JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02735707

JAMA. 2020;324(13):1317-1329. doi:10.1001/jama.2020.17022
Published online September 2, 2020. Corrected on November 6, 2020.

Visual Abstract

Editorial page 1292

Related articles pages 1298, 1307, and 1330

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.

Corresponding Author: Derek C. Angus, MD, MPH, Department of Critical Care Medicine, University of Pittsburgh, 3550 Terrace St, 614 Scaife Hall, Pittsburgh, PA 15261 (angusdc@upmc.edu).

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Karen Parry-Billings on 04/13/2021

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

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Karen Parry-Billings on 04/13/2021

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

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Karen Parry-Billings on 04/13/2021

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).

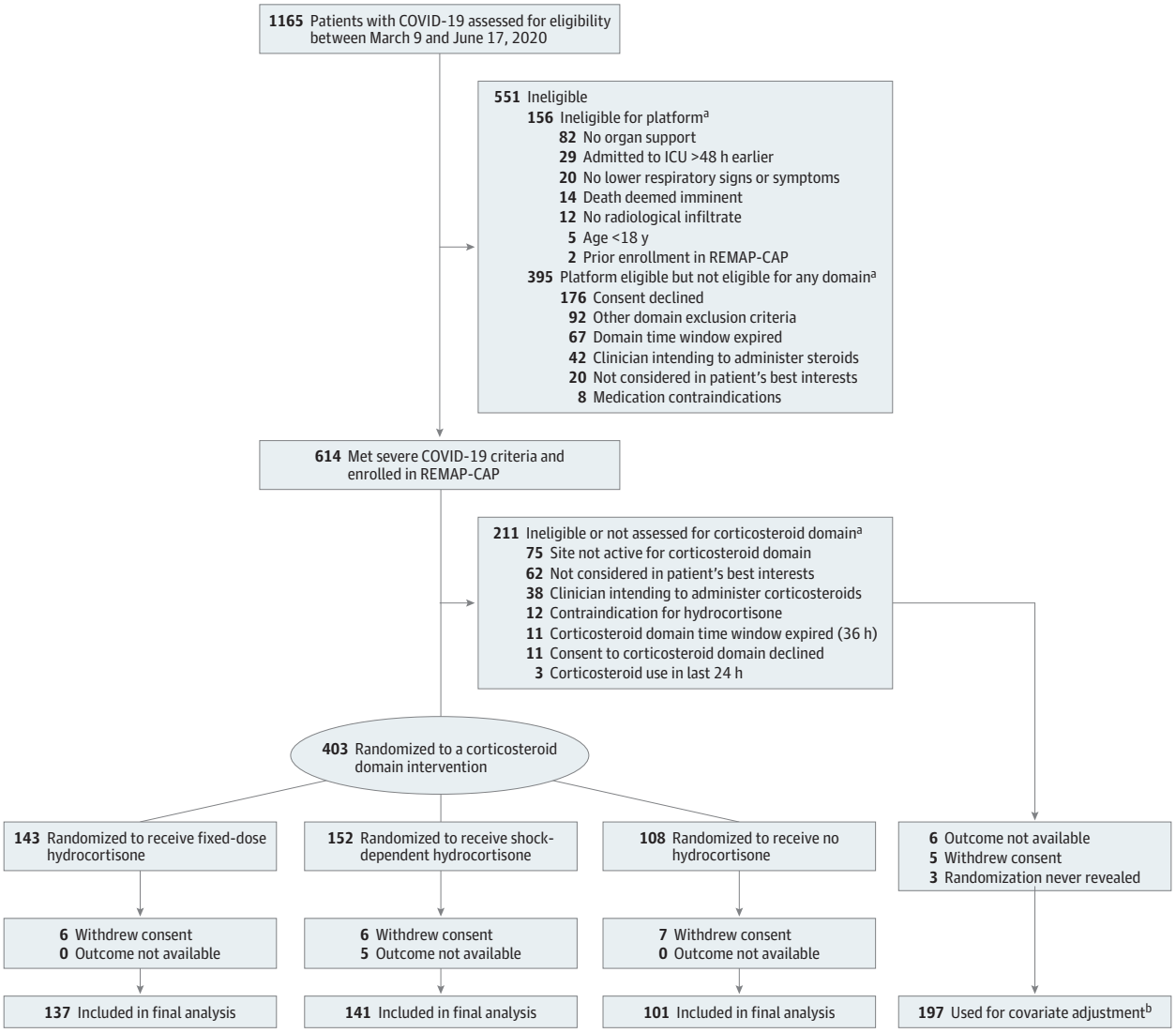
Analysis of the primary outcome was then repeated in a second model using only data from those patients enrolled in the corticosteroid domain with no adjustment for assignment to interventions in other domains. Although using less information, this analysis is more typical for an RCT. Further secondary 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

