data, including

Table 2. Primary Outcome

Outcome/analysis[a]	Fixed-dose hydrocortisone (n = 137)	Shock-dependent hydrocortisone (n = 141)	No hydrocortisone (n = 101)
Primary outcome, organ support–free days			
Median (IQR)	0 (-1 to 15)	0 (-1 to 13)	0 (-1 to 11)
Subcomponents of organ support–free days			
In-hospital deaths, No. (%)	41 (30)	37 (26)	33 (33)
Organ support–free days among survivors, median (IQR)	11.5 (0 to 17)	9.5 (0 to 16)	6 (0 to 12)
Primary analysis of the primary outcome, using covariate data from all severe-state participants with COVID-19 (n = 576)[b]			
Adjusted odds ratio			
Mean (SD)	1.47 (0.35)	1.26 (0.31)	1 [Reference]
Median (95% CrI)	1.43 (0.91 to 2.27)	1.22 (0.76 to 1.94)	1 [Reference]
Probability of superiority to no hydrocortisone, %	93	80	
Secondary analysis of the primary outcome, restricted to corticosteroid domain participants (n = 379) with no adjustment for intervention assignment in other domains[c]			
Adjusted odds ratio			
Mean (SD)	1.49 (0.35)	1.28 (0.30)	1 [Reference]
Median (95% CrI)	1.45 (0.93 to 2.30)	1.24 (0.80 to 1.95)	1 [Reference]
Probability of superiority to no hydrocortisone, %	95	83	

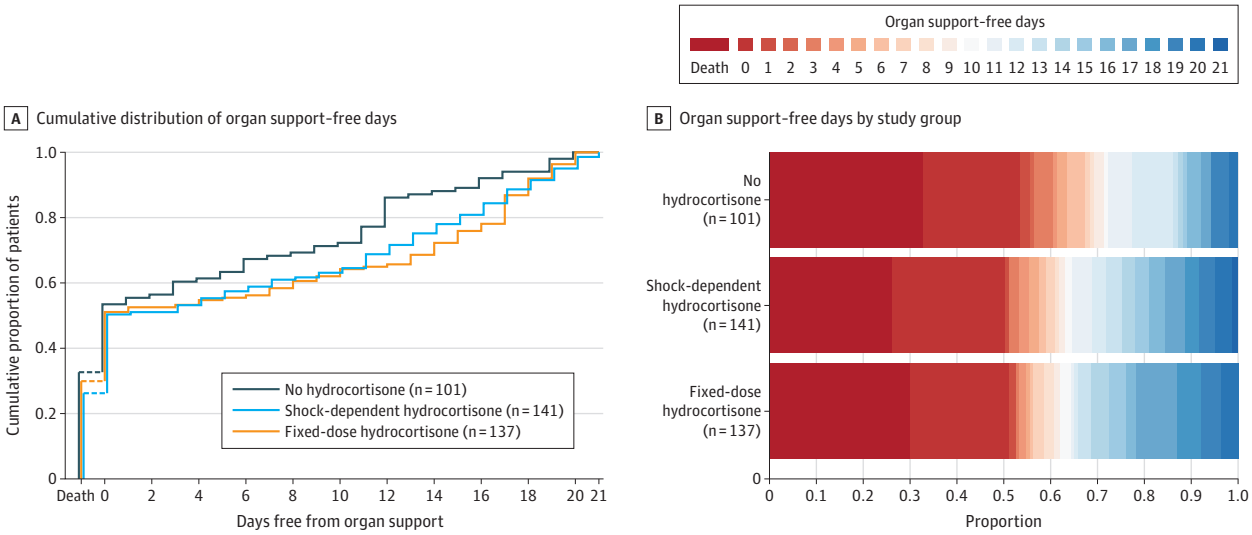
Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; CrI, credible interval.

[a] Definitions of organ support–free days and other outcomes are provided in the Methods section and the study protocol (Supplement 1). Models are structured such that a higher odds ratio is favorable. Other sensitivity analyses are described in the Results section and provided in eTables 1 and 2 and eAppendices 3 and 4 in Supplement 2.

[b] The primary analysis used data from all participants enrolled in the trial who met COVID-19 severe state criteria and were randomized within at least 1 domain (n = 576), adjusting for age, sex, time period, site, region, domain and intervention eligibility, and intervention assignment (see COVID-19 Corticosteroid Domain statistical analysis plan in Supplement 1 and full report from the statistical analysis committee in eAppendix 3 in Supplement 2).

[c] The secondary analysis was restricted to participants enrolled in the corticosteroid domain (n = 379) and did not include information on assignment to interventions other than hydrocortisone.

Figure 2. Organ Support–Free Days



A, Distributions of organ support–free days (see the Methods section for definition) by study group as the cumulative proportion (y-axis) for each study group by day (x-axis), with death listed first. Curves that rise more slowly are more favorable. B, Organ support–free days as horizontally stacked proportions by study group. Red represents worse values and blue represents better values. The median adjusted odds ratios from the primary analysis, using a bayesian cumulative logistic model, were 1.43 (95% credible interval, 0.91-2.27) and 1.22 (95% credible interval, 0.76-1.94) for the fixed-dose and shock-dependent hydrocortisone groups compared with the no hydrocortisone group, yielding 93% and 80% probabilities of superiority over the no hydrocortisone group, respectively.

data following unplanned cessation in enrollment, can be analyzed and quantified as posterior probabilities, which is arguably more useful and is more quantitative than a frequentist finding of failure to reject a null hypothesis possibly because of lack of power.[22,23] The platform trial design allows efficient enrollment into multiple therapeutic domains

Table 3. Secondary Outcomes and Serious Adverse Events

Outcome/analysis[a]	Fixed-dose hydrocortisone (n = 137)	Shock-dependent hydrocortisone (n = 141)	No hydrocortisone (n = 101)
Primary in-hospital mortality model, using covariate data from all severe state participants with COVID-19 (n = 576)[b]			
Adjusted odds ratio			
Mean (SD)	1.08 (0.37)	1.16 (0.40)	1 [Reference]
Median (95% CrI)	1.03 (0.53-1.95)	1.10 (0.58-2.11)	1 [Reference]
Probability of superiority to no hydrocortisone, %	54	62	
Other secondary outcomes, restricted to corticosteroid domain participants (n = 379) with no adjustment for intervention assignment in other domains[c]			
Time to death			
Adjusted hazard ratio			
Mean (SD)	0.97 (0.22)	1.01 (0.23)	1 [Reference]
Median (95% CrI)	0.94 (0.61-1.46)	0.98 (0.63-1.54)	1 [Reference]
Probability of superiority to no hydrocortisone, %	40	47	
Respiratory support–free days			
Adjusted odds ratio			
Mean (SD)	1.45 (0.34)	1.31 (0.30)	1 [Reference]
Median (95% CrI)	1.42 (0.90-2.24)	1.28 (0.81-2.00)	1 [Reference]
Probability of superiority to no hydrocortisone, %	94	85	
Cardiovascular organ support–free days			
Adjusted odds ratio			
Mean (SD)	1.68 (0.40)	1.32 (0.31)	1 [Reference]
Median (95% CrI)	1.63 (1.03-2.59)	1.29 (0.81-2.02)	1 [Reference]
Probability of superiority to no hydrocortisone, %	98	86	
Length of ICU stay			
Adjusted hazard ratio			
Mean (SD)	0.93 (0.14)	0.86 (0.13)	1 [Reference]
Median (95% CrI)	0.92 (0.68-1.24)	0.85 (0.62-1.15)	1 [Reference]
Probability of superiority to no hydrocortisone, %	29	14	
Length of hospital stay			
Adjusted hazard ratio			
Mean (SD)	0.99 (0.16)	0.94 (0.15)	1 [Reference]
Median (95% CrI)	0.97 (0.72-1.32)	0.93 (0.69-1.26)	1 [Reference]
Probability of superiority to no hydrocortisone, %	43	31	
WHO scale at day 14[d]			
Adjusted odds ratio			
Mean (SD)	1.33 (0.32)	1.06 (0.26)	1 [Reference]
Median (95% CrI)	1.29 (0.83-2.05)	1.03 (0.65-1.65)	1 [Reference]
Probability of superiority to no hydrocortisone, %	87	55	
Progression to invasive mechanical ventilation, ECMO, or death, restricted to those not intubated at baseline (n = 168)			
Free of invasive mechanical ventilation at baseline, No.	50	70	48
Progression to intubation, ECMO, or death, No. (%)	23 (46)	42 (60)	37 (77)
Adjusted odds ratio			
Mean (SD)	3.02 (1.40)	1.36 (0.59	1 [Reference]
Median (95% CrI)	2.74 (1.18-6.56)	1.24 (0.56-2.82)	1 [Reference]
Probability of superiority to no hydrocortisone, %	99	70	
Serious adverse events			
Patients with >1 serious adverse event, No. (%)	4 (3)	5 (4)	1 (1)

Abbreviations: COVID-19, coronavirus disease 2019; CrI, credible interval; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; WHO, World Health Organization.

[a] Definitions of outcomes are provided in the Methods section and the study protocol (Supplement 1). Models are structured such that a higher odds ratio or hazard ratio is favorable.

[b] The primary analysis of in-hospital mortality used data from all participants enrolled in the trial who met COVID-19 severe-state criteria and were randomized within at least 1 domain (n = 576), adjusting for age, sex, time period, site, region, domain and intervention eligibility, and intervention assignment (see COVID-19 Corticosteroid Domain statistical analysis plan in Supplement 1 and full report from the statistical analysis committee in eAppendix 3 in Supplement 2).

[c] Other analyses were restricted to participants enrolled in the corticosteroid domain (n = 379) and did not include information on assignment to interventions other than hydrocortisone. Other sensitivity analyses are described in the Results section and provided in eTables 2 and 3 and eAppendices 3 and 4 in Supplement 2.

[d] The WHO scale ranges from 0 (no disease) to 8 (death).

simultaneously. One concern could have been potential confounding because of treatment-by-treatment interactions. However, the results were similar with and without adjustment for other treatment assignments.

Limitations

The study has several limitations. First, the results are presented before reaching any prespecified internal trigger. Nonetheless, to our knowledge, this trial represents the largest randomized data on hydrocortisone in this patient population. Second, the study used an open-label design, although clinician and patient awareness of study assignment likely had minimal effect on the primary outcome. Third, 15% of the no hydrocortisone group received systemic corticosteroids, although typically only for a short period. This usage is similar to that in RECOVERY[18] and may often have been unavoidable (eg, to treat postextubation stridor). Nonetheless, it could have biased the results toward smaller effect sizes than would have been observed had corticosteroid use been lower in the no hydrocortisone group.

