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ORIGINAL

Effect of hydrocortisone on mortality in patients with severe community-acquired pneumonia

The REMAP-CAP Corticosteroid Domain Randomized Clinical Trial

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Abstract

Purpose: To determine whether hydrocortisone improves mortality in severe community-acquired pneumonia (CAP).

Methods: In an international adaptive randomized controlled platform trial testing multiple interventions, adults admitted to the intensive care unit (ICU) with severe CAP were randomized to a 7-day course of intravenous hydrocortisone (50 mg every 6 h) or control (no corticosteroid). The primary end point was 90-day all-cause mortality, analyzed iteratively by a Bayesian hierarchical model estimating distinct treatment effects for patients presenting with influenza (Y/N) and shock (Y/N).

Results: Fixed 7-day course hydrocortisone enrollment was stopped for futility (< 5% probability of > 20% relative improvement). Of 658 patients enrolled, 536 were randomized to hydrocortisone and 122 to control. Vital status at day 90 was missing for 15 patients. Day 90 mortality was 15% (78/521) and 9.8% (12/122) for the hydrocortisone and control groups. The adjusted odds ratio ranged from 1.52 to 1.63 (with all 95% CrI crossing 1), while the probability of > 20% relative reduction of day 90 mortality ranged from 7.1 to 3.3% across influenza and shock strata. Results were consistent in sensitivity and pre-specified secondary outcomes. In exploratory analyses, the duration of shock appeared lower in the hydrocortisone group compared with control (median (IQR) of 2 (2–5) days compared to control 3 (2–6.75) days, *p* value = 0.05).

Conclusions: Among patients with severe CAP, treatment with a 7-day course of hydrocortisone, compared with no hydrocortisone, appears unlikely to yield a large reduction in mortality. Smaller benefits and possible harm are not excluded.

Trial registration: Clinicaltrials.gov identifier: NCT02735707 (registration date: November 4th, 2016).

Keywords: Adaptive platform trial, Intensive care, Pneumonia, Shock, Hydrocortisone, Corticosteroid

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Introduction

Corticosteroids may reduce mortality in patients hospitalized with severe community-acquired pneumonia (CAP) [1]. Possible benefits include amelioration of organ damage secondary to excessive host inflammatory responses via their anti-inflammatory properties, or mitigation of septic shock via their effects on the renin–angiotensin–aldosterone axis [2, 3]. Corticosteroids lowered mortality in patients with severe COVID-19 pneumonia [4], in a recent study of severe CAP [5], and in a post hoc analysis of CAP patients in a larger trial of steroids for septic shock [6]. A recent guideline statement now recommends corticosteroid administration for severe CAP [7]. However, other studies yielded inconsistent results [8–13], corticosteroids carry known side effects, and uncertainty persists regarding the type and dose of corticosteroids and whether treatment should be given broadly or to particular subgroups of patients.

REMAP-CAP is an ongoing international platform trial (NCT02735707) designed to evaluate treatments for patients with severe CAP in pandemic and non-pandemic settings [14–23]. The REMAP-CAP investigators previously reported that hydrocortisone appeared to be beneficial in patients with severe COVID-19, administered either as a fixed-dose 1-week course or titrated depending on the presence and duration of shock [18]. REMAP-CAP also contains a corticosteroid domain for non-COVID-19 pneumonia, where patients were randomized to one of several corticosteroid strategies or control. On December 6th, 2023, the platform ceased randomization to one of the corticosteroid strategies, fixed-duration hydrocortisone, on the recommendation of the Data Safety and Monitoring Board (DSMB) after that arm triggered a pre-specified stopping rule for futility compared to control (no corticosteroid). Data were locked after the last patient completed follow-up for the primary end point and the results are presented here.

Take-home message

In a large international platform trial evaluating multiple interventions for patients hospitalized with severe pneumonia, we found that, for adults admitted to the ICU with CAP and either cardiovascular or respiratory failure, the addition of a 7-day course of hydrocortisone to usual care was unlikely to reduce mortality.

Methods

Study design and oversight

The design of REMAP-CAP was reported previously [24, 25]. Patients eligible for the platform are assessed for eligibility to be randomized to interventions within one or more domains. We report here on patients randomized in the non-pandemic corticosteroid domain to fixed-duration hydrocortisone or control.

The trial is managed by a blinded International Trial Steering Committee (ITSC) and an unblinded independent DSMB. The trial had multiple international funders and sponsors. The funders had no role in study design, analysis, or reporting. The trial protocol was approved by relevant research ethics committees in each jurisdiction. Informed consent was obtained before randomization from all patients or their surrogates, or in a deferred fashion, in accordance with local legislation. The trial was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All authors vouch for these data and analyses, as well as for the fidelity of this report to the trial protocol and statistical analysis plan. There are no confidentiality agreements that preclude the investigators publishing the findings.

Participants

Adult patients ≥ 18 years, who presented with CAP and were admitted within 48 h of hospital presentation to an intensive care unit (ICU) for respiratory or cardiovascular organ support, were eligible for enrollment in the platform. CAP was defined as signs and symptoms consistent with lower respiratory tract infection and radiological evidence of new-onset infiltrate of infective origin [26]. Respiratory organ support was defined as invasive or noninvasive mechanical ventilation or high flow nasal cannula if flow rate ≥ 30 L/min and $FiO_2 \geq 0.4$. Cardiovascular organ support was defined as the intravenous infusion of any vasopressor or inotrope. Exclusion criteria included residents of a nursing home or long-term care facility, patients known to have been an inpatient in any healthcare facility within the last 30 days, presumption that death was imminent with lack of commitment to full support, and participation in REMAP-CAP in the prior 90 days. Additional exclusion criteria for the non-pandemic corticosteroid domain included a diagnosis of known or presumed COVID-19 infection, known hypersensitivity to corticosteroids, chronic systemic corticosteroid use, and a lapse of > 24 h since ICU admission. Further eligibility details are provided in the electronic supplementary material. The non-pandemic corticosteroid domain was recently extended to allow children and patients with moderate CAP (hospitalization without requirement for organ support). However, no children had been enrolled during the study period reported here and patients with moderate state CAP were ineligible for fixed-duration hydrocortisone.

Achieving a racially and ethnically diverse and sex-balanced sample was a goal of REMAP-CAP because of evidence of disparities in outcome and treatment effectiveness in pandemic and non-pandemic CAP [27, 28].

Participants (or their surrogates) self-reported their race/ethnicity and birth-assigned sex via fixed categories appropriate to their region.

Treatment allocation

The non-pandemic corticosteroid domain compares several interventions, including fixed-duration hydrocortisone, shock-dependent hydrocortisone (where hydrocortisone is only administered while the patient is receiving vasopressor therapy), fixed-duration dexamethasone, and control (no corticosteroid). Only the 7-day fixed-duration hydrocortisone arm met stopping criteria, and therefore this report only compares patients randomized to that arm or to control; other arms are ongoing and their results remain blinded. Sites participated in this domain if their investigators and clinicians were prepared, based on local equipoise, to randomize to ≥ 2 arms. If sites routinely gave corticosteroids for severe CAP, they could decline participation in the control arm, but still randomize to the different corticosteroid arms. This report therefore includes analysis of an additional subset of patients, those randomized within sites offering both fixed-dose hydrocortisone and control. Participants were randomized to each locally available arm, beginning with balanced assignment. Response-adaptive randomization was applied in a concealed fashion using allocation probabilities derived from each intervention's probability that it was most favorable, based on the accumulating evidence within the platform at each adaptive analysis [24].