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Karen Parry-Billings on 04/13/2021

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

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Karen Parry-Billings on 04/13/2021

(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

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Karen Parry-Billings on 04/13/2021

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)

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Karen Parry-Billings on 04/13/2021

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]			
Pa_{O_2}/F_{IO_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; F_{IO_2}, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; Pa_{O_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

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Karen Parry-Billings on 04/13/2021

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	

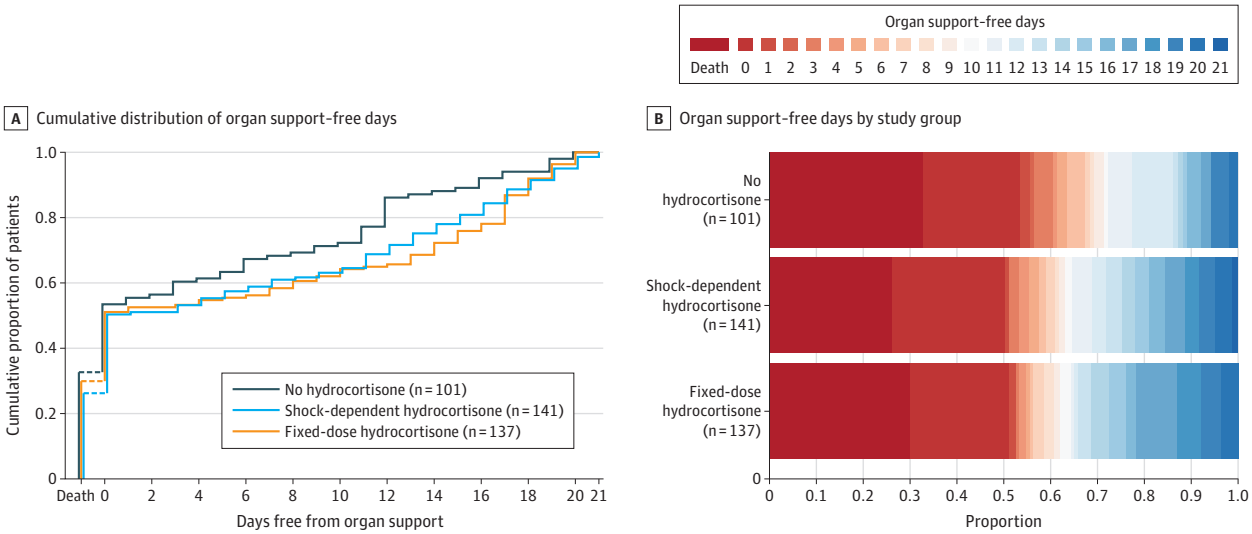
Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; CrI, credible interval.

[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

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Karen Parry-Billings on 04/13/2021

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).

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Karen Parry-Billings on 04/13/2021

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.

ARTICLE INFORMATION

Accepted for Publication: August 21, 2020.