Conclusions

Among patients with severe COVID-19, treatment with a 7-day fixed-dose course of hydrocortisone or shock-dependent dosing of hydrocortisone, compared with no hydrocortisone, resulted in 93% and 80% probabilities of superiority with regard to the odds of improvement in organ support–free days within 21 days. However, the trial was stopped early and no treatment strategy met prespecified criteria for statistical superiority, precluding definitive conclusions.

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Conflict of Interest Disclosures: Dr Angus reported receiving personal fees from Ferring Pharmaceuticals Inc, Bristol-Myers Squibb, Bayer AG, and ALung Technologies Inc outside the submitted work; in addition, Dr Angus had a patent to selepressin—compounds, compositions, and methods for treating sepsis pending and a patent to proteomic biomarkers of sepsis in elderly patients pending. Dr Annane reported receiving grants from French Ministry of Health during the conduct of the study. Dr Bentum-Puijk reported receiving European Union FP7-Health-2013-INNOVATION-1 grant No. 602525 and H2020 RECOVER grant agreement No. 101003589 during the conduct of the study. Dr L. Berry reported receiving grants for PREPARE Network from the European Commission; Australia funding grants for OPTIMISE-CAP; and New Zealand funding grants for REMAP-CAP during the conduct of the study. Dr S. 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Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19
A Randomized Clinical Trial

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IMPORTANCE Coronavirus disease 2019 (COVID-19) is associated with severe lung damage. Corticosteroids are a possible therapeutic option.

OBJECTIVE To determine the effect of hydrocortisone on treatment failure on day 21 in critically ill patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and acute respiratory failure.

DESIGN, SETTING, AND PARTICIPANTS Multicenter randomized double-blind sequential trial conducted in France, with interim analyses planned every 50 patients. Patients admitted to the intensive care unit (ICU) for COVID-19–related acute respiratory failure were enrolled from March 7 to June 1, 2020, with last follow-up on June 29, 2020. The study intended to enroll 290 patients but was stopped early following the recommendation of the data and safety monitoring board.

INTERVENTIONS Patients were randomized to receive low-dose hydrocortisone (n = 76) or placebo (n = 73).

MAIN OUTCOMES AND MEASURES The primary outcome, treatment failure on day 21, was defined as death or persistent dependency on mechanical ventilation or high-flow oxygen therapy. Prespecified secondary outcomes included the need for tracheal intubation (among patients not intubated at baseline); cumulative incidences (until day 21) of prone position sessions, extracorporeal membrane oxygenation, and inhaled nitric oxide; Pa_{O_2}:F_{IO_2} ratio measured daily from day 1 to day 7, then on days 14 and 21; and the proportion of patients with secondary infections during their ICU stay.

RESULTS The study was stopped after 149 patients (mean age, 62.2 years; 30.2% women; 81.2% mechanically ventilated) were enrolled. One hundred forty-eight patients (99.3%) completed the study, and there were 69 treatment failure events, including 11 deaths in the hydrocortisone group and 20 deaths in the placebo group. The primary outcome, treatment failure on day 21, occurred in 32 of 76 patients (42.1%) in the hydrocortisone group compared with 37 of 73 (50.7%) in the placebo group (difference of proportions, −8.6% [95.48% CI, −24.9% to 7.7%]; $P = .29$). Of the 4 prespecified secondary outcomes, none showed a significant difference. No serious adverse events were related to the study treatment.

CONCLUSIONS AND RELEVANCE In this study of critically ill patients with COVID-19 and acute respiratory failure, low-dose hydrocortisone, compared with placebo, did not significantly reduce treatment failure (defined as death or persistent respiratory support) at day 21. However, the study was stopped early and likely was underpowered to find a statistically and clinically important difference in the primary outcome.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02517489

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As of August 17, 2020, more than 20 million people worldwide have been infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and nearly 800 000 people have died of coronavirus disease 2019 (COVID-19).[1] Acute respiratory failure is a major cause of intensive care unit (ICU) admission for patients with COVID-19.[2,3] In the absence of specific intervention, the treatment of COVID-19 relies on relieving symptoms and organ support. The potential shorter recovery associated with remdesivir, an antiviral drug, was not observed in the subgroup of critically ill patients.[4] Until recently, no drug had been shown to improve survival.

Although the pathophysiology of COVID-19 remains incompletely understood, organ damage, especially diffuse lung injury, results from both the direct cytotoxicity of the virus and dysregulated immune response. The importance of a cytokine storm has been discussed[5,6] and debated[7,8]; regardless, it is clear that excessive inflammation plays a role in the development of pulmonary disease.[9] Immunomodulatory drugs, such as corticosteroids, are therefore being investigated as therapeutic options for COVID-19.[10]

The efficacy and safety of corticosteroids in patients with viral pneumonia remains largely uncertain because of a scarcity of randomized trials and inconclusive observational studies.[11] At the onset of the pandemic, there was equipoise regarding use of corticosteroids for severe COVID-19.[12] Corticosteroids may impair immune defenses and hamper viral clearance, potentially leading to subsequent excess mortality such as has been suggested in patients with severe influenza.[13] Yet one observational study reported that methylprednisolone was associated with a 25% relative reduction in short-term mortality among patients with COVID-19–related acute respiratory distress syndrome.[14] Recently, an open-label randomized trial found that dexamethasone improved day-28 survival in patients hospitalized with COVID-19.[15] The purpose of this study was to evaluate the effect of hydrocortisone for the treatment of ICU patients with COVID-19–related acute respiratory failure.

Key Points

Question Does low-dose hydrocortisone decrease treatment failure in patients with COVID-19–related acute respiratory failure?

Findings In this randomized clinical trial that included 149 patients and was terminated early following the recommendation of the data and safety monitoring board, there was no significant difference in the rate of treatment failure (defined as death or persistent respiratory support with mechanical ventilation or high-flow oxygen therapy) on day 21 between the hydrocortisone and placebo groups (42.1% vs 50.7%, respectively).

Meaning Low-dose hydrocortisone did not significantly reduce treatment failure in patients with COVID-19–related acute respiratory failure; however, the study was stopped early and was therefore likely underpowered.

Methods

Ethical and Regulatory Issues

The ethics committee (Comité de Protection des Personnes Ouest 1, France) as well as the French regulatory agency approved this trial, as an adaptation of the design of a parent trial, focused on the group of patients with SARS-CoV-2 infection (see below). The ClinicalTrials.gov website was updated as soon as ethical and regulatory approvals were obtained. Each patient or surrogate provided either written or oral informed consent prior to inclusion. If the patient could not consent and no surrogate was available, the ethics committee authorized emergency inclusion in the study, in which case deferred consent was obtained as soon as possible from the patient or surrogate.

Design

The present trial was embedded in the ongoing Community-Acquired Pneumonia: Evaluation of Corticosteroids (CAPE COD) trial. Methodological issues relating to this original approach have been described elsewhere.[16] The protocol, including the statistical analysis plan, is presented in Supplement 1 and Supplement 2. Briefly, the CAPE COD trial was designed to determine the superiority of low-dose hydrocortisone compared with placebo in reducing mortality on day 28 in ICU patients with community-acquired pneumonia. When the COVID-19 outbreak developed, it was rapidly recognized that the benefits and risks of corticosteroids needed to be assessed, particularly in severe forms of the disease; the design of the ongoing trial allowed the inclusion of patients with COVID-19; there was a unique opportunity to assess the efficacy and safety of corticosteroids in a trial of high methodological standard, albeit in an unprecedented pandemic context (eg, centers trained in the trial procedures and already active, availability of the drug and the placebo in a form guaranteeing double-blinding, electronic case report form in place, only minor amendments required to obtain regulatory authorizations); and the methodology had to be adapted to this pandemic context.

The Community-Acquired Pneumonia: Evaluation of Corticosteroids in Coronavirus Disease (CAPE COVID) trial was therefore embedded within the parent trial. Because all participating centers were exclusively admitting only patients with COVID-19 during the initial phase of the pandemic, inclusion of patients with pneumonia of other origin were discontinued. Patients with COVID-19 had been included in the parent trial, from March 7, 2020. The use of a different primary outcome from the parent trial (ie, better suited to the epidemic emergency) and a sequential mode analysis for patients with COVID-19, including those who had already been enrolled, was approved by the ethics committee on March 30 and by the regulatory agency on April 9, 2020. By this time, 26 patients with COVID-19 had been included in the parent trial. This embedded trial was planned as a placebo-controlled group sequential design using the Lan and DeMets approach,[17] with a planned interim analysis every 50 patients. Thus, the first analysis could be performed for the first 50 patients according to the method approved for the subtrial devoted to COVID-19.

Participants

Patients aged at least 18 years admitted to 1 of the 9 participating French ICUs for acute respiratory failure could be

included if they had a biologically confirmed (reverse transcriptase-polymerase chain reaction) or suspected (suggestive chest computed tomography scan result in the absence of any other cause of pneumonia) COVID-19. The experimental treatment had to be administered within 24 hours of the onset of the first severity criterion (see below) or within 48 hours for patients referred from another hospital. One of 4 severity criteria had to be present: need for mechanical ventilation with a positive end-expiratory pressure (PEEP) of 5 cm H_20 or more; a ratio of Pao_2 to fraction of inspired oxygen (Fio_2) less than 300 on high-flow oxygen therapy with an Fio_2 value of at least 50%; for patients receiving oxygen through a reservoir mask, a Pao_2:Fio_2 ratio less than 300, estimated using prespecified charts; or a Pulmonary Severity Index[18] greater than 130. Patients receiving vasopressors to correct hypotension related to sedative drugs and mechanical ventilation at high PEEP levels could be included. Principal exclusion criteria were septic shock and do-not-intubate orders.

Randomization and Allocation Concealment

Randomization was centralized and performed electronically. Allocation sequences were generated in a 1:1 ratio by a computer-generated random number using a blocking schema; the range of block sizes remains confidential until the completion of the parent trial. Randomization was stratified by center and by use of mechanical ventilation at the time of inclusion.