Procedures

Because patients can be randomized to multiple interventions, REMAP-CAP has primarily used an open-label design, avoiding complex multiple placebo regimens. When a patient was randomized to one of the non-control arms, the clinical team was provided prescribing instructions for the intervention. All corticosteroids were 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, causative pathogens, corticosteroid use, and adverse events and outcomes by site investigators via an interactive web-based response technology with 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 until a result was unblinded and released publicly.

Interventions

Participants randomized to the fixed-duration hydrocortisone arm were prescribed intravenous hydrocortisone bolus of 50 mg every 6 h for 7 days, without tapering. For patients discharged from hospital before the end of the 7-day course, hydrocortisone was discontinued at hospital discharge. In all patients, systemic corticosteroid therapy was permitted if a new clinical indication developed for which corticosteroids are an established treatment, such as post-extubation stridor, bronchospasm, or anaphylaxis. In addition to assignment to interventions in the non-pandemic corticosteroid domain, participants could be randomly assigned to other interventions within other therapeutic domains [24] (see the electronic supplementary material and www.remapcap.org).

Outcomes

The primary outcome was all-cause mortality, determined 90 days after randomization. Secondary outcomes were: ICU mortality, hospital length of stay (LOS), and ICU LOS, censored at 90 days; ventilator-free days (VFD), organ-support free days (OSFD), and proportion of intubated patients who receive a tracheostomy, censored at 28 days; progression to intubation and mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or death, and readmission to the index ICU, each during the index hospitalization, censored at 90 days; destination at hospital discharge (home, rehabilitation hospital, nursing home or long-term care facility, or another acute hospitalization); and serious adverse events.

Statistical analysis

REMAP-CAP uses a Bayesian design with no maximum sample size. Planned adaptive analyses are performed and randomization continues until predefined statistical criteria are met for stopping a domain or intervention arm. The primary analysis of any intervention's effect is generated from an overarching Bayesian logistic model where the dependent variable is the primary outcome, 90-day mortality. The model is updated as the trial progresses, generating updated posterior probability distributions from the latest trial data and prior distributions, where the initial prior distributions for treatment effects were set as neutral. Full details of the overarching model and statistical analysis plan (SAP) governing the entire platform have been described previously [24]. In keeping with platform rules, following the DSMB's recommendation to cease enrollment into the fixed-duration hydrocortisone arm, blinded ITSC members wrote a specific SAP for this comparison of fixed-duration hydrocortisone to control. The plan was posted online (www.remap

cap.org) before data lock and analysis (see the electronic supplementary material).

The primary estimate of the effect of hydrocortisone compared to control was generated from a model that compared the outcome of patients randomized to either hydrocortisone or control within the non-pandemic corticosteroid domain. The estimate was adjusted for other covariates that affect outcome: location (site, nested within country), age (categorized into 6 groups), sex, time period (3-month epochs), shock (yes/no), influenza (yes/no), and degree of respiratory compromise and support (not intubated, intubated, and intubated with severe hypoxemia [PEEP $\geq$ 5cmH_20 and PaO_2/FiO_2 ratio < 200 mmHg]). As per the overarching design, to estimate the coefficients for these factors as robustly as possible, the primary model used information not only from patients randomized to hydrocortisone or control but rather from all randomized patients who met severe CAP criteria across all domains, regardless of whether patients were included in the corticosteroid domain or not, and inclusive of those patients whose CAP was due to COVID-19 and who were enrolled in domains open to both COVID-19 and non-COVID-19 patients. Thus, for example, any effect of 'site' could be estimated, and adjusted for, using information from all patients enrolled at that site, and not just those randomized to hydrocortisone or control. Although not all sites offered both control and hydrocortisone, the model's adjustment for site addressed potential differences in sites that offered one versus both arms.

Because patients were also being randomized (or not) within other domains and to other interventions, the model also accounted both for each patient's random assignment to any other intervention in any other domain and for their eligibility for any domain or intervention (depending on site participation, baseline entry criteria, and patient or surrogate preference). Although the effect of hydrocortisone in patients with COVID was also evaluated in REMAP-CAP [18], the current estimate of the effect of hydrocortisone in non-pandemic CAP was estimated separately.

Because the primary model included information about assignment to interventions within domains whose evaluation is ongoing, it was run by the unblinded Statistical Analysis Committee (SAC) (electronic supplementary material), who conduct all protocol-specified trial update analyses and report those results to the DSMB. The model was run on all patients enrolled up to December 6th, 2023 for whom complete follow-up was ascertained by April 2nd, 2024. Vital status following randomization was determined through medical records, contact with the participant, their next of kin, or other health care professionals. Patients were analyzed according to the group to which they were assigned. Those missing the primary end point ($n = 15$) were ignored; there was no imputation of missing end point values. The primary analysis was expressed as an odds ratio (OR), where an OR < 1 implies benefit. Separate treatment effects of hydrocortisone compared to control were estimated in those with and without vasopressor-dependent shock at enrollment and those with and without confirmed or suspected influenza infection. The model used an additive factorial prior with a non-informative prior (mean 0, standard deviation 10) on the hydrocortisone main effect and informative priors centered on 0 (with standard deviation 0.15) for the additive log odds ratio interaction effects of hydrocortisone with shock and influenza. This prior structure assumes no knowledge of treatment effect at trial launch and allows separate estimates across influenza and shock strata by shrinking the posterior distributions for the hydrocortisone effects toward the overall effect. In pretrial simulation, these priors performed well across scenarios where treatment effects were either homogenous or heterogenous across equal-sized subgroups.

The model was fit using a Markov chain Monte Carlo algorithm that drew iteratively (20,000 draws) from the joint posterior distribution, allowing calculation of ORs with their 95% credible intervals (CrI). The statistical triggers for an intervention were superiority (> 99% probability of OR < 1), futility (< 5% probability of > 20% reduction [OR < 1/1.2]), and inferiority (< 0.25% probability that an intervention was optimal in the domain).

Sensitivity analyses were conducted to generate estimates of the effect of hydrocortisone relative to control with full borrowing (pooled estimate across strata) and with no borrowing (independent estimates across strata). Additional sensitivity and secondary analyses were undertaken using only data from patients in the hydrocortisone and non-pandemic corticosteroid domain control groups. These analyses were conducted first on all patients randomized to either of these groups and second restricted to the subset of these patients who were enrolled at sites that offered both options (hydrocortisone or control; see SAP for detail in the electronic supplementary material). This last analysis most closely mimics a traditional 2-arm RCT. Wilcoxon Mann-Whitney tests were used to compare the duration of cardiovascular support in the hydrocortisone and control groups. Data management and summaries were created using R version 4.1.2, the primary analysis was computed in R version 4.3.3 (2024-02-29), using the rstan package version 2.32.2.