Published Online: September 2, 2020. doi:10.1001/jama.2020.17022

Correction: This article was corrected on November 6, 2020, to fix the names of some listed group members and update site information in eAppendix 5 in Supplement 2.

Authors/Writing Committee for REMAP-CAP: Derek C. Angus, MD, MPH; Lennie Derde, MD; Farah Al-Beidh, PhD; Djillali Annane, MD, PhD; Yaseen Arabi, MD; Abigail Beane, MSc; Wilma van Bentum-Puijk, MS; Lindsay Berry, PhD; Zahra Bhimani, MPH, PMP; Marc Bonten, MD; Charlotte Bradbury, MD, PhD; Frank Brunkhorst, MD; Meredith Buxton, PhD; Adrian Buzgau, MSc; Allen C. Cheng, MD; Menno de Jong, MD; Michelle Detry, PhD; Lise Estcourt, MD; Mark Fitzgerald, PhD; Herman Goossens, MD; Cameron Green, MSc; Rashan Haniffa, MD; Alisa M. Higgins, PhD; Christopher Horvat, MD, MHA; Sebastiaan J. Hullegie, MD; Peter Kruger, MD; Francois Lamontagne, MD; Patrick R. Lawler, MD; Kelsey Linstrum, MS; Edward Litton, MD; Elizabeth Lorenzi, PhD; John Marshall, MD; Daniel McAuley, MD; Anna McGlothin, PhD; Shay McGuinness, MD; Bryan McVerry, MD; Stephanie Montgomery, MS; Paul Mouncey, MSc; Srinivas Murthy, MD; Alistair Nichol, MD; Rachael Parke, RN, PhD; Jane Parker, RN; Kathryn Rowan, PhD; Ashish Sanil, PhD; Marlene Santos, MSc; Christina Saunders, PhD; Christopher Seymour, MD, MSc; Anne Turner, RN, MPH; Frank van de Veerdonk, MD; Balasubramanian Venkatesh, MD; Ryan Zarychanski, MD; Scott Berry, PhD; Roger J. Lewis, MD, PhD; Colin McArthur, MD; Steven A. Webb, MD, PhD; Anthony C. Gordon, MD.

