ORIGINAL ARTICLE

Hydrocortisone in Severe Community-Acquired Pneumonia

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ABSTRACT

BACKGROUND

Whether the antiinflammatory and immunomodulatory effects of glucocorticoids may decrease mortality among patients with severe community-acquired pneumonia is unclear.

METHODS

In this phase 3, multicenter, double-blind, randomized, controlled trial, we assigned adults who had been admitted to the intensive care unit (ICU) for severe community-acquired pneumonia to receive intravenous hydrocortisone (200 mg daily for either 4 or 8 days as determined by clinical improvement, followed by tapering for a total of 8 or 14 days) or to receive placebo. All the patients received standard therapy, including antibiotics and supportive care. The primary outcome was death at 28 days.

RESULTS

A total of 800 patients had undergone randomization when the trial was stopped after the second planned interim analysis. Data from 795 patients were analyzed. By day 28, death had occurred in 25 of 400 patients (6.2%; 95% confidence interval [CI], 3.9 to 8.6) in the hydrocortisone group and in 47 of 395 patients (11.9%; 95% CI, 8.7 to 15.1) in the placebo group (absolute difference, –5.6 percentage points; 95% CI, –9.6 to –1.7; P=0.006). Among the patients who were not undergoing mechanical ventilation at baseline, endotracheal intubation was performed in 40 of 222 (18.0%) in the hydrocortisone group and in 65 of 220 (29.5%) in the placebo group (hazard ratio, 0.59; 95% CI, 0.40 to 0.86). Among the patients who were not receiving vasopressors at baseline, such therapy was initiated by day 28 in 55 of 359 (15.3%) of the hydrocortisone group and in 86 of 344 (25.0%) in the placebo group (hazard ratio, 0.59; 95% CI, 0.43 to 0.82). The frequencies of hospital-acquired infections and gastrointestinal bleeding were similar in the two groups; patients in the hydrocortisone group received higher daily doses of insulin during the first week of treatment.

CONCLUSIONS

Among patients with severe community-acquired pneumonia being treated in the ICU, those who received hydrocortisone had a lower risk of death by day 28 than those who received placebo. (Funded by the French Ministry of Health; CAPE COD ClinicalTrials.gov number, NCT02517489.)

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*A list of the members of the CRICS-TriGGERSep Network is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on March 21, 2023, at NEJM.org.

DOI: 10.1056/NEJMoa2215145

Community-acquired pneumonia remains a major public health issue. Worldwide, 489 million lower respiratory infections occurred in 2019.[1] In the United States, more than 1.5 million adults are hospitalized for community-acquired pneumonia annually.[2] In 2019, pneumonia was the ninth leading cause of death in the United States and the leading cause of death from infection (approximately 50,000 deaths).[3] In high-income countries, the monthly rate of death among patients who are hospitalized with community-acquired pneumonia is approximately 10 to 12%.[4,5] Among patients who receive any type of mechanical ventilation, mortality may reach 30%.[6]

Pneumonia may lead to intense pulmonary and systemic inflammation, which results in impaired gas exchange, sepsis and organ failure, and an increased risk of death. Glucocorticoids have powerful antiinflammatory and immunomodulatory activities that mitigate the consequences of pneumonia. Seven randomized, controlled trials[7-13] showed that glucocorticoids had positive effects in patients with community-acquired pneumonia of varying severity; however, with the exception of one trial,[7] none of these trials showed a between-group difference regarding mortality. A meta-analysis of six of these trials[7-12] suggested that glucocorticoids reduced the time until clinical stabilization and length of hospital stay without improving survival.[14] Another meta-analysis that included trials that were open label or were deemed to have a risk of bias suggested that glucocorticoids decreased mortality among patients with severe community-acquired pneumonia, with a moderate quality of evidence.[15]

We conducted the Community-Acquired Pneumonia: Evaluation of Corticosteroids (CAPE COD) trial to evaluate whether early treatment with hydrocortisone reduced mortality at 28 days among patients admitted to an intensive care unit (ICU) for severe community-acquired pneumonia.

Methods

Trial Design

This double-blind, randomized, controlled superiority trial was conducted in 31 French centers by the members of the Clinical Research in Intensive Care and Sepsis–Trial Group for Global Evaluation and Research in Sepsis (CRICS-TriGGERSep) Network. The ethics committee and the French regulatory agency approved the protocol, which is available with the full text of this article at NEJM.org. Patients or their legally authorized representative provided written informed consent. Neither the funder (the French Ministry of Health) nor the trial-coordination sponsor (University Hospital, Tours, France) was involved in the design or execution of the trial, in the interpretation of the data, or in the writing of the manuscript. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patients

Adult patients (≥18 years of age) were eligible for inclusion if they had been admitted to one of the participating ICUs for severe community-acquired pneumonia. The diagnosis of pneumonia was supported by clinical and radiologic criteria, as detailed in the Supplementary Appendix, available at NEJM.org. The search for a pathogen was left to the discretion of each medical team. However, it was recommended to test for influenza during epidemic periods.