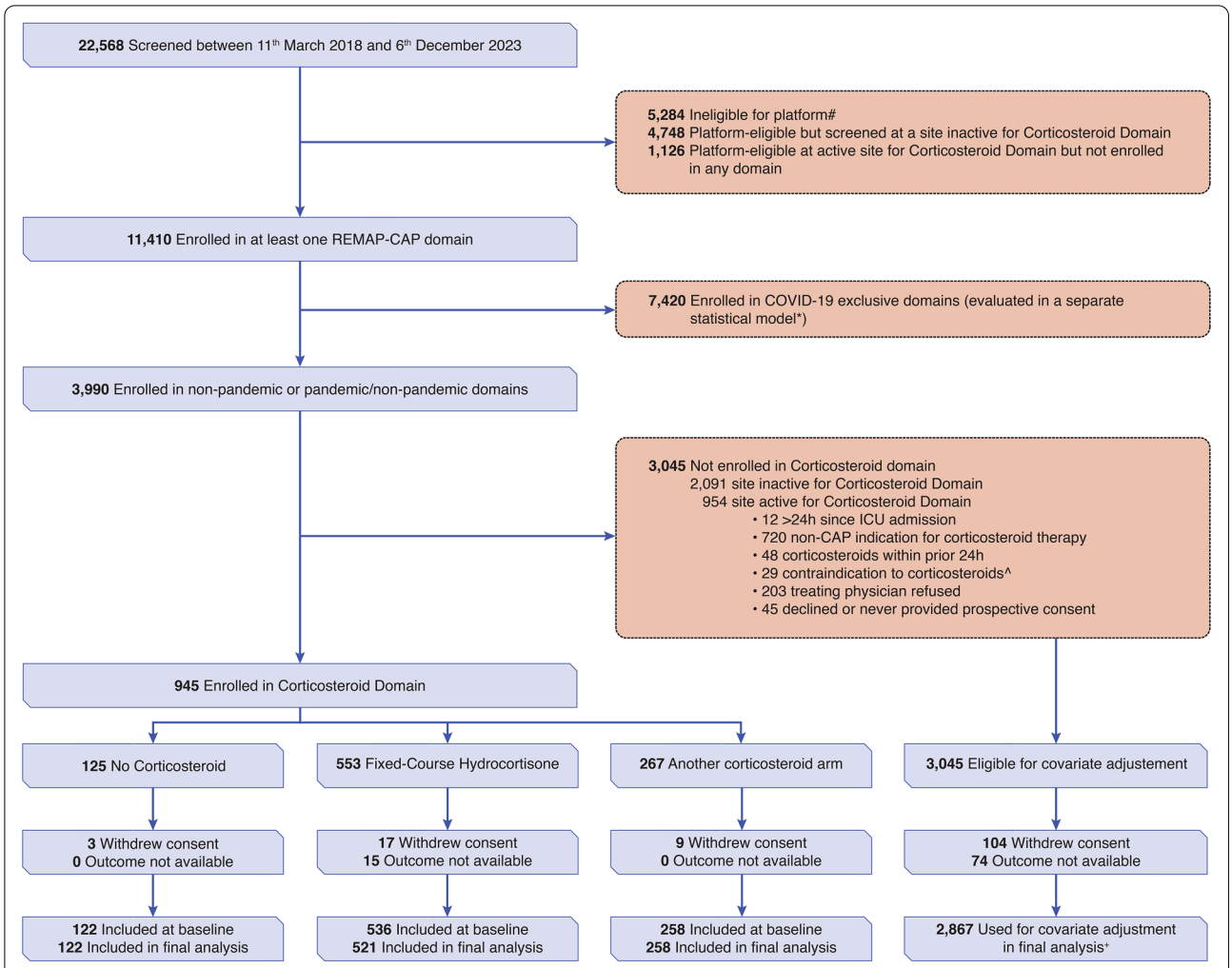

Fig. 1 Screening, randomization, and follow-up of participants in the REMAP-CAP Corticosteroid Domain Randomized Clinical Trial. #Patients could meet more than one ineligibility criterion. Full details are provided in the supplement. *Currently, there are two primary statistical models for the REMAP-CAP platform: the pandemic model (including participants with suspected or proven COVID-19 infection) and the interpandemic model (including participants with non-pandemic CAP and with COVID-19 infection who were randomized in domains eligible to both pandemic and non-pandemic CAP). +The primary model estimates treatment effects directly from those patients randomized within the corticosteroid domain, comparing the outcomes of those randomized in one arm to the outcomes of those who could have been randomized to that arm, but were in fact randomized to another. However, the model also adjusts for other patient and site characteristics and other intervention effects within other domains that affect outcome. To provide the most reliable and stable estimation of these patient, site, and intervention factors, the model uses data from all patients with non-pandemic CAP or with pandemic CAP in domains eligible to both pandemic and non-pandemic CAP. ^Contraindications include known hypersensitivity, current treatment with a medicine that cannot be co-administered with a corticosteroid, and pregnancy

Results

Participant accrual, randomization, and baseline characteristics

Between March 11th, 2018, and December 6th, 2023, of 22,568 screened patients, 11,410 met platform enrollment criteria and were enrolled in REMAP-CAP. Of these, 3990 were eligible for inclusion in the primary model either, because they had non-pandemic CAP ($n=2606$) or because they met COVID-19 criteria and were included in an intervention domain that included both pandemic and non-pandemic CAP ($n=1384$). Of the 3990, 133 (3.3%) patients subsequently requested removal of all their data. Of the remaining 3857, by data lock, there were 3768 (97.7%) individuals for whom 90-day outcome had been ascertained, comprising the primary analysis cohort (Fig. 1).

Within the 2606 non-pandemic CAP cohort, 945 patients were enrolled in the corticosteroid domain, 29 of whom withdrew consent. Of the remaining 916, 658 patients were randomized to fixed-duration