Affiliations of Authors/Writing Committee for REMAP-CAP: The Clinical Research Investigation and Systems Modeling of Acute Illness (CRISMA) Center, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (Angus, Horvat, Linstrum, Montgomery, Seymour); The UPMC Health System Office of Healthcare Innovation, Pittsburgh, Pennsylvania (Angus, Horvat, Montgomery, Seymour); Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands (Derde, van Bentum-Puijk, Bonten, Hullegie); Intensive Care Center, University Medical Center Utrecht, Utrecht, the Netherlands (Derde); Division of Anaesthetics, Pain Medicine and Intensive Care Medicine, Department of Surgery and Cancer, Imperial College London and Imperial College Healthcare NHS Trust, London, United Kingdom (Al-Beidh, Gordon); Intensive Care Unit, Raymond Poincaré Hospital (AP-HP), Paris, France (Annane); Simone Veil School of Medicine, University of Versailles, Versailles, France (Annane); University Paris Saclay, Garches, France (Annane); Intensive Care Department, College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, King Abdulaziz Medical City, Riyadh, Saudi Arabia (Arabi); Nuffield Department of Clinical Medicine, University of Oxford, Oxford, United Kingdom (Beane); Berry Consultants LLC, Austin, Texas (L. Berry, Detry, Fitzgerald, Lorenzi, McGlothin, Sanil, Saunders, S. Berry, Lewis); Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Ontario, Canada (Bhimani, Marshall, Santos); Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, the Netherlands (Bonten); Bristol Royal Informatory, Bristol, United Kingdom (Bradbury); University of Bristol, Bristol, United Kingdom (Bradbury); Center for Clinical Studies and Center for Sepsis Control and Care (CSCC), Department of Anesthesiology and Intensive Care Medicine, Jena University Hospital, Jena, Germany (Brunkhorst); Global Coalition for Adaptive Research, San Francisco, California (Buxton); Helix, Monash University, Melbourne, Victoria, Australia (Buzgau); Infection Prevention and Healthcare Epidemiology Unit, Alfred Health, Melbourne, Victoria, Australia (Cheng); Australian and New Zealand Intensive Care Research Centre, School of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia (Cheng, Green, Higgins, McGuinness, Nichol, Parker, Webb); Department of Medical Microbiology, Amsterdam University Medical Center, University of Amsterdam, the Netherlands (de Jong); Department of Microbiology, Antwerp University Hospital, Antwerp, Belgium (Goossens); NHS Blood and Transplant, Bristol, United Kingdom (Estcourt); Transfusion Medicine, Medical Sciences Division, University of Oxford, Oxford, United Kingdom (Estcourt); Network for Improving Critical Care Systems and Training, Colombo, Sri Lanka (Haniffa); Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand (Haniffa); Intensive Care Unit, Princess Alexandra Hospital, Brisbane, Queensland, Australia (Kruger); Université de Sherbrooke, Sherbrooke, Quebec, Canada (Lamontagne); Cardiac Intensive Care Unit, Peter Munk Cardiac Centre, University Health Network, Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada (Lawler); School of Medicine and Pharmacology, University of Western Australia, Crawley, Western Australia, Australia (Litton, Webb); Interdepartmental Division of Critical Care, University of Toronto, Toronto, Ontario, Canada (Marshall); Centre for Experimental Medicine, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, United Kingdom (McAuley); Cardiothoracic and Vascular Intensive Care Unit, Auckland City Hospital, Auckland, New Zealand (McGuinness, Parke); The Health Research Council of New Zealand, Wellington, New Zealand (McGuinness, Parke); Medical Research Institute of New Zealand, Wellington, New Zealand (McGuinness, Parke, Turner, McArthur); Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (McVerry); Clinical Trials Unit, Intensive Care National Audit & Research Centre (ICNARC), London, United Kingdom (Mouncey, Rowan); University of British Columbia School of Medicine, Vancouver, Canada (Murthy); Department of Anesthesia and Intensive Care, St Vincent's University Hospital, Dublin, Ireland (Nichol); School of Medicine and Medical Sciences, University College Dublin, Dublin, Ireland (Nichol); Department of Intensive Care, Alfred Health, Melbourne, Victoria, Australia (Nichol); School of Nursing, University of Auckland, Auckland, New Zealand (Parke); Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, the Netherlands (van de Veerdonk); Southside Clinical Unit, Princess Alexandra Hospital, Brisbane, Queensland, Australia (Venkatesh); The George Institute for Global Health, Sydney, Australia (Venkatesh); Department of Medicine, Critical Care and Hematology/Medical Oncology, University of Manitoba, Winnipeg, Manitoba, Canada (Zarychanski); Department of Emergency Medicine, Harbor-UCLA Medical Center, Torrance, California (Lewis); Department of Emergency Medicine, David Geffen School of

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Karen Parry-Billings on 04/13/2021

Medicine at University of California, Los Angeles (Lewis); Department of Critical Care Medicine, Auckland City Hospital, Auckland, New Zealand (McArthur); St John of God Hospital, Subiaco, Western Australia, Australia (Webb).