Treatments and Blinding

Patients received a continuous intravenous infusion of hydrocortisone at an initial dose of 200 mg/d or its placebo (saline). Both hydrocortisone and placebo were provided in industrially prepared packaging (Serb Specialty Pharmaceuticals). Treatment was continued at 200 mg/d until day 7 and then decreased to 100 mg/d for 4 days and 50 mg/d for 3 days, for a total of 14 days. If the patient's respiratory and general status had sufficiently improved by day 4, a short treatment regimen was used (200 mg/d for 4 days, followed by 100 mg/d for 2 days and then 50 mg/d for the next 2 days, for a total of 8 days). All of the following criteria had to be present to consider this adaptive scheme: patient breathing spontaneously; Pao_2:Fio_2 ratio greater than 200; Sequential Organ Failure Assessment (SOFA)[19] score on day 4 less than or equal to SOFA score on day 1; and strong probability of being discharged from the ICU (including intermediate-care units) before day 14, according to the physician of record. In all cases, treatment was stopped on ICU discharge. Patients otherwise received standard care for acute respiratory failure.[20] Since no antiviral treatment improved survival or clinically relevant parameters, adjunctive treatments could be administered at the discretion of the patients' primary physicians.

Outcome Measures and Data Collection

The primary outcome was treatment failure on day 21, defined as death or persistent dependency on mechanical ventilation or high-flow oxygen therapy.

Prespecified secondary outcomes included the use of tracheal intubation (for patients not intubated at inclusion); the use of prone position (with the number of sessions), extracorporeal membrane oxygenation or inhaled nitric oxide (with the number of days the treatment was used); the Pao_2:Fio_2 ratio recorded daily from day 1 to day 7 and then on days 14 and 21; and the proportion of patients with and the number of episodes of nosocomial infections recorded during the ICU stay. Because some patients were still hospitalized in the ICU when the data were analyzed, nosocomial infections were recorded up to day 28 (which was a post hoc decision). The diagnosis of nosocomial infection was made by the clinician in charge and provided that an antibiotic therapy had been prescribed.

Death on day 21 and status on day 21 (determined using a 5-item scale: death, presence in the ICU on mechanical ventilation, high-flow or low-flow oxygen therapy, ICU discharge) were post hoc outcomes.

Apart from death, the adverse events expected in this context (such as the need for intubation in a patient breathing spontaneously at baseline) were only reported if the clinician thought they might be related to the study treatment.

Sample Size

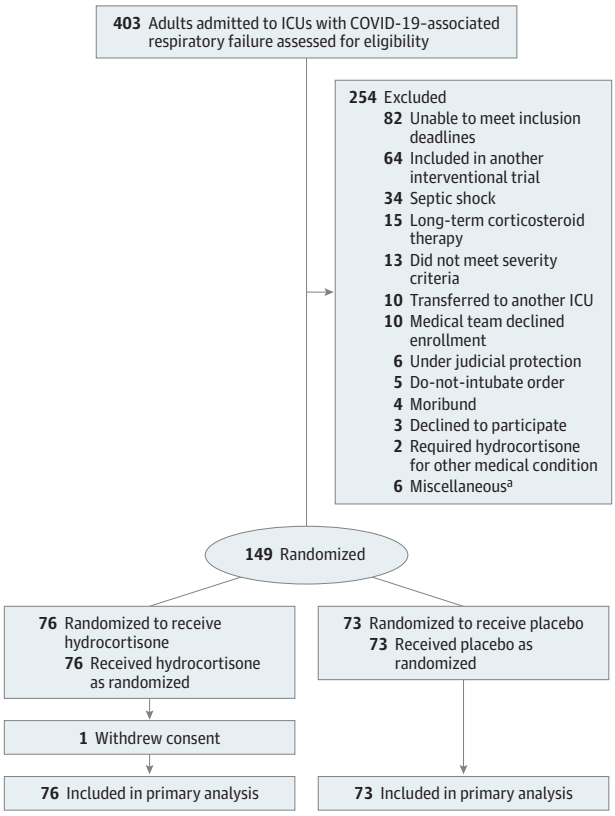
The event rate, defined as treatment failure on day 21 (ie, death or persistent dependency on mechanical ventilation or high-flow oxygen therapy), was assumed to be 30% in the control group, acknowledging a high level of uncertainty owing to the unprecedented nature of COVID-19. The trial was designed to test the superiority of hydrocortisone over placebo with an assumed event rate of 15% in the hydrocortisone group,[21] with 80% power and a 5% 2-sided type I error rate. Because of the sequential nature of the design, with 6 analyses (5 interim and a final one), the maximal required sample size was 290.

Statistical Analysis

Patients were analyzed according to their randomization group. For the primary analysis, missing data were considered treatment failure. No imputation was made for secondary outcomes. All performed statistical tests were 2-sided. $P \leq .0452$ was considered a significant difference in the primary outcome because of the interim analyses, and $P \leq .05$ as indicating statistical significance for secondary outcomes. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. Categorical variables were summarized as frequencies and percentages and continuous variables as medians (interquartile ranges). Treatment failure on day 21 was reported as proportions in each group and compared using a 2-proportion z test based on normal approximation. Difference of proportions was also estimated with its 95% confidence interval.

A sensitivity analysis was performed on patients without missing data. Cumulative incidence of patients with at least 1 prone-position session, and incidence of patients experiencing secondary infections during their ICU stay, were estimated using a competing-risk approach,[22] with death and end of ICU stay as competing events. For competing-risk models, proportionality assumptions were studied including an interaction term with the time in Fine and Gray models; results of these tests were not significant. Given the limited number

Figure 1. Study Flow of the CAPE COVID Trial



Randomization was stratified by center and use of mechanical ventilation at the time of inclusion. CAPE COVID indicates Community-Acquired Pneumonia: Evaluation of Corticosteroids in Coronavirus Disease; COVID-19, coronavirus disease 2019; ICU, intensive care unit.

[a] One patient had aspiration of gastric content associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Five patients had hospital-acquired SARS-CoV-2 infection, which was misinterpreted as a criterion of noninclusion.

of events, analyses of extracorporeal membrane oxygenation and inhaled nitric oxide were only descriptive. Evolution of Pa_{O_2}:FI_{O_2} ratio was analyzed using a mixed linear model. The status on day 21 was analyzed using a Fisher exact test. For death on day 21, difference of proportion was estimated with its 95% confidence interval and compared between the 2 groups using a 2-proportion *z* test.

Data were analyzed with SAS version 9.4 (SAS Institute Inc), and R version 3.3.1 (R Foundation for Statistical Computing) was used for the statistical analyses.

Data and Safety Monitoring Board and Trial Suspension

The data and safety monitoring board (DSMB) met when the primary end point was collected for the first 50 and 100 patients and each time recommended further inclusions. When enrollment slowed at the end of the first wave of the epidemic in France, the DSMB agreed to meet on June 30, 2020, to analyze the results of the first 149 patients, which the Lan and DeMets approach allows because of its flexibility. On June 30, 2020, the DSMB recommended suspension of inclusions pending publication of the results of the RECOVERY trial and possible changes in treatment recommendations. The sponsor decided to discontinue the study on July 3, 2020, considering that it would be unethical to resume a corticosteroid vs placebo trial, and that the results should be published and included in the prospective meta-analysis conducted by the World Health Organization.[23]

Results

Trial Flow and Baseline Characteristics of Participants

Between March 7 and June 1, 2020, 149 patients were enrolled, of whom 76 were randomized to the hydrocortisone group and 73 to the placebo group (**Figure 1**). The mean age was 62.2 years and 30.2% were women (**Table 1**; eTable in Supplement 3). One patient withdrew consent; and for the primary outcome this patient was considered to have experienced treatment failure on day 21. Results of SARS-CoV-2 reverse transcriptase–polymerase chain reaction testing were positive in 96.6% of patients. Median durations of symptoms prior to randomization were 9 days in the hydrocortisone group and 10 days in the placebo group. All patients were hypoxemic, and 121 of 149 (81.2%) were mechanically ventilated at baseline. No patient was included solely based on the Pulmonary Severity Index. Vasopressors were administered in 18 of 76 patients (23.7%) in the hydrocortisone group and 13 of 73 patients (17.8%) in the placebo group.

The median duration of study treatments was 10.5 days (interquartile range, 6.0-14.0) for hydrocortisone and 12.8 days (interquartile range, 8.0 to 13.0) for placebo (P = .25).

Primary Outcome

Treatment failure on day 21 occurred in 32 of 76 patients (42.1%) in the hydrocortisone group compared with 37 of 73 (50.7%) in the placebo group (difference of proportions, -8.6% [95.48% CI, -24.9% to 7.7%]; P = .29). (**Table 2**, eFigure 1 in Supplement 3).

Secondary Outcomes

Of the 16 patients in each group who did not require invasive mechanical ventilation at baseline, 8 (50%) in the hydrocortisone group and 12 (75%) in the placebo group required subsequent intubation. A total of 137 of 149 patients (92%) were intubated, either before inclusion or during treatment. There was no significant between-group difference in rates of prone positioning (36/76 patients [47.4%] in the hydrocortisone group vs 39/73 [53.4%] in the placebo group; hazard ratio, 0.85 [95% CI, 0.55 to 1.32]; P = .47) (Table 2; eFigure 2 in Supplement 3). Too few patients were treated with extracorporeal membrane oxygenation or inhaled nitric oxide to allow statistical testing.

Daily evolution of Pa02:FI_{O_2} ratio during the first week and on days 14 and 21 did not significantly differ between the groups (P = .37) (eFigure 3 in Supplement 3).