Table 1 Participant characteristics at baseline

	All patients randomized to hydrocortisone or control		Subset randomized at sites offering hydrocortisone and control	
	Hydrocortisone ($n=536$)	Control ($n=122$)	Hydrocortisone ($n=339$)	Control ($n=116$)
Strata*, *n* (%)				
Shock, influenza	25 (4.7)	4 (3.3)	19 (5.6)	3 (2.6)
Shock, no influenza	238 (44.4)	54 (44.3)	145 (42.8)	54 (46.6)
No shock, influenza	20 (3.7)	5 (4.1)	11 (3.2)	5 (4.3)
No shock, no influenza	253 (47.2)	59 (48.4)	164 (48.4)	54 (46.6)
Age in years, median (IQR)	62.5 (52–73)	58.5 (48–68)	63 (53–73)	58 (47.8–68)
Female sex, *n* (%)	204 (38.1)	54 (44.3)	125 (36.9)	51 (44)
Race/ethnicity[a], *n*/total (%)				
Asian	19/322 (5.9)	2/82 (2.4)	18/207 (8.7)	2/80 (2.5)
Black	3/322 (0.9)	0/82 (0)	0/207 (0)	0/80 (0)
Mixed	0/322 (0)	0/82 (0)	0/207 (0)	0/80 (0)
White	235/322 (73)	52/82 (63.4)	145/207 (70)	52/80 (65)
Other	65/322 (20.2)	28/82 (34.1)	44/207 (21.3)	26/80 (32.5)
BMI[b], median (IQR)	27.7 (23.8–33.1) ($n=487$)	27.7 (23.5–35.6) ($n=113$)	27.2 (23.7–32.8) ($n=312$)	27.7 (23.5–35.7) ($n=107$)
APACHE II score[c], median (IQR)	18 (13–24) ($n=511$)	18 (13–22) ($n=119$)	19 (14–24) ($n=323$)	18 (13–22) ($n=114$)
Clinical Frailty Score[d], median (IQR)	3 (2–4) ($n=532$)	3 (2–4)	3 (2–4) ($n=336$)	3 (2–4)
Preexisting condition[e], *n*/total (%)				
Diabetes	161/532 (30.3)	27 (22.1)	101/336 (30.1)	26 (22.4)
Respiratory disease	183/533 (34.3)	42 (34.4)	120/337 (35.6)	41 (35.3)
Kidney disease	63/439 (14.4)	20/90 (22.2)	36/260 (13.8)	20/86 (23.3)
Severe cardiovascular disease	44/533 (8.3)	9 (7.4)	29/337 (8.6)	9 (7.8)
Any immunosuppressive condition	35/532 (6.6)	6 (4.9)	21/336 (6.2)	5 (4.3)
Time to enrollment, median (IQR)				
From hospital admission, days	0.8 (0.5–1.1)	0.7 (0.4–1)	0.8 (0.4–1.1)	0.7 (0.4–1)
From ICU admission, hours	8.2 (2.8–16.1)	7.4 (2.4–13.5)	7.4 (2.6–15.3)	7.1 (2.3–13.2)
Acute respiratory support, *n*/total (%)				
Invasive mechanical ventilation	213 (39.7)	46 (37.7)	139 (41)	44 (37.9)
Noninvasive ventilation only	76 (14.2)	21 (17.2)	39 (11.5)	21 (18.1)
High-flow nasal cannula	206 (38.4)	39/118 (33.1)	134 (39.5)	35/112 (31.2)
None/supplemental oxygen	41 (7.6)	12/118 (10.2)	27 (8)	12/112 (10.7)
PaO_2/FiO_2, median (IQR)	156 (114–214) ($n=457$)	168 (127.5–235.5) ($n=107$)	155 (113–215) ($n=281$)	167 (127–234) ($n=101$)
Extended cardiovascular SOFA score, median (IQR)[f]	2 (0–3) ($n=522$)	1 (0–3) ($n=109$)	3 (0–3) ($n=326$)	1 (0–3) ($n=103$)
Median laboratory values (IQR)[g]				
Lactate, mmol/L	1.6 (1.1–2.3) ($n=514$)	1.5 (1–2.3)	1.7 (1.2–2.4) ($n=326$)	1.6 (1–2.3)
Creatinine, mg/dL	1.1 (0.8–1.5) ($n=526$)	1.1 (0.8–1.8) ($n=120$)	1.1 (0.8–1.6) ($n=334$)	1.2 (0.8–1.8) ($n=114$)
eGFR, min/min/1.73 m^2	73.4 (45.6–100.2) ($n=526$)	68.5 (35.7–99.7) ($n=120$)	70.4 (46–97) ($n=334$)	67.5 (36.5–100) ($n=114$)
No pathogen isolated, *n*/total (%)	278/532 (52.2)	71/119 (59.7)	166/336 (49.4)	65/113 (57.5)
Bacterial pathogen isolated, *n*/total (%)	221/532 (41.5)	44/119 (37)	145/336 (43.2)	44/113 (38.9)
Streptococcus pneumoniae	110/532 (20.7)	24/119 (20.2)	66/336 (19.6)	23/113 (20.4)
Atypical bacterial pathogen[h]	54/528 (10.2)	8/119 (6.7)	38/335 (11.3)	8/113 (7.1)
Viral pathogen isolated, *n*/total (%)	57/531 (10.7)	12/119 (10.1)	38/335 (11.3)	11/113 (9.7)
SARS-CoV-2[i], n/total (%)	8/520 (1.5)	2/107 (1.9)	5/311 (1.6)	2/93 (2.2)
Influenza[i], *n*/total (%)	39 (7.3)	8 (6.6)	27/293 (9.2)	7/85 (8.2)
Both viral and bacterial pathogens isolated, *n*/total (%)	25/531 (4.7)	8/119 (6.7)	13/335 (3.9)	7/113 (6.2)
Other pathogen isolated, *n*/total (%)	2/532 (0.4)	1/118 (0.8)	0/336 (0)	1/112 (0.9)

Table 1 (continued)

	All patients randomized to hydrocortisone or control		Subset randomized at sites offering hydrocortisone and control	
	Hydrocortisone ($n=536$)	Control ($n=122$)	Hydrocortisone ($n=339$)	Control ($n=116$)
Continent, *n* (%)				
Asia	18 (3.4)	0 (0)	1 (0.3)	0 (0)
Australia	304 (56.7)	73 (59.8)	197 (58.1)	71 (61.2)
Europe	178 (33.2)	38 (31.1)	105 (31)	36 (31)
North America	36 (6.7)	11 (9)	36 (10.6)	9 (7.8)

Percentages may not sum to 100 because of rounding. Within the control arm, six patients were randomized in sites offering shock-dependent hydrocortisone, but not fixed-duration hydrocortisone

SD standard deviation, *IQR* interquartile range, *ICU* intensive care unit, FiO_2 fraction of inspired oxygen, Pao_2 arterial partial pressure of oxygen, *eGFR* estimated glomerular filtration rate, *SARS-CoV-2* severe acute respiratory syndrome coronavirus-2

*Strata were determined at enrollment. Patients were classified as 'influenza' if influenza was confirmed or suspected

[a] Data collection was not approved in Canada and continental Europe. 'Other' includes 'declined' and 'other ethnic group'. Participants (or their surrogates) self-reported their race/ethnicity via fixed categories appropriate to their region. "Declined" does not simply represent missing data. A patient may decline to provide their race at the time of registration or the person performing the registration may decline to ask the patient to clarify race at the time of registration

[b] BMI (body-mass index) is the weight in kilograms divided by the square of the height in meters

[c] Acute Physiology and Chronic Health Evaluation II scores range 0–71, with higher scores indicating greater severity of illness

[d] The Clinical Frailty Score is a global measure of fitness and frailty, with increasing scores—ranging from 1 (very fit) to 9 (terminally ill)—reflecting worse fitness and increasing frailty