Author Contributions: Dr Angus had full access to all corticosteroid domain data and all baseline data in the study; Dr Lewis had full access to all data required for the primary analyses. Together, Drs Angus and Lewis take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Angus, S. Berry, Bonten, Cheng, de Jong, Derde, Fitzgerald, Goossens, Gordon, Green, Horvat, Kruger, Lawler, Lewis, Litton, Marshall, McArthur, McGuinness, Montgomery, Murthy, Nichol, Parke, Parker, Rowan, Seymour, Venkatesh, Webb.
Acquisition, analysis, or interpretation of data: Angus, Al-Beidh, Annane, Arabi, Bentum-Puijk, Beane, L. Berry, S. Berry, Mouncey, Bhimani, Bonten, Bradbury, Brunkhorst, Buxton, Buzgau, Cheng, Derde, Detry, Estcourt, Fitzgerald, Gordon, Green, Haniffa, Higgins, Horvat, Hullegie, Kruger, Lamontagne, Lewis, Linstrum, Lorenzi, Marshall, McArthur, McAuley, McGlothlin, McGuinness, McVerry, Murthy, Nichol, Parker, Rowan, Sanil, Santos, Saunders, Seymour, Turner, van de Veerdonk, Webb, Zarychanski.
Drafting of the manuscript: Angus, S. Berry, Gordon, Horvat, Marshall, McArthur, Murthy, Santos.
Critical revision of the manuscript for important intellectual content: Angus, Al-Beidh, Annane, Arabi, Bentum-Puijk, Beane, L. Berry, S. Berry, Mouncey, Bhimani, Bonten, Bradbury, Brunkhorst, Buxton, Buzgau, Cheng, de Jong, Derde, Detry, Estcourt, Fitzgerald, Goossens, Gordon, Green, Haniffa, Higgins, Horvat, Hullegie, Kruger, Lamontagne, Lawler, Lewis, Linstrum, Litton, Lorenzi, Marshall, McArthur, McAuley, McGlothlin, McGuinness, McVerry, Montgomery, Nichol, Parke, Parker, Rowan, Sanil, Saunders, Seymour, Turner, van de Veerdonk, Venkatesh, Webb, Zarychanski.
Statistical analysis: Angus, L. Berry, S. Berry, Detry, Fitzgerald, Higgins, Lewis, Lorenzi, McGlothlin, Sanil, Saunders, Seymour, Webb.
Obtained funding: Annane, Bonten, Buxton, Cheng, de Jong, Derde, Estcourt, Goossens, Gordon, Higgins, Kruger, Litton, Marshall, McArthur, Montgomery, Murthy, Nichol, Rowan, Turner, Webb.
Administrative, technical, or material support: Angus, Al-Beidh, Arabi, Bentum-Puijk, Mouncey, Bhimani, Brunkhorst, Buxton, Buzgau, Cheng, Derde, Gordon, Green, Higgins, Horvat, Hullegie, Kruger, Lewis, Linstrum, Marshall, McArthur, McGuinness, Montgomery, Nichol, Parker, Rowan, Santos, Seymour, Turner, Webb.
Supervision: Angus, Arabi, Mouncey, Bonten, Buxton, Kruger, Lewis, McArthur, McGuinness, Montgomery, Murthy, Nichol, Parke, Rowan, Seymour.