On day 28, 58 patients (38.9%) had at least 1 episode of nosocomial infection, 28 of 75 (37.3%) in the hydrocortisone group vs 30 of 73 (41.1%) in the placebo group, for a total of

Table 1. Baseline Patient Characteristics in the CAPE COVID Trial

Characteristic	No. (%)	
	Hydrocortisone (n = 76)	Placebo (n = 73)
Demographics and past medical history		
Sex		
Women	22 (28.9)	23 (31.5)
Men	54 (71.1)	50 (68.5)
Age, median (IQR), y	63.1 (51.5-70.8)	66.3 (53.5-72.7)
Never smoker, No./total (%)	57/75 (76.0)	57/72 (79.2)
COPD or asthma	7 (9.2)	4 (5.4)
Diabetes	13 (17.1)	14 (19.2)
Immunosuppression	6 (7.9)	3 (4.1)
BMI, median (IQR)[a]	27.5 (25.3-32.4) [n = 59]	28.4 (26.0-31.2) [n = 61]
Clinical data at inclusion, median (IQR)		
Symptom duration, d	9.0 (7.0-11.5) [n = 76]	10.0 (8.0-12.0) [n = 72]
Heart rate, bpm	85.0 (68.0-100.0) [n = 55]	81.0 (72.0-100.0) [n = 57]
Systolic blood pressure, mm Hg	112.0 (104.0-133.0)	126.5 (111.0-145.0)
Temperature, °C	37.7 (36.8-38.6) [n = 66]	37.8 (36.9-38.6) [n = 66]
Laboratory values at inclusion, median (IQR)[b]		
RT-PCR-positive	72 (94.7)	72 (98.6)
C-reactive protein, mg/L	154.0 (113.0-271.0) [n = 57]	185.0 (119.0-237.0) [n = 53]
Procalcitonin, ng/mL	0.4 (0.2-0.7) [n = 52]	0.4 (0.2-0.8) [n = 46]
Lymphocytes, $\times 10^9$/L	0.9 (0.5-1.4) [n = 65]	0.7 (0.6-1.3) [n = 57]
Lactate, mg/dL	9.9 (8.1-12.6) [n = 73]	9.9 (8.1-14.4) [n = 64]
Arterial pH	7.4 (7.3-7.5) [n = 75]	7.4 (7.3-7.5) [n = 72]
$Paco_2$, mm Hg	39.0 (34.0-47.0)	38.9 (34.0-45.4)
Pao_2:Fio_2	130.0 (96.7-188.0) [n = 75]	133.0 (89.8-174.8) [n = 72]
Respiratory support at inclusion		
Mechanical ventilation	62 (81.6)	59 (80.8)
Noninvasive ventilation, No./total (%)	2/62 (3.2)	2/59 (3.4)
Positive end-expiratory pressure, median (IQR), cm H_2O	10.0 (8.0-12.0)	10.0 (8.0-12.0)
Fio_2, median (IQR)	95.0 (60.0-100.0)	90.0 (60.0-100.0)
High-flow oxygen therapy, No. (%)	10 (13.2)	9 (12.3)
Nonrebreathing mask with a reservoir bag, No. (%)	4 (5.3)	5 (6.8)
Scores, median (IQR)		
Pneumonia severity index[c]	101.0 (82.0-121.0) [n = 43]	102.0 (80.0-120.0) [n = 51]
Simplified Acute Physiology Score II[d]	32.5 (25.0-38.5)	32.0 (27.0-39.0)
Sequential Organ Failure Assessment[e]	6.0 (4.0-8.0) [n = 74]	6.0 (4.0-7.5) [n = 72]
Concomitant therapy, No. (%)		
≥1	44 (57.9)	47 (64.4)
Hydroxychloroquine	11 (14.5)	8 (11.0)
Hydroxychloroquine + azithromycin	23 (30.3)	28 (38.4)
Ritonavir-lopinavir	10 (13.2)	11 (15.1)
Eculizumab	3 (3.9)	2 (2.7)
Remdesivir	2 (2.6)	3 (4.1)
Tocilizumab	1 (1.3)	2 (2.7)

Abbreviations: BMI, body mass index; CAPE COVID, Community-Acquired Pneumonia: Evaluation of Corticosteroids in Coronavirus Disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; Fio_2, fraction of inspired oxygen; IQR, interquartile range; RT-PCR, reverse transcriptase–polymerase chain reaction.

SI conversion factor: To convert lactate values to mmol/L, multiply by 0.111.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Reported values are those designated in the original parent trial. Additional data available at inclusion are reported in eTable 1 in Supplement 3.

[c] Calculated at inclusion. The index[18] classifies pneumonia into 5 classes of increasing severity; the median value observed corresponds to class IV, with a mortality of 9.3% in community-acquired pneumonia (but this score has not been specifically validated in COVID-19).

[d] Calculated during the first 24 hours of intensive care unit (ICU) stay. The score[24] is an overall severity score for ICU patients. For a patient population, the relationship between mortality and score is sinusoidal. The median score observed corresponds to a predicted mortality of 13% and the first and third quartiles to a predicted mortality of 6% and 23%, respectively.

[e] Calculated at inclusion. The assessment[19] evaluates from 1 to 4 for each organ the severity of neurologic, cardiovascular, respiratory, kidney, hematologic, and hepatic dysfunctions. The evolution of the score during hospitalization is a better prognostic parameter than an isolated value. In patients with severe acute respiratory failure, a median score of 6 probably corresponds to moderate impairment of other functions.

Table 2. Treatment Failures, Secondary Outcomes, and Post Hoc Analyses in the CAPE COVID Trial

	No. (%)			
	Hydrocortisone (n = 76)	Placebo (n = 73)	Difference in proportions, % (CI)[a]	*P* value
Primary outcome				
Treatment failure on day 21 (death or persistent dependence of mechanical ventilation or high-flow oxygen therapy)	32 (42.1)	37 (50.7)	−8.6 (−24.9 to 7.7)	.29
Secondary outcomes				
Endotracheal intubation (for patients noninvasively ventilated at inclusion)	8/16 (50.0)	12/16 (75.0)		
Prone position				
No. (%)	36 (47.4)	39 (53.4)	HR, 0.85 (0.55 to 1.32)	.47
No. of sessions per patient, median (IQR)	2.0 (1.0-3.0)	2.0 (2.0-4.0)		
Extracorporeal membrane oxygenation				
No. (%)	2 (2.7)	2 (2.7)		
Inhaled nitric oxide				
No. (%)	5 (6.7)	11 (15.0)		
Duration, median (IQR), d	3.0 (1.0 to 5.0)	2.0 (1.0 to 8.0)		
Nosocomial infections on day 28[b]				
No. (%)	28 (37.7)	30 (41.1)	HR, 0.81 (0.49 to 1.35)	.42
Post hoc outcomes				
Status on day 21 (5-item scale)				
Death[c]	11 (14.7)	20 (27.4)	−12.7 (−25.7 to 0.3)	.057
Mechanical ventilation	17 (22.7)	17 (23.3)		
High-flow oxygen therapy	3 (4.0)	0		
Low-flow oxygen therapy	1 (1.3)	4 (5.5)		
Discharged from ICU[d]	43 (57.3)	32 (43.8)		

Abbreviations: CAPE COVID, Community-Acquired Pneumonia: Evaluation of Corticosteroids in Coronavirus Disease; HR, hazard ratio.

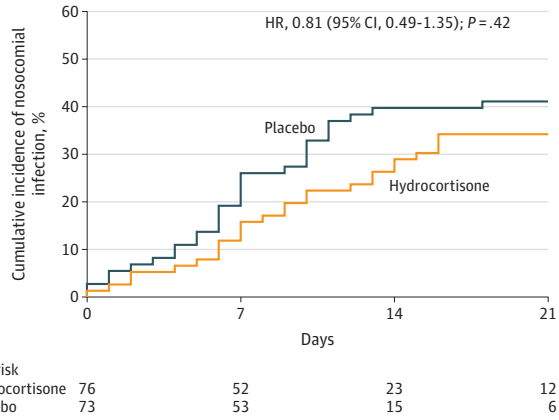
[a] For the primary outcome, the single missing outcome in the hydrocortisone group was presumed to be a treatment failure. The confidence interval is 95.48% for the primary outcome (owing to the sequential design with multiple analyses) and 95% for secondary outcomes. No statistical test was used when it was clear that the number of events was too few and a test was unnecessary. The incidence of patients with at least 1 prone-position session and the incidence of patients with at least 1 nosocomial infection used a competing risk approach, with the patient who withdrew consent censored on the last reported date. For nosocomial infections, data were censored on day 28 as a post hoc analysis.

[b] Nosocomial infections were defined when they were diagnosed by the clinician in charge and antibiotic treatment was prescribed.

[c] Death on day 21 was both a component of status on day 21 (ordinal variable analyzed by a Fisher exact test, *P* = .06) and a categorical variable analyzed by a 2-proportion *z* test.

[d] Patients discharged alive from the ICU were transferred to the floor.

Figure 2. Nosocomial Infections Cumulative Incidence



Cumulative proportion of patients who have had at least 1 nosocomial infection. Nosocomial infections were defined when they were diagnosed by the clinician in charge and antibiotic treatment was prescribed. All patients were observed to death or 28 days (the patient who withdrew consent being censored on the last reported date). HR indicates hazard ratio.

90 infections (40 vs 50). At least 1 episode of ventilator-associated pneumonia occurred in 22 of 75 patients (29.0%) in the hydrocortisone group, vs 20 of 73 patients (27.4%) in the placebo group. The proportions of bacteremia were 6.6% in the hydrocortisone group and 11.0% in the placebo group. **Figure 2** shows the cumulative incidence of nosocomial infections.

Post Hoc Outcomes

The status on day 21 did not significantly differ between both groups (*P* = .06) (Table 2; eFigure 1 in Supplement 3). The proportion of patients still ventilated at day 21 was 17 of 75 (22.7%) in the hydrocortisone group vs 17 of 73 (23.3%) in the placebo group. Additionally, 4 of 75 patients were treated with high-flow oxygen therapy in the hydrocortisone group, vs 0 of 73 in the placebo group. In the hydrocortisone group, 43 of 75 patients (57.3%) were discharged from the ICU on day 21, vs 32 of 73 (43.8%) in the placebo group. The proportion of patients who died did not significantly differ between both groups (11/75 [14.7%] in the hydrocortisone group vs 20/73 [27.4%] in the placebo group; difference of proportion, -12.7% [95% CI, -25.7% to 0.3%]; *P* = .06).

Serious Adverse Events

Apart from deaths, 3 serious adverse events were reported, all in the hydrocortisone group: 1 episode of cerebral vasculitis possibly related to SARS-CoV-2, 1 episode of cardiac arrest related to a pulmonary embolism, and 1 episode of intra-abdominal hemorrhage related to anticoagulant therapy for pulmonary embolism. No serious adverse events were attributed to the study treatment.

Discussion

In this randomized clinical trial that was terminated early, hydrocortisone, compared with placebo, did not significantly reduce the rate of treatment failure, defined as death or persistent dependency on mechanical ventilation or high-flow oxygen therapy, on day 21 among critically ill patients with COVID-19. In addition, hydrocortisone, compared with placebo, did not significantly reduce the proportion of patients receiving mechanical ventilation on day 21.

The primary end point was deemed to be relevant both at the individual level and at the population level, by combining a clinically robust criterion (mortality) with criteria indicative of constraint resources utilization in a pandemic context. This outcome was also consistent with outcomes used in trials of corticosteroids in non-ICU patients with community-acquired pneumonia, namely speeding recovery and shortening hospital stays.[25] The failure rate was initially estimated to be 30% in the control group, with substantial uncertainty at the beginning of the epidemic. The observed rate of the primary outcome in the placebo group was much higher than expected (50.7% cases vs 30.0%).