[e] Kidney disease was determined from the most recent serum creatinine level prior to this hospital admission, except in patients who were receiving dialysis. Abnormal kidney function was defined as a creatinine level of 130 µmol/L or greater (1.5 mg/dL) for males or 100 µmol/L or greater (1.1 mg/dL) for females not previously receiving dialysis. Cardiovascular disease was defined as New York Heart Association class IV symptoms. Immunosuppression was defined by the receipt of recent chemotherapy, radiation, high-dose or long-term steroid treatment, or presence of immunosuppressive disease

[f] Extended Cardiovascular Sequential Organ Failure Assessment (SOFA) Score reflects criteria for blood pressure and inotropic or vasoactive support, with higher scores indicating worse cardiovascular organ failure

[g] Laboratory results available when captured for clinical care

[h] Including *Legionella*, *Mycoplasma* and *Chlamydophila* spp

[i] Infection was confirmed by respiratory tract polymerase chain reaction test

hydrocortisone ($n=536$) or control ($n=122$) at 101 sites in 18 countries. Of the 658 patients, 455 were randomized to hydrocortisone ($n=339$) or control ($n=116$) at the 70 sites that offered both options. Outcome was known for 100% of control patients, 97.2% (521/536) of patients assigned hydrocortisone, and 97.6% (331/339) of patients assigned hydrocortisone at sites where control was also available (Fig. 1). Two factors contribute to the high proportion of patients assigned to fixed-duration hydrocortisone. First, one third ($n=197$, of whom outcome was known for 190 patients) of patients assigned to fixed-duration hydrocortisone were randomized at sites that offered > 1 corticosteroid intervention, but not control, due to perceived lack of equipoise. Second, the first adaptive analysis (conducted on 132 patients in the corticosteroid domain with known outcomes, at which point only control and fixed-duration hydrocortisone were available in the trial) used a dataset provided to the SAC with a transposition error from the data vendor for some sites, such that 13 and 15 patients in the hydrocortisone and control groups were incorrectly labeled as belonging to the opposite group. The adaptive analysis based on these erroneously labeled data led to updated response-adaptive randomization proportions that assigned more patients to fixed-duration hydrocortisone (electronic supplementary material).

The subsequent adaptive analysis used correctly-labeled data and triggered the futility threshold, halting further enrollment. The initial data error was only detected on February 23rd, 2024, after enrollment was closed and data were unblinded, at which point it was determined that the error was an isolated incident concerning only one data transfer to the SAC. Incorrect labeling only affected the corticosteroid domain, no other domains were impacted. All safety data provided to the DSMB throughout were correctly labelled. Nonetheless, the investigators filed an immediate incident report with relevant jurisdictions and implemented a corrective action plan (electronic supplementary material).

Baseline characteristics among both the entire group randomized to hydrocortisone or control ($n=658$) and the subset randomized at sites where both options were available ($n=455$) are presented in Table 1. Though the groups were broadly similar, patients randomized to hydrocortisone were slightly older and had slightly worse baseline respiratory dysfunction

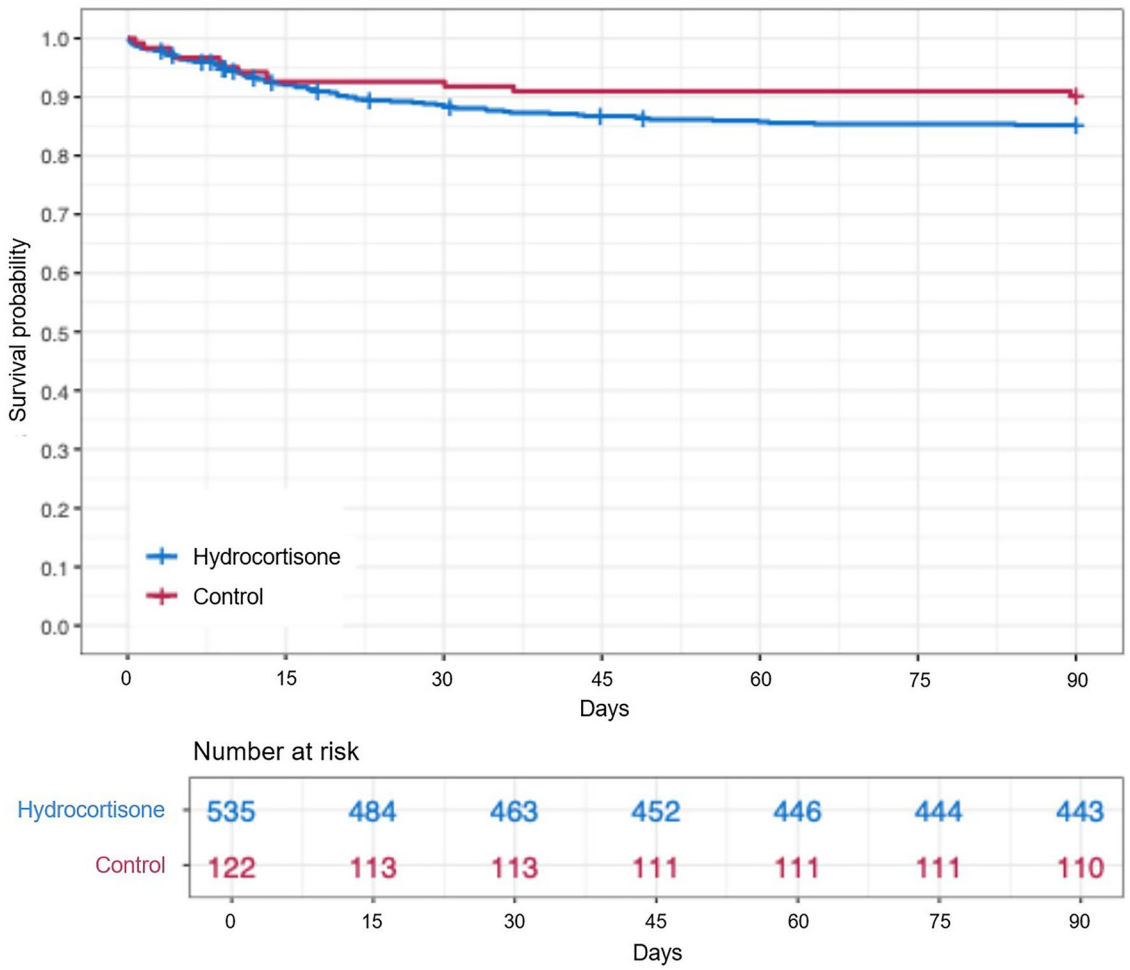

Fig. 2 Primary outcome. Kaplan–Meier curves for day 90 survival according to intervention group. Of the 536 patients randomized to hydrocortisone, 535 (99.8%) are included because one was lost to follow-up with no known date of last contact, precluding an ability to provide a censoring date

(higher mechanical ventilation rate and lower PaO_2/FiO_2 ratio) and cardiovascular dysfunction (slightly higher cardiovascular SOFA score). Although ethnicity was balanced, Asian sites (which only joined after the first adaptive analysis) contributed no patients to the control arm. Causative pathogens were evenly distributed among groups (Table 1 and electronic supplementary material).