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. 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 Mouncey reported receiving grants from European Commission FP7 and the National Institute for Health Research (NIHR) during the conduct of the study. Dr Bhimani reported receiving grants from the Canadian Institutes of Health Research during the conduct of the study. Dr Bradbury reported receiving personal fees from Bristol-Myers Squibb, Pfizer, Janssen, Amgen, Novartis, Portola, Bayer, and Ablynx outside the submitted work. Dr Brunkhorst reported receiving grants from the European Union during the conduct of the study. Dr Buxton reported receiving grants from the Breast Cancer Research Foundation during the conduct of the study and grants from Bayer, Amgen, Eli Lilly and Company, Janssen, Kazia Therapeutics, DelMar Pharma, Eisai, the National Brain Tumor Society, the National Foundation for Cancer Research, and the Asian Foundation for Cancer Research; gifts from the Yousefzadeh Family Foundation and Jeffrey Tarrant; and personal fees from Berry Consultants LLC outside the submitted work. Dr Cheng reported receiving grants from the National Health and Medical Research Council (NHMRC) during the conduct of the study. Dr de Jong reported receiving personal fees from Roche, Janssen, Vertex, and Visterra outside the submitted work. Dr Derde reported receiving European Union FP7-HEALTH-2013-INNOVATION-1 grant 602525 and H2020 RECOVER grant agreement No. 101003589 during the conduct of the study and being a member of the COVID-19 guideline committee for the Society of Critical Care Medicine/European Society of Intensive Care Medicine (ESICM)/Surviving Sepsis Campaign, member of the ESICM COVID-19 taskforce, and chair of the Dutch intensivists (NVIC) taskforce on infectious threats. Dr Detry reported receiving grants for the 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 Estcourt reported receiving grants from the NIHR during the conduct of the study. Dr Fitzgerald reported receiving grants for PREPARE Network from the European Commission, Australian funding grants for OPTIMISE-CAP, and New Zealand funding grants for REMAP-CAP during the conduct of the study. Dr Gordon reported receiving grants from the NIHR and the NIHR Research Professorship; nonfinancial support from the NIHR Clinical Research Network and the NIHR Imperial Biomedical Research Centre during the conduct of the study; and personal fees from GlaxoSmithKline and Bristol-Myers Squibb outside the submitted work. Dr Haniffa reported the Critical Care Asia project, where he is co-coordinator, is supported by the Wellcome Trust through the University of Oxford. Dr Higgins reported receiving grants from the NHMRC, the Health Research Council of New Zealand, and the Minderoo Foundation during the conduct of the study. Dr Horvat reported receiving grants from the Eunice Kennedy Shriver National Institute of Child Health and Human Development during the conduct of the study. Dr Hullegie reported receiving grants from the European Commission during the conduct of the study. Dr Kruger reported receiving personal fees from Smiths Medical outside the submitted work. Dr Lamontagne reported serving as methodological chair (nonvoting) for the World Health Organization (WHO) guideline on corticosteroids for COVID-19. The WHO guideline was initiated before any data from REMAP-CAP was made available. The first guideline panel meeting only reviewed data from the RECOVERY trial and the GLUCOCOVID trial. At a subsequent guideline panel meeting, the panel reviewed a meta-analysis commissioned by the WHO that included data from REMAP-CAP. Both the WHO-led meta-analysis and the guideline document are under review at the time of writing. Dr Lewis reported being the senior medical scientist at Berry Consultants LLC during the conduct of the study. Dr Lorenzi reported receiving grants from the European Commission for the PREPARE Network, Australia funding grants for OPTIMISE-CAP, and New Zealand funding grants for REMAP-CAP during the conduct of the study. Dr Marshall reported receiving personal fees from AM Pharma outside the submitted work and being a member of the international trial steering committee for REMAP-CAP; Canadian principal investigator for REMAP-CAP; chair of the International Forum for Acute Care Trialists; and co-chair of the WHO Working Group on Clinical Characterization and Management. Dr McArthur reported receiving grants from the Health Research Council of New Zealand during the conduct of the study. Dr McAuley reported receiving personal fees from GlaxoSmithKline, Boehringer Ingelheim, and Bayer for consultancy outside the submitted work; in addition, Dr McAuley reported a patent for a novel treatment for acute respiratory distress syndrome issued to his institution. Dr McGlothlin reported receiving grants from the European Commission for the PREPARE Network, Australian funding grants for OPTIMISE-CAP, and New Zealand funding grants for REMAP-CAP during the conduct of the study. Dr McVerry reported receiving salary support from UPMC Learning While Doing Program and the Translational Breast Cancer Research Foundation during the conduct of the study and grants from Bayer Pharmaceuticals Inc and the NIH/National Heart, Lung, and Blood Institute outside the submitted work. Dr Murthy reported receiving grants from the Canadian Institutes of Health Research during the conduct of the study. Dr Nichol reported receiving grants from the Health Research Board of Ireland during the conduct of the study. Dr Parke reported that research in the CVICU Auckland City Hospital is supported in part by an unrestricted grant from Fisher and Paykel Healthcare Limited, New Zealand. Dr Sanil reported receiving grants from the European Commission for PREPARE Network, Australia funding grants for OPTIMISE-CAP, and New Zealand funding grants for REMAP-CAP during the conduct of the study. Dr Saunders reported receiving grants from the European Commission for PREPARE Network, Australia funding grants for OPTIMISE-CAP, and New Zealand funding grants from REMAP-CAP during the conduct of the study. Dr Seymour reported receiving grants from the NIH's National Institute of General Medical Sciences and personal fees from Beckman Coulter Inc and Edwards