The trial was terminated prematurely after the press release of the dexamethasone trial. According to those findings, dexamethasone may reduce mortality on day 28 in mechanically ventilated patients and, to a lesser extent, in oxygen-dependent patients.[15] The DSMB therefore recommended stopping the trial after 149 patients of the planned maximum of 290 had been enrolled. This trial is therefore likely underpowered. The observed difference in the post hoc outcome of proportion of deaths at day 21 was not statistically significant; however, the finding was consistent with the reduced mortality observed with dexamethasone in the subgroup of mechanically ventilated patients.[15] A dose of 6 mg of dexamethasone is approximatively equivalent to 160 mg of hydrocortisone, very close to the initial daily dose used in this trial.

In severe community-acquired pneumonia, meta-analysis of the few available randomized trials suggest a reduction in mortality in patients treated with corticosteroids[26]; however, these findings need to be confirmed. In previous outbreaks of coronavirus pneumonia, the lack of high-quality trials precluded any conclusions regarding the use of corticosteroids in severe acute respiratory syndrome (SARS)[27] or Middle East respiratory syndrome (MERS).[28] In these reports, increased rates of adverse effects with corticosteroids, related to the use of high doses, have been observed.[12] Clearance of viral RNA may be decreased by corticosteroids in SARS[29] and MERS,[28] but this effect has not been proven for COVID-19, and its clinical relevance is uncertain. In influenza pneumonia, despite the absence of randomized trials and conflicting results from observational studies, it has been suggested that corticosteroids may increase the risk of death.[12] In patients with COVID-19, the risk of worsening the viral diffusion in the body, worsening the cytotoxic effect of the virus, or both is uncertain. However, the observed numerically lower rate of deaths in hydrocortisone-treated patients in this trial is reassuring in this regard. Most of the patients were included more than 1 week after the onset of their symptoms. It is possible that the peak of viral excretion occurs earlier in the course of COVID-19 and that the deterioration leading to ICU hospitalization is related to the deregulation of the pulmonary inflammatory response. The favorable effect of dexamethasone was more likely in patients treated after 7 days from onset of symptoms compared with those treated earlier.[15]

In this trial, hydrocortisone therapy was not associated with an increase in the rate of secondary infections, a concerning risk with corticosteroids,[30] especially in mechanically ventilated patients with ventilator-associated pneumonia.

Limitations

This study has several limitations. First, the trial was stopped early and lacked power. Second, while this study was embedded within an existing trial, it had not been planned to record certain data relevant to COVID-19, such as the prevalence of hypertension. Third, the COVID-19 pandemic context has not, to date, allowed for the capture and analysis of all the data provided for in the parent protocol. Fourth, diagnosis of nosocomial infections was not adjudicated; however, the double-blind nature of the trial suggests that the comparison of the rate of secondary infections between the 2 groups may still be valid.

Conclusions

In this study of critically ill patients with COVID-19 and acute respiratory failure, low-dose hydrocortisone, compared with placebo, did not significantly reduce treatment failure (defined as death or persistent respiratory support) at day 21. However, the study was stopped early and likely was underpowered to find a statistically and clinically important difference in the primary outcome.

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Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19
The CoDEX Randomized Clinical Trial

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IMPORTANCE Acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19) is associated with substantial mortality and use of health care resources. Dexamethasone use might attenuate lung injury in these patients.

OBJECTIVE To determine whether intravenous dexamethasone increases the number of ventilator-free days among patients with COVID-19–associated ARDS.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, randomized, open-label, clinical trial conducted in 41 intensive care units (ICUs) in Brazil. Patients with COVID-19 and moderate to severe ARDS, according to the Berlin definition, were enrolled from April 17 to June 23, 2020. Final follow-up was completed on July 21, 2020. The trial was stopped early following publication of a related study before reaching the planned sample size of 350 patients.

INTERVENTIONS Twenty mg of dexamethasone intravenously daily for 5 days, 10 mg of dexamethasone daily for 5 days or until ICU discharge, plus standard care (n =151) or standard care alone (n = 148).

MAIN OUTCOMES AND MEASURES The primary outcome was ventilator-free days during the first 28 days, defined as being alive and free from mechanical ventilation. Secondary outcomes were all-cause mortality at 28 days, clinical status of patients at day 15 using a 6-point ordinal scale (ranging from 1, not hospitalized to 6, death), ICU-free days during the first 28 days, mechanical ventilation duration at 28 days, and Sequential Organ Failure Assessment (SOFA) scores (range, 0-24, with higher scores indicating greater organ dysfunction) at 48 hours, 72 hours, and 7 days.

RESULTS A total of 299 patients (mean [SD] age, 61 [14] years; 37% women) were enrolled and all completed follow-up. Patients randomized to the dexamethasone group had a mean 6.6 ventilator-free days (95% CI, 5.0-8.2) during the first 28 days vs 4.0 ventilator-free days (95% CI, 2.9-5.4) in the standard care group (difference, 2.26; 95% CI, 0.2-4.38; $P = .04$). At 7 days, patients in the dexamethasone group had a mean SOFA score of 6.1 (95% CI, 5.5-6.7) vs 7.5 (95% CI, 6.9-8.1) in the standard care group (difference, −1.16; 95% CI, −1.94 to −0.38; $P = .004$). 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, mechanical ventilation duration at 28 days, or the 6-point ordinal scale at 15 days. Thirty-three patients (21.9%) in the dexamethasone group vs 43 (29.1%) in the standard care group experienced secondary infections, 47 (31.1%) vs 42 (28.3%) needed insulin for glucose control, and 5 (3.3%) vs 9 (6.1%) experienced other serious adverse events.

CONCLUSIONS AND RELEVANCE Among patients with COVID-19 and moderate or severe ARDS, use of intravenous dexamethasone plus standard care compared with standard care alone resulted in a statistically significant increase in the number of ventilator-free days (days alive and free of mechanical ventilation) over 28 days.

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Three months after the emergence of the coronavirus disease 2019 (COVID-19)[1] caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the World Health Organization declared it a pandemic.[2] Estimates have suggested that up to 12% of patients hospitalized with COVID-19 have required invasive mechanical ventilation,[3,4] with the majority developing acute respiratory distress syndrome (ARDS).[5] Diffuse alveolar damage with hyaline membranes,[6] hallmarks of ARDS, have been found on pulmonary histological examination of patients with COVID-19. Furthermore, an uncontrolled inflammatory state is frequent with COVID-19[7,8] and may contribute to multiorgan failure in these patients. Corticosteroids might exert an effect in controlling this exacerbated response.[9]

Several trials evaluated the role of corticosteroids for non-COVID-19 ARDS with conflicting results.[10,11] Observational studies of other viral diseases suggested that corticosteroids might increase viral load in patients with SARS-CoV[12] and Middle East respiratory syndrome (MERS).[13] A meta-analysis identified an association between corticosteroids and higher mortality among patients with influenza.[14] Findings from a randomized clinical trial involving patients with COVID-19 indicated that the use of dexamethasone decreased mortality in hospitalized patients requiring supplemental oxygen or mechanical ventilation.[15]

The COVID-19 Dexamethasone (CoDEX) randomized clinical trial was conducted to evaluate the efficacy of intravenous dexamethasone in patients with moderate to severe ARDS due to COVID-19. The hypothesis was that dexamethasone would increase the number of days alive and free from mechanical ventilation during the first 28 days.

Key Points

Question In patients with coronavirus disease 2019 (COVID-19) and moderate or severe acute respiratory distress syndrome (ARDS), does intravenous dexamethasone plus standard care compared with standard care alone increase the number of days alive and free from mechanical ventilation?

Findings In this randomized clinical trial that included 299 patients, the number of days alive and free from mechanical ventilation during the first 28 days was significantly higher among patients treated with dexamethasone plus standard care when compared with standard care alone (6.6 days vs 4.0 days).

Meaning Intravenous dexamethasone plus standard care, compared with standard of care alone, resulted in a statistically significant increase in the number of days alive and free of mechanical ventilation over 28 days.

Methods

Study Design and Oversight

We conducted an investigator-initiated, multicenter, randomized, open-label, clinical trial in 41 intensive care units (ICUs) in Brazil. The trial protocol (Supplement 1) and the statistical analysis plan were submitted for publication before the first interim analysis[16] (Supplement 2). The study was approved at the Brazilian Health Regulatory Agency, the Brazilian National Commission for Research Ethics, and all ethics committees at the participating sites. Written or oral informed consent was obtained before randomization from each patient's legal representative. The trial was overseen by an external and independent data and safety monitoring committee (DSMC).

Patients

Patients were enrolled who were at least 18 years old, had confirmed or suspected COVID-19 infection (eMethods in Supplement 3), and were receiving mechanical ventilation within 48 hours of meeting criteria for moderate to severe ARDS with partial pressure of arterial blood oxygen to fraction of inspired oxygen (Pao_2:FIo_2) ratio of 200 or less. An ARDS diagnosis was made according to the Berlin Definition criteria.[17] Exclusion criteria were pregnancy or active lactation, known history of dexamethasone allergy, corticosteroid use in the past 15 days for nonhospitalized patients, use of corticosteroids during the present hospital stay for more than 1 day, indication for corticosteroid use for other clinical conditions (eg, refractory septic shock), use of immunosuppressive drugs, cytotoxic chemotherapy in the past 21 days, neutropenia due to hematological or solid malignancies with bone marrow invasion, consent refusal, or expected death in the next 24 hours (**Figure 1**). During the study period we refined some of the inclusion and exclusion criteria. Full details are provided in Supplement 3.