Intervention fidelity

At the time of data lock, we had not been able to verify corticosteroid dosing for 3 patients, such that we had dosing information on 655 (99.5%) of the 658 participants randomized in the corticosteroid domain to fixed-duration hydrocortisone ($n=533$) or control ($n=122$). Among those assigned to fixed-duration hydrocortisone, 98.9% (527/533) received at least one dose of hydrocortisone, an additional 0.4% (2/533) received an alternative systemic corticosteroid, and only 0.8% (4/533) received no corticosteroid. The first dose of hydrocortisone was given before midnight of the first study day in 94.2% (502/533) of patients and the median (IQR) duration of hydrocortisone therapy was 7 (4–8) days. Among those assigned to control, 23% (28/122) received a systemic corticosteroid (16 of whom received hydrocortisone). For those receiving a corticosteroid, the median (IQR) duration of treatment was 4 (2–5.3) days. Only one patient (0.8%) among those assigned to the control arm received a full dose (>6 days of 200 mg hydrocortisone-equivalent per day) of corticosteroids.

Primary outcome

By day 90, 78 (15%) of 521 patients assigned to hydrocortisone and 12 (9.8%) of 122 patients assigned to control had died (Fig. 2). The median adjusted OR for the effect of hydrocortisone, relative to control, on 90-day mortality, estimated from the primary model (which

Table 2 Primary outcome and sensitivity analyses in the full dataset

90-day mortality	Hydrocortisone ($n = 536$)				Control ($n = 122$)			
Primary analysis using the full model								
Vasopressor-dependent shock	Yes	Yes	No	No	Yes	Yes	No	No
Influenza	Yes	No	Yes	No	Yes	No	Yes	No
# Patients evaluated/total #	25/25	233/238	16/20	247/253	4/4	54/54	5/5	59/59
Deaths n (%)	4 (16)	38 (16.3)	2 (12.5)	34 (13.8)	0 (0)	7 (13)	1 (20)	4 (6.8)
Median adjusted OR (95% CrI)	1.52 (0.69–3.56)	1.53 (0.76–3.29)	1.62 (0.73–3.84)	1.63 (0.80–3.59)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Mean adjusted OR (SD)	1.67 (0.75)	1.65 (0.66)	1.79 (0.83)	1.78 (0.73)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Probability of superiority, %	15.7	12.1	12.6	9.2	–	–	–	–
Probability of harm, %	84.3	87.9	87.4	90.8	–	–	–	–
Probability of > 20% reduction in odds of death, %	7.1	4.4	5.3	3.3	–	–	–	–
Sensitivity analyses								
Independent treatment effects for each stratum (no borrowing) using the full model								
Median adjusted OR (95% CrI)	1.21 (0.19–8.96)	1.46 (0.63–3.70)	1.53 (0.23–11.69)	1.82 (0.72–5.18)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Mean adjusted OR (SD)	2.05 (2.81)	1.65 (0.83)	2.63 (3.78)	2.12 (1.23)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Probability of superiority, %	42.3	19.6	33.4	10.4	–	–	–	–
Probability of harm, %	57.7	80.4	66.6	89.6	–	–	–	–
Probability of > 20% reduction in odds of death, %	35.2	9.8	27.2	5	–	–	–	–
Pooled treatment effect across strata using the full model								
Median adjusted OR (95% CrI)	1.56 (0.80–3.31)				1 (Reference)			
Mean adjusted OR (SD)	1.69 (0.65)				1 (Reference)			
Probability of superiority, %	10				–			
Probability of harm, %	90				–			
Probability of > 20% reduction in odds of death, %	3.4				–			
Analyses restricted to patients randomized to either fixed-duration hydrocortisone or control								
Median adjusted OR (95% CrI)	1.49 (0.69–3.68)	1.48 (0.73–3.57)	1.45 (0.70–3.65)	1.48 (0.73–3.50)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Mean adjusted OR (SD)	1.69 (0.76)	1.68 (0.73)	1.67 (0.76)	1.67 (0.73)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Probability of superiority, %	13.8	12.0	13.9	12.3	–	–	–	–
Probability of harm, %	86.2	88.0	86.1	87.7	–	–	–	–

Table 2 (continued)

90-day mortality	Hydrocortisone ($n=536$)				Control ($n=122$)			
Probability of > 20% reduction in odds of death, %	6.5	5.4	6.6	5.2	–	–	–	–

The model adjusts for age, sex, site (nested within country), domain ineligibility, randomization within each domain, strata (vasopressor dependent shock versus no vasopressor dependent shock and influenza versus no influenza), disease state (not on invasive mechanical ventilation, ventilated but not severely hypoxic, or ventilated and severely hypoxic) and time epochs. Odds ratios (OR) < 1 indicate improved outcomes. Probability of harm (OR > 1) is the inverse of probability of superiority (OR < 1)

SD denotes standard deviation, *CrI* denotes credible interval

generates OR for each stratum with fixed borrowing) was 1.52 (95% CrI, 0.69 to 3.56) for vasopressor-dependent shock due to influenza; 1.53 (0.76 to 3.29) for vasopressor-dependent shock not due to influenza; 1.62 (0.73 to 3.84) for influenza without vasopressor-dependent shock, and; 1.63 (0.80 to 3.59) for severe CAP with neither influenza nor vasopressor-dependent shock. These OR yielded posterior probabilities of > 20% reduction in the odds of death at 90 days of 7.1%, 4.4%, 5.3%, and 3.3%, respectively. Probabilities of superiority (OR < 1) were 15.7%, 12.1%, 12.6%, and 9.2%, respectively, with corresponding probabilities of harm (OR > 1) 84.3%, 87.9%, 87.4%, and 90.8%, respectively (Table 2).

Pre-specified sensitivity and secondary analyses

Repeating the primary analysis, but generating a single treatment effect for hydrocortisone (as opposed to separate effects for each stratum), the overall median adjusted OR for death at day 90 with hydrocortisone was 1.56 (95% CrI, 0.80–3.31), yielding a 10% probability of superiority, a 3.4% probability of improving the odds of death at day 90 by > 20%, and a 90% probability of harm. Sensitivity analyses exploring the effect of less borrowing across strata generated considerably less certain probabilities of superiority or futility for the two influenza strata. However, the low probabilities of superiority and high probabilities of futility overall and in the non-influenza strata persisted, regardless of whether the models included borrowing across strata (see Table 2).

When restricting analyses to data from patients enrolled at sites where they could be randomized to either the fixed-dose hydrocortisone or the control arm, the median adjusted OR for death at day 90 with hydrocortisone was 1.55 (95% CrI, 0.75–3.63), yielding a 14.4% probability of superiority, a 4.4% probability of improving the odds of death at day 90 by > 20%, and a 85.6% probability of harm (electronic supplementary material).