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Karen Parry-Billings on 04/13/2021

Lifesciences Inc outside the submitted work. Dr Turner reported receiving grants from the Health Research Council of New Zealand during the conduct of the study. Dr Venkatesh reported receiving institutional research support from Baxter outside the submitted work. Dr Webb reported receiving grants from the NHMRC and the Minderoo Foundation during the conduct of the study. Dr Zarychanski reported receiving research operating support from the Canadian Institutes of Health Research and the Lyonel G. Professorship of Hematology at the University of Manitoba. No other disclosures were reported.

Funding/Support: This study was supported by the Platform for European Preparedness Against (Re-) emerging Epidemics (PREPARE) consortium by the European Union, FP7-HEALTH-2013-INNOVATION-1 (grant 602525), the Australian National Health and Medical Research Council (grant APP1101719), the New Zealand Health Research Council (grant 16/631), the Canadian Institute of Health Research Strategy for Patient-Oriented Research Innovative Clinical Trials Program (grant 158584), the UK National Institute for Health Research (NIHR) and the NIHR Imperial Biomedical Research Centre, the Health Research Board of Ireland (grant CTN 2014-012), the UPMC Learning While Doing Program, the Breast Cancer Research Foundation, the French Ministry of Health (grant PHRC-20-0147), and the Minderoo Foundation.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The study has 4 regional nonprofit sponsors (Monash University, Melbourne, Australia [Australasian sponsor]; Utrecht Medical Center, Utrecht, the Netherlands [European sponsor]; St Michael's Hospital, Canada [Canadian sponsor], and GCAR, San Francisco, California [US sponsor]). Several authors are employees of these organizations. However, beyond the declared author contributions, the sponsors had no additional role.

The REMAP-CAP Investigators: See eAppendix 5 in Supplement 2 for a list of all REMAP-CAP Investigators.

Disclaimer: Dr Angus is Senior Editor at *JAMA*, but he was not involved in any of the decisions regarding review of the manuscript or its acceptance.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We are grateful to the NIHR Clinical Research Network (UK), UPMC Health System Health Services Division (US), and the Direction de la Recherche Clinique et de l'Innovation de l'AP-HP (France) for their support of participant recruitment. Dr Gordon is funded by an NIHR Research Professorship (RP-2015-06-18).

REFERENCES

1. Johns Hopkins University of Medicine Coronavirus Resource Center.COVID-19 in the USA. Accessed July 30, 2020. https://coronavirus.jhu.edu/

2. Siemieniuk RA-O, Bartoszko JJ, Ge L, et al. Drug treatments for COVID-19: living systematic review and network meta-analysis. *BMJ*. 2020;370:m2980. doi:10.1136/bmj.m2980

3. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for treating sepsis in children and adults. *Cochrane Database Syst Rev*. 2019;12:CD002243. doi:10.1002/14651858.CD002243.pub4

4. Ewald H, Raatz H, Boscacci R, Furrer H, Bucher HC, Briel M. Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV infection. *Cochrane Database Syst Rev*. 2015;(4):CD006150. doi:10.1002/14651858.CD006150.pub2

5. Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ*. 2020;192(27):E756-E767. doi:10.1503/cmaj.200645