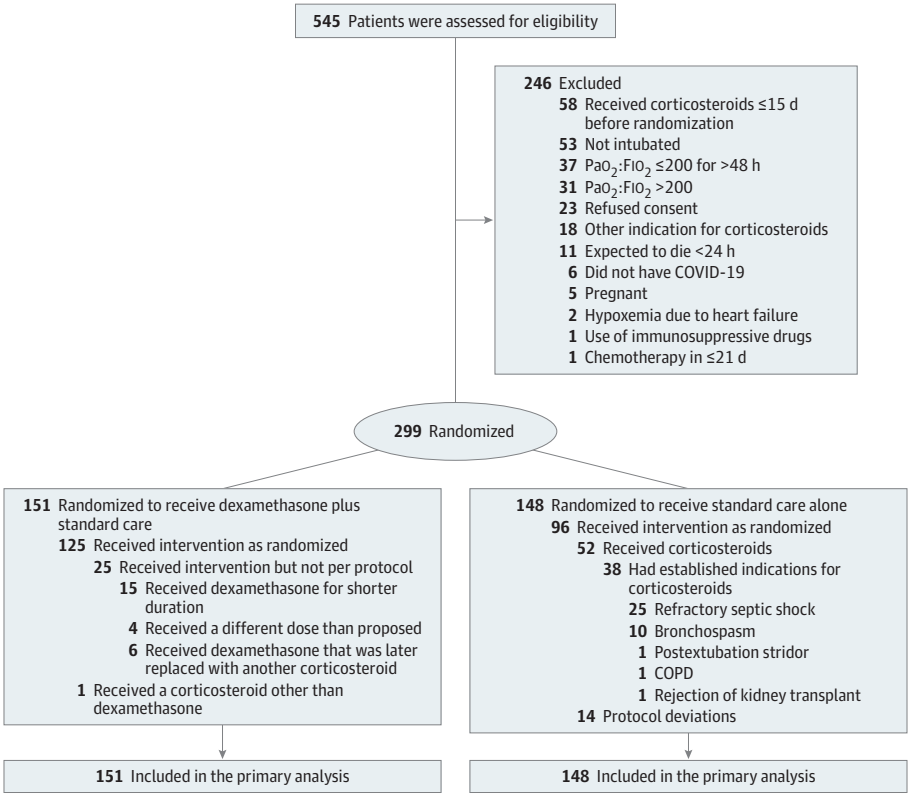
Trial Procedures

Randomization was performed through an online web-based system[18] using computer-generated random numbers and blocks of 2 and 4, unknown to the investigators, and was stratified by center. The group treatment was disclosed to the investigator only after all information regarding patient enrollment was recorded in the online system (eMethods in Supplement 3).

Eligible patients were randomly assigned in a 1:1 ratio to receive dexamethasone 20 mg intravenously once daily for 5 days, followed by 10 mg intravenously once daily for additional 5 days or until ICU discharge, whichever occurred first, plus standard care. Patients in the control group received standard care only. Physicians, patients, and individuals who assessed the outcomes were not blinded for the assigned treatment. Each study center was encouraged to follow the best practice guidelines and their institutional protocol for the care of critically ill patients with COVID-19. All clinical interventions, such as use of antibiotics, ventilatory strategy, laboratory testing, and hemodynamic management were left at the discretion of the ICU team for both groups.

Protocol adherence was assessed daily until day 10. Unjustified corticosteroid use or use for treating ARDS or COVID-19 in the control group was not recommended and considered a protocol deviation. The use of nonstudy corticosteroids was permitted in the control group for usual ICU indications, such as bronchospasm and refractory septic shock.[19] Additionally, any dexamethasone dosage change or early interruption in the intervention group was considered a protocol violation.

Figure 1. Flow of Patients in the Coronavirus Dexamethasone (CoDEX) Trial



Abbreviations: COVID-19, coronavirus disease 2019; Pao_2:FIO_2 partial pressure of arterial oxygen to the fraction of inspired oxygen ratio, COPD, chronic obstructive pulmonary disease.

Clinical and Laboratory Data

Data on demographic characteristics, physiological variables, corticosteroid use before randomization, timing from ARDS diagnosis to randomization, insulin use for hyperglycemia, and other clinical and laboratory data were collected. Use of neuromuscular blocking agents, prone positioning, and extracorporeal membrane oxygenation (ECMO) were collected daily through day 14. Use of mechanical ventilation and other oxygen supportive therapies (high-flow nasal cannula, noninvasive positive pressure ventilation, and use of supplemental oxygen) were collected daily through 28 days. Diagnosis of new infections were reported daily through day 28. Individual patient data on infections were adjudicated by a blinded investigator (eMethods in Supplement 3). Patients were followed up for 28 days after randomization or until hospital discharge, whichever occurred first.

Outcomes

The primary outcome was ventilator-free days during the first 28 days, defined as the number of days alive and free from mechanical ventilation for at least 48 consecutive hours.[20] Patients discharged from the hospital before 28 days were considered alive and free from mechanical ventilation at 28 days. Nonsurvivors at day 28 were considered to have no ventilator-free days. More details on the definitions are provided in the eMethods section of Supplement 3.

Prespecified secondary outcomes were all-cause mortality during 28 days, clinical status of patients at day 15 using a 6-point ordinal scale adapted from the World Health Organization R&D Blueprint expert group[21]—(1) not hospitalized, (2) hospitalized, not requiring supplemental oxygen, (3) hospitalized, requiring supplemental oxygen, (4) hospitalized, requiring noninvasive ventilation or nasal high-flow oxygen therapy, (5) hospitalized, requiring invasive mechanical ventilation or ECMO, and (6) death; ICU-free days during the first 28 days; mechanical ventilation duration at 28 days; and Sequential Organ Failure Assessment (SOFA) scores, which range from 0 to 24, with higher scores indicating greater dysfunction, at 48 hours, 72 hours, and 7 days. For post hoc analyses, we evaluated the components of ventilator-free days during the first 28 days, the cumulative proportions of the 6-point ordinal scale at 15 days, and the outcome of discharge from hospital alive within 28 days. For patients who died, the number of ventilator-free days was 0; for patients who were alive, the ventilator-free days were the days they did not require mechanical ventilation.

Statistical Analysis

No reliable data were available at the trial design to allow for an accurate sample size calculation. Therefore, we used data from a multicenter randomized trial of non–COVID-19 ARDS in Brazil[22] for our sample size calculation. We originally estimated a 2-sided α level of .05 and power of 80% to detect a difference of 3 ventilator-free days between groups; assuming a mean of 8 (SD, 9) ventilator-free days in the control group, 290 patients had to be enrolled. Before the first interim analysis,

without any study data review and after discussing the protocol with the DSMC, the study steering committee decided to increase the sample size to 350 patients based on necessary adjustments regarding the uncertainty about the normality of the distribution of ventilator-free days. Thus, the original sample size was increased by 15% based on the Pitman asymptotic relative efficiency[23] to preserve study power.

Two preplanned interim analyses for efficacy and safety evaluation after 96 and 234 patients with complete follow-up were programmed. The stopping rule for safety was $P < .01$ and for efficacy $P < .001$ (Haybittle-Peto boundary).[24] There was no adjustment in the final threshold for statistical significance for sequential analysis.

To estimate treatment effects on the primary outcome, a generalized linear model was used with 0-1 inflated beta-binomial distribution, with center as random effect and adjusted for age and the Pao_2:FIO_2 ratio at randomization. The effect size was estimated as mean difference and its respective 95% confidence interval.

The all-cause mortality rate at 28 days was analyzed using a mixed Cox model, with centers as the random effects. The treatment effect on the SOFA score at 48 hours, 72 hours, and 7 days after randomization was analyzed by a linear mixed model with patients as random effects adjusted for the baseline SOFA score. For the clinical status of patients, if the proportional odds assumption was met, a mixed ordinal logistic regression was used. All secondary outcomes were adjusted for age and the Pao_2:FIO_2 ratio to increase statistical power and improve the efficiency of the analysis. Further details on model assumptions and model fit are provided in the eMethods section of Supplement 3. Adverse events are expressed as counts and percentages and compared between groups using the χ^2 test.

All patients were included in the primary analysis. There was no loss to follow-up, and data on the primary outcome, mortality within 28 days, clinical status at day 15, ICU-free days at 28 days, and mechanical ventilation duration were available for all patients. Missing values on individual SOFA components were imputed as normal (eMethods in Supplement 3). We assessed the consistency of the primary analysis results through prespecified sensitivity analyses considering the per-protocol population, patients who received corticosteroids vs patients who did not (as-treated population), patients with confirmed COVID-19, and patients with confirmed or probable COVID-19 (eMethods in Supplement 3).

We performed prespecified subgroup analysis on the primary outcome testing interactions for age (<60 and ≥60 years), Pao_2:FIO_2 ratio (≤100 and >100), symptoms duration at randomization (≤7 and >7 days), Simplified Acute Physiology Score III (SAPS III) (<60 and ≥60), position at randomization (prone or supine), and use of vasopressor at randomization (eMethods in Supplement 3).

Patients were analyzed according to their randomization groups, and no adjustments for multiplicity were performed. Thus, the results of secondary outcomes and subgroup analyses should be interpreted as exploratory. A 2-sided P value of less than .05 was considered statistically significant. All analyses were performed using the R software version 4.0.2 (R Core Team).

Early Trial Termination

On June 25, 2020, the DSMC discussed the implications of the results of the dexamethasone group in the RECOVERY (Randomized Evaluation of COVID-19 Therapy) trial,[15] stating that given the study results,[15] it was no longer ethical to continue the trial, which led to the recommendation to stop the trial. This recommendation was accepted by the CoDEX Steering Committee on June 25, 2020 (eMethods in Supplement 3).

Results

Patients

From April 17 to June 23, 2020, 299 patients were randomized. Of the enrolled patients, 151 were randomly assigned to receive dexamethasone and 148 to the control group (Figure 1).

Baseline characteristics were well balanced between groups (**Table 1**; eTable 1 in Supplement 3), including severity of ARDS and the use of rescue therapies at randomization. Remdesivir was not available in Brazil during the trial period. Only 1 patient received lopinavir-ritonavir treatment. Other therapeutic strategies such as tocilizumab and convalescent plasma were limited and not widely available.

Interventions

Only 1 patient in the intervention group did not receive any dexamethasone. The rate of dexamethasone use within 10 days was 94.8 per 100 patient-days (eTable 2 in Supplement 3). The median duration of dexamethasone treatment was 10 days (interquartile range [IQR], 6-10 days). In the standard care group, 52 patients (35.1%) received at least 1 dose of corticosteroids, of whom 38 (73.1%) had other established clinical indications for corticosteroid use. The use of corticosteroids in 14 patients (9.4%) was considered a protocol deviation, and the rate of corticosteroid use within 10 days was 16.5 per 100 patient-days (eTable 3 in Supplement 3).

Primary Outcome

The mean number of days alive and free from mechanical ventilation during the first 28 days was significantly higher in the dexamethasone group than in the standard care group (6.6; 95% CI, 5.0-8.2 days vs 4.0; 95% CI, 2.9-5.4 days; difference, 2.26; 95% CI, 0.2-4.38; $P = .04$) (**Table 2**; eFigure 1 in Supplement 3). The cumulative frequency of ventilator-free days according to study group is shown in **Figure 2**.