Secondary outcomes

Secondary outcomes are reported in Table 3. ICU and hospital length of stay were similar in both arms, as were the proportions of intubated patients who received a tracheostomy; the rates of progression to intubation, mechanical ventilation, ECMO, or death; the readmission rates to the index ICU, and; the distributions of hospital discharge destinations. OSFDs are a composite of death and duration of support. Although the observed mortality rates were higher in the hydrocortisone arm, the median OSFD adjusted OR was 0.82 (0.56–1.22), yielding an 85.4% probability that hydrocortisone was superior to control. Restricted to sites where patients could be randomized to either arm, the median adjusted OR was 0.83 (95% CrI, 0.53–1.13), yielding a 91.3% probability that hydrocortisone was superior to control. This possible improvement in OSFDs appeared to be due to a shorter duration of cardiovascular support. The duration of cardiovascular support was median (IQR) 2(2–5) days in the hydrocortisone arm compared to control 3(2–6.75) days, p value = 0.05.

Serious adverse events were reported in seven patients (1.3%) randomized to the hydrocortisone arm and one patient (0.8%) randomized to the control arm. Because of the limited number of events, there was no formal statistical comparison (Table 3).

Discussion

Among patients enrolled in REMAP-CAP with severe non-pandemic CAP, there was a low probability that a 7-day fixed-duration course of hydrocortisone improved 90-day mortality. Enrollment was halted when the predefined threshold for futility was reached, meaning that there was < 5% probability of demonstrating > 20% reduction in the odds of death compared to control. A smaller effect on mortality could not be excluded. The findings were consistent in sensitivity analyses and across secondary outcomes, regardless of whether patients presented in septic shock or not. Though the observed mortality frequency was higher in the hydrocortisone group, both the adverse event reporting and secondary outcome analyses did not suggest obvious harm. Although the adaptive analysis triggered futility in all groups, the futility trigger was no longer met in the influenza groups with the addition of data from all patients enrolled until December 6th, 2023. Only a small

Table 3 Secondary outcomes in patients randomized to either fixed-duration hydrocortisone or control

	All patients randomized to hydrocortisone or control		Subset randomized at sites offering hydrocortisone and control	
	Hydrocortisone ($n = 536$)	Control ($n = 122$)	Hydrocortisone ($n = 339$)	Control ($n = 116$)
ICU mortality				
# Patients with known outcome	535	122	338	116
Deaths, n (%)	50 (9.3)	7 (5.7)	42 (12.4)	7 (6)
Median adjusted OR (95% CrI)	1.49 (0.62–4.18)	1 (Reference)	1.73 (0.65–5.07)	1 (Reference)
Mean adjusted OR (SD)	1.73 (0.97)	1 (Reference)	2.00 (1.19)	1 (Reference)
Probability of superiority, %	19.3	–	13.6	–
Probability of harm, %	80.7	–	86.4	–
Probability of > 20% reduction in odds of death, %	10.1	–	7.1	–
ICU Length of stay (LOS)				
# Patients with known outcome	535	122	339	116
LOS (days) median (10th to 90th percentile)	5 (1–43)	5.5 (2–34)	5 (1 to –)	5.5 (2–37)
Median adjusted HR (95% CrI)	1.05 (0.84–1.31)	1 (Reference)	1.04 (0.81–1.35)	1 (Reference)
Mean adjusted HR (SD)	1.06 (0.12)	1 (Reference)	1.05 (0.13)	1 (Reference)
Probability of superiority, %	32.3	–	38.9	–
Probability of harm, %	67.7	–	61.1	–
Probability of > 20% reduction in LOS, %	2.2	–	4.4	–
Ventilator-free days (VFD)				
# Patients with known outcome	535	122	338	116
VFD (days) median (IQR)	27 (19–28)	28 (19–28)	26 (17–28)	28 (18.75–28)
Median adjusted OR (95% CrI)	0.85 (0.60 to 1.41)	1 (Reference)	0.85 (0.58 to 1.43)	1 (Reference)
Mean adjusted OR (SD)	0.89 (0.22)	1 (Reference)	0.92 (0.21)	1 (Reference)
Probability of superiority, %	72.8	–	72.3	–
Probability of harm, %	27.3	–	27.7	–
Probability of > 20% improvement in odds of VFD, %	47.6	–	70.9	–
Organ support-free days (OSFD)				
# Patients with known outcome	535	122	338	116
OSFD (days) median (IQR)	24 (16–26)	22.5 (15–26)	24 (13.25–26)	22 (15–26)
Median adjusted OR (95% CrI)	0.82 (0.56–1.22)	1 (Reference)	0.83 (0.53–1.13)	1 (Reference)
Mean adjusted OR (SD)	0.83 (0.16)	1 (Reference)	0.82 (0.16)	1 (Reference)
Probability of superiority, %	85.4	–	91.3	–
Probability of harm, %	14.6	–	8.7	–
Probability of > 20% improvement in odds of OSFD, %	54.9	–	49.4	–
Hospital Length of stay (LOS)				
# Patients with known outcome	536	122	339	116
LOS (days) median (10th to 90th percentile)	12 (4 to –)	14 (4–55)	12 (4 to –)	14 (3–58)
Median adjusted HR (95% CrI)	1.07 (0.85 to 1.34)	1 (Reference)	1.03 (0.80 to 1.31)	1 (Reference)
Mean adjusted HR (SD)	1.07 (0.13)	1 (Reference)	1.03 (0.13)	1 (Reference)
Probability of superiority, %	29.7	–	42.4	–
Probability of harm, %	70.3	–	57.6	–
Probability of > 20% reduction in LOS, %	1.9	–	5.4	–
Progression to intubation, ECMO, or death, *n*/total (%)	64/323 (19.8)	16/76 (21.1)	41/200 (20.5)	15/72 (20.8)
Tracheostomy rate in intubated patients, *n*/total (%)	22/210 (10.5)	6/46 (13)	14/137 (10.2)	6/44 (13.6)
Destination at hospital discharge, *n*/total (%)				
Deceased	66/534 (12.4)	9 (7.4)	53/337 (15.7)	9 (7.8)
Home	387/534 (72.5)	92 (75.4)	236/337 (70)	88 (75.9)
Nursing home or long-term care facility	10/534 (1.9)	2 (1.6)	5/337 (1.5)	1 (0.9)

Table 3 (continued)