6. Lansbury LE, Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Shen Lim W. Corticosteroids as adjunctive therapy in the treatment of influenza: an updated Cochrane systematic review and meta-analysis. *Crit Care Med*. 2020;48(2):e98-e106. doi:10.1097/CCM.0000000000004093

7. Li H, Chen C, Hu F, et al. Impact of corticosteroid therapy on outcomes of persons with SARS-CoV-2, SARS-CoV, or MERS-CoV infection: a systematic review and meta-analysis. *Leukemia*. 2020;34(6):1503-1511. doi:10.1038/s41375-020-0848-3

8. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet*. 2020;395(10223):473-475. doi:10.1016/S0140-6736(20)30317-2

9. China National Health Commission. Chinese clinical guidance for COVID-19 pneumonia diagnosis and treatment (7th edition). Updated March 16, 2020. Accessed August 3, 2020. http://kjfy.meetingchina.org/msite/news/show/cn/3337.html

10. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med*. 2020;48(6):e440-e469. doi:10.1097/CCM.0000000000004363

11. World Health Organization. The WHO clinical management of COVID-19 interim guidance. Updated May 27, 2020. Accessed August 3, 2020. https://www.who.int/publications/i/item/clinical-management-of-covid-19

12. Chopra A, Chieng HC, Austin A, et al. Corticosteroid administration is associated with improved outcome in patients with severe acute respiratory syndrome coronavirus 2-related acute respiratory distress syndrome. *Crit Care Explor*. 2020;2(6):e0143. doi:10.1097/CCE.0000000000000143

13. Fadel R, Morrison AR, Vahia A, et al; Henry Ford COVID-19 Management Task Force. Early short course corticosteroids in hospitalized patients with COVID-19. *Clin Infect Dis*. Published online May 19, 2020. doi:10.1093/cid/ciaa601

14. Brenner EJ, Ungaro RC, Gearry RB, et al. Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. *Gastroenterology*. 2020;159(2):481-491.e3. doi:10.1053/j.gastro.2020.05.032

15. Horby P, Lim WS, Emberson JR, et al; RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med*. Published online July 17, 2020. doi:10.1056/NEJMoa2021436

16. Angus DC, Berry S, Lewis RJ, et al. The REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) Study: rationale and design. *Ann Am Thorac Soc*. 2020;17(7):879-891. doi:10.1513/AnnalsATS.202003-192SD

17. Angus DC. Fusing randomized trials with big data: the key to self-learning health care systems? *JAMA*. 2015;314(8):767-768. doi:10.1001/jama.2015.7762

18. Laterre PF, Berry SM, Blemings A, et al; SEPSIS-ACT Investigators. Effect of selepressin vs placebo on ventilator- and vasopressor-free days in patients with septic shock: the SEPSIS-ACT randomized clinical trial. *JAMA*. 2019;322(15):1476-1485. doi:10.1001/jama.2019.14607

19. WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis*. 2020;20(8):e192-e197. doi:10.1016/S1473-3099(20)30483-7

20. Beigel JH, Tomashek KM, Dodd LE, et al; ACTT-1 Study Group Members. Remdesivir for the treatment of Covid-19: preliminary report. *N Engl J Med*. Published online May 22, 2020. doi:10.1056/NEJMoa2007764

21. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA*. Published online September 2, 2020. doi:10.1001/jama.2020.17023

22. Bittl JA, He Y. Bayesian analysis: a practical approach to interpret clinical trials and create clinical practice guidelines. *Circ Cardiovasc Qual Outcomes*. 2017;10(8):e003563. doi:10.1161/CIRCOUTCOMES.117.003563

23. Quintana M, Viele K, Lewis RJ. Bayesian analysis: using prior information to interpret the results of clinical trials. *JAMA*. 2017;318(16):1605-1606. doi:10.1001/jama.2017.15574

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Karen Parry-Billings on 04/13/2021