Secondary Outcomes and Adverse Events

There was no significant difference in all-cause mortality at 28 days (56.3% in the dexamethasone group vs 61.5% the standard care group; hazard ratio, 0.97; 95% CI, 0.72 to 1.31; $P = .85$), in the 6-point ordinal scale at day 15 (median, 5; IQR, 3-6 for the dexamethasone group vs median, 5; IQR, 5-6 for standard care group; odds ratio [OR], 0.66; 95% CI, 0.39 to 1.13; $P = .07$), ICU-free days at 28 days (mean, 2.1; 95% CI, 1.0 to 4.5 days for the dexamethasone group vs mean, 2.0; 95% CI, 0.8 to 4.2 days for the standard care group; difference, 0.28; 95% CI, −0.49 to 1.02; $P = .50$), and mechanical ventilation duration (12.5; 95% CI, 11.2 to 13.8 days for the dexamethasone group vs 13.9, 95%

Table 1. Baseline Characteristics[a]

Characteristic	No. (%) Dexamethasone (n = 151)	Control (n = 148)
Age, mean (SD), y	60.1 (15.8)	62.7 (13.1)
Sex		
Women	61 (40.4)	51 (34.5)
Men	90 (59.6)	97 (65.6)
SAPS III[b]	69.4 (12.6)	71.1 (12.6)
SOFA, median (IQR)[c]	9 (7-10.5)	8 (7-11)
Time since symptom onset, median (IQR), d	9 (7-11)	10 (6-12)
Mechanical ventilation prior to randomization, median (IQR), d	1 (0-2)	1 (0-1)
COVID-19 status[d]		
Positive	144 (95.4)	142 (95.9)
Probable	7 (4.6)	5 (3.4)
Negative	0	1 (0.7)
Comorbidities and risk factors		
Hypertension	91 (60.3)	107 (72.3)
Diabetes	57 (37.8)	69 (46.6)
Obesity	46 (30.5)	35 (23.7)
Heart failure	11 (7.3)	12 (8.1)
Chronic kidney failure	7 (4.6)	9 (6.1)
Current smoker	6 (4.0)	7 (4.7)
Corticosteroids before randomization	7 (4.6)	3 (2)
Moderate or severe ARDS prior to randomization, h		
≤24	136 (90.1)	138 (93.9)
>24-≤48	15 (9.9)	9 (6.1)
Vasopressor use	99 (65.6)	101 (68.2)
Intravenous sedation	150 (99.3)	147 (100)
RASS[e]	−4.8 (0.8)	−4.6 (1.1)
Neuromuscular blockade use[f]	87 (57.6)	94 (63.5)
Prone position	33 (21.8)	33 (22)
Additional medication		
Hydroxychloroquine	36 (23.8)	28 (18.9)
Azithromycin	104 (68.9)	109 (73.6)
Other antibiotics	133 (88.1)	128 (86.5)
Oseltamivir	44 (29.1)	52 (35.1)
Respiratory variables, mean (SD)		
Tidal volume, mL/kg of predicted body weight	6.5 (1.1)	6.5 (1.4)
Minute ventilation, L/min	9.4 (2.3)	9.8 (2.7)
Inspiratory plateau pressure, cm H_2O	23.8 (4.8)	23.9 (5)
PEEP, cm H_2O	11.6 (2.9)	11.8 (2.7)
Driving pressure, cm H_2O	12.5 (3.1)	12.6 (3.6)
Pao_2, mm Hg	89 (29)	88.5 (27.1)
Pao_2:Fio_2	131.1 (46.2)	132.6 (45.7)
Laboratory variables[g]		
Serum creatinine, mg/dL, median (IQR)	1.3 (0.9-2.1)	1.3 (1-2.3)
Hemoglobin, mean (SD), g/dL	12.3 (2.3)	12.5 (2.0)
White blood cell count, median (IQR), $\times 10^9$/L	9.6 (7.7-14.0)	10.4 (7.2-14.6)
Lymphocyte count, median (IQR), $\times 10^9$/L	0.84 (0.62-1.27)	0.82 (0.58-1.21)
Platelets count, mean (SD), $\times 10^9$/L	246.2 (98.3)	247.5 (113)

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; Fio_2, fraction of inspired oxygen; IQR, interquartile range; Pao_2, partial pressure of arterial oxygen; Pao_2:Fio_2, partial pressure of arterial oxygen to the fraction of inspired oxygen ratio; PEEP, positive end expiratory pressure; RASS, Richmond Agitation–Sedation Scale; SAPS III, Simplified Acute Physiology Score III; SOFA, Sequential Organ Failure Assessment.

SI conversion factor: To convert creatinine from mg/dL to μmol/L multiply by 88.4.

[a] Continuous variables are presented as mean (SD) unless otherwise indicated. The Pao_2 is from the arterial blood gas immediately prior to randomization.

[b] The Simplified Acute Physiology Score III ranges from 0 to 217, with higher scores indicating a higher risk of death. It is calculated from 20 variables at admission of the patient. A score of 70 corresponds to a mortality risk of 70.9% in South America and 46.6% in North America.

[c] Sequential Organ Failure Assessment scores were measured in 6 organ systems (cardiovascular, hematologic, gastrointestinal, renal, pulmonary and neurologic), with each organ scored from 0 to 4, resulting in an aggregated score that ranges from 0 to 24, with higher scores indicating greater dysfunction. An initial SOFA score up to 9 predicts a mortality risk of less than 33%. An unchanged or increasing score in the first 48 hours predicts a mortality rate of 60% when the initial score is 8 to 11.

[d] Patients with initial negative COVID-19 test result had the diagnosis probability evaluated by a blinded committee (eMethods in Supplement 3)

[e] Richmond Agitation–Sedation Scale, which ranges from −5 to 4, with more negative scores indicating deeper sedation and more positive scores indicating increasing agitation, and with 0 representing the appearance of calm and normal alertness. It was calculated at the time of randomization.

[f] Neuromuscular blockade was defined as continuous infusion of neuromuscular blocking agents at the time of randomization.

[g] From the day of randomization.

CI, 12.7 to 15.1 days for the standard care group; difference, −1.54; 95% CI, −3.24 to −0.12; P = .11). The mean SOFA score at 7 days was significantly lower in the treatment group (6.1; 95% CI, 5.5 to 6.7 for dexamethasone vs 7.5; 95% CI, 6.9 to 8.1 for standard care; difference, −1.16; 95% CI, −1.94 to −0.38; P = .004) (Table 2).

Both groups had a comparable need for insulin use for hyperglycemia: 47 patients (31.1%) in the dexamethasone group

Table 2. Study Outcomes

Outcomes	Mean (95% CI)		Effect statistic	Between-group effect			
				Adjusted[a]		Unadjusted	
	Dexamethasone (n = 151)	Standard care (n = 148)		Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
Primary outcome							
Days alive and ventilator free at 28 d							
Mean (95% CI)	6.6 (5.0 to 8.2)	4.0 (2.9 to 5.4)	MD	2.26 (0.2 to 4.38)[b]	.04	2.55 (0.46 to 4.6)	.02
Median (IQR)	0 (0 to 17)	0 (0 to 3)					
Secondary outcomes							
6-Point ordinal scale at day 15, median (IQR)[c]	5 (3 to 6)	5 (5 to 6)	OR	0.66 (0.43 to 1.03)	.07	0.62 (0.41 to 0.94)	.03
28-Day results							
All-cause mortality No. (%)	85 (56.3)	91 (61.5)	HR	0.97 (0.72 to 1.31)	.85	0.86 (0.64 to 1.15)	.31
ICU free, d	2.1 (1.0 to 4.5)	2.0 (0.8 to 4.2)	MD	0.28 (−0.49 to 1.02)	.50	0.14 (−0.92 to 1.27)	.78
MV duration, d	12.5 (11.2 to 13.8)	13.9 (12.7 to 15.1)	MD	−1.54 (−3.24 to 0.12)	.11	−1.46 (−3.10 to 0.57)	.18
SOFA score[d]							
48 h	8.1 (7.6 to 8.6)	8.4 (7.8 to 8.9)	MD	−0.11 (−0.86 to 0.63)	.76	−0.24 (−1 to 0.51)	.53
No. of patients	151	147					
72 h	7.7 (7.2 to 8.3)	8.3 (7.8 to 8.9)	MD	−0.38 (−1.13 to 0.37)	.32	−0.6 (−1.37 to 0.16)	.12
No. of patients	145	144					
7 d	6.1 (5.5 to 6.7)	7.5 (6.9 to 8.1)	MD	−1.16 (−1.94 to −0.38)	.004	−1.38 (−2.21 to −0.55)	.001
No. of patients	127	120					

Abbreviations: ICU, intensive care unit; HR, hazard ratio; IQR interquartile range, MD, mean difference; MV, mechanical ventilation; OR, odds ratio; SOFA, Sequential Organ Failure Assessment.

[a] All models are adjusted for age and baseline at Pao_2:FIO_2 ratio with random intercept by site.

[b] Average marginal effect from generalized additive model with 0-inflated beta-binomial distribution adjusted for age and baseline Pao_2:FIO_2 ratio with random intercept by site. For the primary model coefficients see eTable 5 in Supplement 2.

[c] See the Methods section for the definitions of the 6-point ordinal scale. The distribution of values among the categories in the dexamethasone and control groups was 6 (35.8% vs 43.9%), 5 (31.8% vs 36.5%), 4 (4.6% vs 2.7%), 3 (16.6% vs 11.5%), 2 (0% vs 0%), and 1 (11.3% vs 5.4%).

[d] Measured in 6 organ systems (cardiovascular, hematologic, gastrointestinal, renal, pulmonary and neurologic), with each organ scored from 0 to 4, resulting in an aggregated score that ranges from 0 to 24, with higher scores indicating greater dysfunction. An initial SOFA score up to 9 predicts a mortality risk of less than 33%. An unchanged or increasing score in the first 48 hours predicts a mortality rate of 60% when the initial score is 8 to 11. Missing values on individual SOFA components were imputed as normal (eMethods in Supplement 2).