	All patients randomized to hydrocortisone or control		Subset randomized at sites offering hydrocortisone and control	
	Hydrocortisone ($n=536$)	Control ($n=122$)	Hydrocortisone ($n=339$)	Control ($n=116$)
Rehabilitation hospital	38/534 (7.1)	7 (5.7)	22/337 (6.5)	7 (6)
Transfer to another acute hospital	33/534 (6.2)	12 (9.8)	21/337 (6.2)	11 (9.5)
ICU readmission*, *n*/total (%)	19 (3.5)	5 (4.1)	13/339 (3.8)	4 (3.4)
Serious adverse events, *n*/total (%)	7 (1.3)	1 (0.8)	3/339 (0.9)	1 (0.9)
90-day mortality in patients with no baseline mechanical ventilation				
# Patients with known outcome/total #	314/323	76/76	195/200	72/72
Deaths, *n* (%)	34 (10.8)	5 (6.6)	24 (12.3)	5 (6.9)
Median adjusted OR (95% CrI)	1.36 (0.47–4.68)	1 (Reference)	1.24 (0.40–4.28)	1 (Reference)
Mean adjusted OR (SD)	1.67 (1.21)	1 (Reference)	1.53 (1.07)	1 (Reference)
Probability of superiority, %	29.2	–	36.7	–
Probability of harm, %	70.8	–	63.2	–
Probability of > 20% reduction in odds of death, %	81.1	–	25.3	–
90-day mortality in patients with baseline invasive mechanical ventilation				
# Patients with known outcome/total #	207/213	46/46	136/139	44/44
Deaths, *n* (%)	44 (21.3)	7 (15.2)	37 (27.2)	7 (15.9)
Median adjusted OR (95% CrI)	1.85 (0.67–5.61)	1 (Reference)	2.05 (0.70–6.31)	1 (Reference)
Mean adjusted OR (SD)	2.18 (1.37)	1 (Reference)	2.41 (1.49)	1 (Reference)
Probability of superiority, %	12.8	–	9.7	–
Probability of harm, %	87.2	–	90.3	–
Probability of > 20% reduction in odds of death, %	93.3	–	5.0	–

Within the control arm, six patients were randomized in sites offering shock-dependent hydrocortisone but not fixed-duration hydrocortisone. The model adjusts for age, sex, site (nested within country), domain ineligibility, randomization within each domain, strata (vasopressor-dependent shock versus no vasopressor-dependent shock and influenza versus no influenza), disease state (not on invasive mechanical ventilation, ventilated but not severely hypoxic, or ventilated and severely hypoxic) and time epochs. Odds ratios < 1 indicate improved outcomes. Probability of harm (OR > 1) is the inverse of probability of superiority (OR < 1)

OR denotes odds ratio, *HR* denotes hazard ratio, *CrI* denotes credible interval, *ECMO* denotes extracorporeal membrane oxygenation, *IQR* denotes interquartile range, *ICU* denotes intensive care unit

*During index hospitalization

portion of the cohort had influenza, and findings are inconclusive in this group.

Previous studies provided conflicting results regarding the efficacy of corticosteroids in severe CAP. Two studies from France both reported benefit. The CAPE-COD trial, comparing hydrocortisone to placebo, reported a large reduction in 28-day mortality with hydrocortisone (absolute difference: 5.6%; 95% CI, − 9.6 to − 1.7) [5]. Patients enrolled in CAPE-COD, while slightly older, appeared less severely ill than those enrolled in the current trial in that septic shock was an exclusion criterion and fewer patients were intubated at enrolment. In post-hoc analysis of the APROCCHSS trial, which compared hydrocortisone and fludrocortisone to placebo for septic shock, Heming et al. showed a large benefit in the subgroup of patients with CAP (OR: 0·60, 95% CI 0.43–0.83) [6]. In contrast, the ESCAPe study, conducted in the US Veterans' Administration, which compared methylprednisolone to placebo, reported no difference in 60-day mortality (adjusted odds ratio 0.90, 95% CI 0.57–1.40), though the study was stopped early for slow recruitment [9]. In aggregate, however, a recent meta-analysis of 18 studies enrolling over 4000 patients hospitalized with CAP concluded corticosteroids reduced mortality (RR 0.62 [95% CI 0.45–0.85]) [8, 10–13, 29] and recent guidelines recommend administrating corticosteroids in severe CAP [7].

In exploratory analysis, it is possible that hydrocortisone reduced the duration of vasopressor requirement. This finding is consistent with two international trials of hydrocortisone in septic shock, CORTICUS and ADRENAL, both of which reported no reduction in mortality but faster resolution of shock [30, 31]. Both the anti-inflammatory and cardiovascular effects of hydrocortisone could explain the short-term ameliorating effects on shock. Why an improvement in the resolution of shock would not improve longer-term outcome is more complicated: patients with severe CAP have multiple factors that contribute to their risk of death, and steroids have pleiotropic effects, of which some may ameliorate and others aggravate patients' risk factors. More broadly, CAP is extremely heterogenous, and the effect

of steroids may vary across patients, both within this trial and between trials, possibly explaining some of the discrepancies. Furthermore, some of this heterogeneity may be related to features that can be difficult to quantify accurately, such as the severity of the inflammatory response, degree and nature of underlying comorbidities, causative pathogen, host–pathogen interactions, and the time in the course of CAP at which patients present to hospital [32].

Limitations

This study has important limitations. First, the futility rule that stopped the study may have been premature. It only ruled out a relatively large effect (>20% relative reduction in mortality), and the sample size was too small to explore subgroup effects. In particular, the limited number of patients in the influenza strata preclude any conclusions about the effect of steroids in these patients. Second, the open-label design meant clinicians were aware of the treatment assignment, which likely influenced their decision to prescribe corticosteroids in some control arm patients, although typically for a much shorter course. If steroids were beneficial, their use in the control arm would have reduced the effect size, but would be unlikely to cause futility and possible harm. Third, a miscoding error prior to the first adaptive analysis led to erroneous updated response-adaptive randomization proportions, which led more patients to be assigned to the fixed-duration hydrocortisone intervention. Though the miscoding may have caused fewer patients to be allocated to receive the optimal treatment, it is unlikely to have changed the overall outcome, as evidenced by the consistent findings across the sensitivity analyses. Fourth, one of the exclusion criteria, chronic corticosteroid therapy was not defined prospectively but by the physician in charge of the patient.

Conclusions

Among patients with severe CAP, treatment with a 7-day fixed-duration course of hydrocortisone, compared with no hydrocortisone, appears unlikely to yield a large reduction in mortality. Smaller benefits and possible harm are not excluded.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00134-025-07861-w.

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DCA, DjA, YA, DiA, AB, LB, SB, JB, MB, CB, FB, AB, MB, MC, AC, MC, LD, LE, AG, CG, RH, LH, AH, TH, DH, NI, FL, DJ, PL, EL, JM, CM, DM, SM, ZM, BM, SuM, PM, SrM, AN, RP, JP, SP, LFR, KR, HS, MS, CS, MS, VS, AIT, AnT, FvV, SW, RZ designed and obtained the funding for the study. LB, EL, SB, RJL, MF, MD, AM, CS performed the statistical analyses. All authors contributed to the conduct of the study, participant recruitment and follow-up, and to the interpretation of study data. NH, DCA wrote the first draft of the paper with input from LB, EL, SM, SB, TH, CG and RJL. All authors read and approved the final manuscript.

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Data availability

See Data Sharing Statement in the electronic supplementary material.

Declarations

Conflict of interest

See submitted ICMJE forms for declared potential conflict of interests.

Ethical approval
All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Helsinki Declaration and its later amendments.

Consent to participate
Informed consent was obtained before randomization from all patients or their surrogates, or in a deferred fashion, in accordance with local legislation.

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