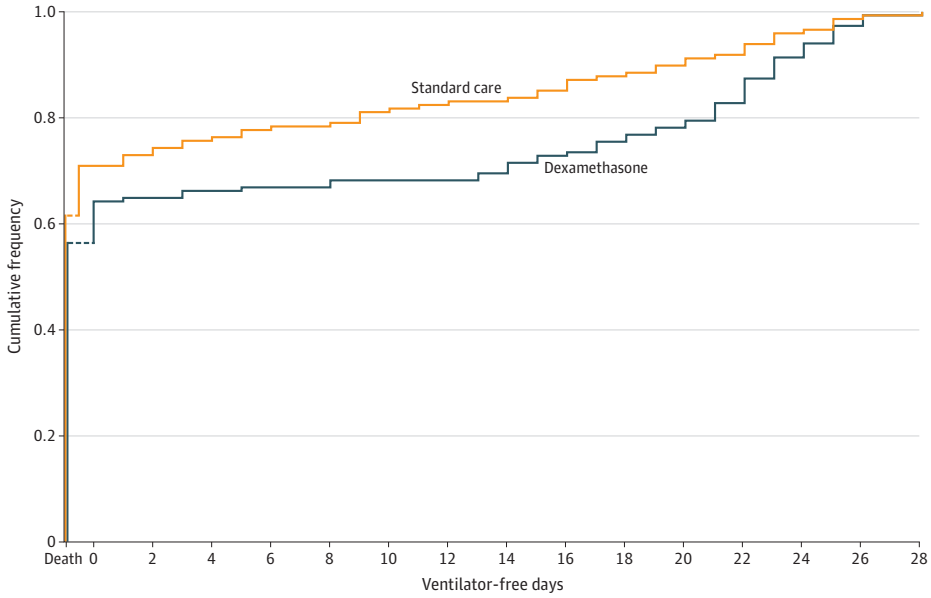
vs 42 (28.4%) in the standard care group. The number of new diagnoses of infection until day 28 was 33 (21.9%) vs 43 (29.1%). Twelve patients (7.9%) in the dexamethasone group had bacteremia vs 14 (9.5%) in the standard care group. Five patients (3.3%) had serious adverse events vs 9 (6.1%) (**Table 3**; eTable 4 in Supplement 3).

Subgroup and Exploratory Analyses

In subgroup analyses, tests for interaction were not statistically significant for subgroups defined by age (P = .21), Pao_2:FIO_2 ratio (P = .73), SAPS III (P = .75), time since symptom onset (P = .12), position at randomization (P = .89), and vasopressor use at randomization (P = .81) (eFigure 2 in Supplement 3).

The post hoc analyses showed no significant difference of the intervention in the components of the primary outcome or in the outcome of discharged alive within 28 days (eTable 6 in Supplement 3). Patients in the dexamethasone group had significantly lower cumulative probability of having died or being mechanically ventilated at day 15 (categories 5-6 on the 6-point scale) than the standard care group (67.5% vs 80.4%; OR, 0.46; 95% CI, 0.26 to 0.81; P = .01) (eTable 6 and eFigure 3 in Supplement 3). In the sensitivity analyses for the primary outcome of ventilator-free days, the treatment effect was not significantly different in the as-treated analysis. The mean number of ventilator-free days was 5.8 (95% CI, 4.6 to 7.3) among 203 patients in the dexamethasone group vs 4.1 (95% CI, 2.6 to 5.5) among 96 patients in the standard care group, for a mean difference of 2.38 (95% CI, −0.6 to 3.32; P = .16). In the per-protocol analysis, the mean number of ventilator-free days among dexamethasone group was 6.4 (95% CI, 5.1 to 8.1) among 125 patients vs 4.1 (95% CI, 2.6 to 5.5) among 96 patients in the standard care group for a difference of 2.36 (95% CI, −0.15 to 4.56; P = .06). The main results remained statistically significant among patients with confirmed COVID-19 in the dexamethasone group, which had a mean number of ventilator-free days of 6.8 (95% CI, 5.4 to 8.4) among 144 patients vs 3.9 (95% CI, 2.7 to 5.1) among 142 patients in the standard care group for a difference of 2.7 (95% CI, 0.8 to 4.74; P = .01). Among the patients with confirmed or probable COVID-19, the mean number of ventilator-free days was 6.6 (95% CI, 5.3 to 8.2) among 151 patients vs 4.1 (95% CI, 2.9 to 5.2) among 147 patients for a difference of 2.38 (95% CI, 0.48 to 4.33; P = .02) (eTable 7 in Supplement 3).

Figure 2. Ventilator-Free Days at 28 Days



The dashed lines represent patients who died (assigned 0 ventilator-free days), and solid lines show the cumulative frequency of patients who were receiving mechanical ventilation all 28 days (at the 0 ventilator-free days tick mark) and then the cumulative frequency of patients who no longer required the ventilator for an increasing number of days.

Table 3. Adverse Events

	No. (%) of patients		
	Dexamethasone (n = 151)	Standard care (n = 148)	Absolute difference (95% CI)
Serious adverse events[a]	5 (3.3)	9 (6.1)	2.8 (−2.7 to 8.2)
New diagnosis of infection until day 28[b]	33 (21.9)	43 (29.1)	7.2 (−3.3 to 17.7)
Ventilator-associated pneumonia	19 (12.6)	29 (19.6)	7.0 (−2.0 to 16.0)
Catheter-related bloodstream infection	10 (6.6)	8 (5.4)	−1.2 (−7.3 to 4.8)
Catheter-associated urinary tract infections	1 (0.7)	0	
Other	6 (4)	7 (4.7)	0.7 (−2.5 to 4.2)
Bacteremia[c]	12 (7.9)	14 (9.5)	1.5 (−5.5 to 8.6)
Insulin use for hyperglycemia[d]	47 (31.1)	42 (28.4)	−2.7 (−13.8 to 8.3)

[a] Adverse events in the study groups. In the dexamethason group, 1 event occurred for each of the following outcomes: acute myocardial infarction, deep vein thrombosis, gastrointestinal perforation, unspecified hyperglycemia, and pneumothorax. Except for 2 myocardial infarctions in the standard care group, 1 event occurred for the following outcomes: bronchospasm, cardiogenic shock, deep vein thrombosis, diabetic ketoacidosis, unspecified hyperglycemia, ischemic hepatitis, nephropathy in transplanted kidney, pneumothorax, and pulmonary embolism.

[b] All investigator-reported infections were adjudicated by an infectious disease specialist using unidentified patients records, microbiological data, and radiological images. Seven patients had 2 episodes each.

[c] Comprises all bloodstream infections plus other infections with bacteremia.

[d] Data on insulin use for hyperglycemia were collected daily during ICU stay until day 14.

Discussion

In this randomized clinical trial involving 299 adults with moderate or severe ARDS due to COVID-19, dexamethasone plus standard care compared with standard care alone significantly increased the number of days alive and free of mechanical ventilation during the first 28 days. Dexamethasone was not associated with increased risk of adverse events in this population of critically ill COVID-19 patients.[15]

This trial included only patients with COVID-19 and moderate or severe ARDS and provided laboratory, physiological, and adverse events data on the use of corticosteroids in this population. The ventilator-free days criterion was chosen as the primary outcome because it comprises both mortality and ventilation duration in surviving patients. The number of days alive and free from mechanical ventilation at 28 days was significantly lower than reported in other trials of non–COVID-19 ARDS,[10,11,25] but consistent with COVID-19 ARDS studies, confirming the disease severity.[26] The difference between groups of 2.26 days was lower than the effect size of 3 days used in the sample size calculation. This reduction is relevant in the context of a pandemic, in which an inexpensive, safe, and widely available intervention like dexamethasone increases even modestly the number of ventilator-free days and may reduce the risk of ventilatory complications, ICU length of stay, and burden to the health care system.

Mortality rates were high and not significantly different between groups, in contrast with the RECOVERY trial of dexamethasone in patients hospitalized for COVID-19[15] and a trial

of dexamethasone in patients with non-COVID-19 ARDS.[11] The high mortality rate might be explained by several factors. The patients had a high risk of death as shown by the low mean Pao_2:FIO_2 ratio and mean SAPS III score of 70, which represents a mortality risk of 70.9% in South America.[27,28] In a previous randomized clinical trial, moderate to severe ARDS not caused by COVID-19 had an elevated mortality rate in Brazil of 52%,[22] and recent data collected by Brazilian Association of Critical Care demonstrated mortality rates of 66% to 70% for ventilated patients with COVID-19 in Brazilian ICUs.[29] This may be explained by the pandemic and its burden to the health care system, especially in a country with limited resources like Brazil. However, even in high-income countries the mortality rate in ventilated patients with COVID-19 might range from 54% to 88%.[30-32] This mortality rate may be similar to that of other low and middle-income countries and is important to consider when translating the scientific evidence to clinical practice. In this sense, the results of this trial expand those of the RECOVERY trial[15] by showing that corticosteroids were effective even when the baseline mortality rate was high.

The dexamethasone dose was chosen based on a previous[11] trial showing the benefit of dexamethasone to patients with non–COVID-19 ARDS. Previous data suggest that high doses of corticosteroids (the equivalent of 30 mg/d of dexamethasone) in viral pneumonia may be associated with unfavorable outcomes.[33] However, there are no currently available data from patients with COVID-19 to determine if higher doses are harmful. In the present study, the number of adverse events, new infections, and the use of insulin were comparable in both groups, in line with previous studies that did not demonstrate an augmented risk of adverse events with corticosteroids in non-COVID-19 ARDS.[10,11,19]

This trial has several strengths. Bias was controlled by ensuring allocation concealment, all patients were analyzed according to their randomization group, and follow-up was complete. Also, adverse events data regarding corticosteroid use among patients with COVID-19 were provided, along with detailed data on ventilatory parameters, ARDS treatment, and laboratory and physiological variables.

Limitations

This study has several limitations. First, it was an open-label trial due to time constraints of producing placebo in a pandemic scenario with an urgent need for reliable and randomized data. Second, 35% of the patients in the control group received corticosteroids during the study period, possibly related to the open-label design, the disease severity of the patients, and other diverse indications for corticosteroid use in critical care.[19] However, the use of corticosteroids in the control group would have biased the results toward the null, and the study identified a benefit of the intervention on the primary outcome. Third, the open-label design and investigator-reported data on adverse events and infections may have led to bias in the description of these events. Fourth, the trial was underpowered for important secondary outcomes like mortality and the study was interrupted before the original sample size was obtained due to external evidence of benefit, and the obtained sample size was limited to demonstrate benefits in secondary outcomes.

Conclusions

In patients with COVID-19 and moderate or severe ARDS, use of intravenous dexamethasone plus standard care, compared with standard care alone, resulted in a statistically significant increase increase in the number of ventilator-free days (days alive and free of mechanical ventilation) over 28 days.

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