The severity of pneumonia was defined by the presence of at least one of four criteria: the initiation of mechanical ventilation (invasive or noninvasive) with a positive end-expiratory pressure level of at least 5 cm of water; the initiation of the administration of oxygen through a high-flow nasal cannula with a ratio of the partial pressure of arterial oxygen to the inspired fraction of oxygen (PaO_2:FIO_2) of less than 300, with a FIO_2 of 50% or more; for patients wearing a nonrebreathing mask, an estimated PaO_2:FIO_2 ratio of less than 300, according to prespecified charts; or a score of more than 130 on the Pulmonary Severity Index, which classifies patients with community-acquired pneumonia into five groups according to increasing severity, with a score of more than 130 defining group V, which is associated with the highest mortality.[16]

Principal noninclusion criteria were a do-not-intubate order, pneumonia caused by influenza (owing to concern about the safety of glucocorticoids), and septic shock. Inclusion and exclusion criteria are detailed in the Supplementary Appendix.

INTERVENTION AND RANDOMIZATION

Patients received state-of-the-art standard therapy for severe community-acquired pneumonia, including antibiotics and supportive care. The choice of respiratory support was left to the discretion of the medical team. In addition, within 24 hours after the onset of any severity criterion described above, patients in the hydrocortisone group received intravenous hydrocortisone administered continuously at a dose of 200 mg per day during the first 4 days. On the fourth day, the medical team used predefined criteria to decide whether to administer hydrocortisone for a total of 8 or 14 days, depending on whether the patient's condition had improved. Regardless of the duration of treatment, the dose of hydrocortisone was gradually tapered according to a prespecified plan. In all cases, treatment was discontinued at the time of discharge from the ICU. Details regarding hydrocortisone treatment are provided in Figure S1 in the Supplementary Appendix. Patients in the control group received intravenous placebo (saline) according to the same regimen that was used in the hydrocortisone group. Both hydrocortisone and placebo were provided in identical packages (SERB Specialty Pharmaceuticals).

Randomization was centralized and performed electronically with the use of a Web-based response system. Patients were randomly assigned in a 1:1 ratio to receive hydrocortisone or placebo according to a computer-generated random list prepared by a statistician who was uninvolved in the enrollment process, with block sizes of four. Randomization was stratified according to trial center and the use or nonuse of mechanical ventilation at the time of enrollment.

OUTCOMES

The primary outcome was death from any cause by day 28. Secondary outcomes were death from any cause by day 90; the length of ICU stay; noninvasive ventilation or endotracheal intubation among patients who were not receiving any type of ventilation at baseline; endotracheal intubation among patients who were receiving noninvasive ventilation at baseline; the initiation of vasopressor therapy by day 28; the number of ventilator-free days and vasopressor-free days by day 28; the change in the PaO_2:FIO_2 ratio by day 7; the change by day 7 in the score on the Sequential Organ Failure Assessment (SOFA),[17] which rates levels of function of six major physiologic systems on a scale from 0 (no failure) to 4 (most severe failure); and quality of life by day 90, as measured on the 36-Item Short-Form Health Survey (SF-36).[18]

Safety criteria included secondary infections or gastrointestinal bleeding by day 28, the daily amount of insulin administered by day 7, and weight gain by day 7.

STATISTICAL ANALYSIS

We estimated that the enrollment of 1146 patients would provide 80% power to detect a 25% relative reduction in mortality by day 28, which was calculated from an estimated mortality of 27.0% in the placebo group[6,19,20] and 20.25% in the hydrocortisone group. With two interim analyses planned after inclusion of one third and two thirds of the patients, the application of Peto's rule[21] required the enrollment of 1165 patients, which we rounded to 1200 to account for the possibility of withdrawal of consent.

At the time of the outbreak of coronavirus disease 2019 (Covid-19) in France, 800 patients had undergone randomization. The opportunity to evaluate hydrocortisone in patients with Covid-19 and acute respiratory failure by relying on the logistics of the ongoing trial prompted us to temporarily suspend enrollment and quickly design a dedicated embedded trial. The methodologic choices relating to this original approach[22] and the results of the embedded trial[23] have been described previously. There was no overlap between patients in the two trials. Our initial plan was to resume enrollment in the original trial at the end of the pandemic. Because of the pandemic-related workload in participating centers, it was only recently possible to conduct the second interim analysis. On the basis of that analysis, the data and safety monitoring board recommended that enrollment be discontinued.

All statistical analyses followed a prespecified statistical analysis plan. A P value of less than 0.049 was considered to indicate statistical significance. Statistical analyses for secondary end points were not adjusted for multiplicity, so the findings should be interpreted as exploratory. Similarly, the widths of confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis test-

ing. Categorical variables were summarized as frequencies and percentages and continuous variables as medians and interquartile ranges. For mortality, missing data were handled on the assumption that patients with missing data had died. The rates of death by day 28 and day 90 were reported as point estimates with 95% confidence intervals in each group. The difference in percentages and the 95% confidence interval were also estimated by means of the Wald method. We used the chi-square test to analyze 28-day mortality. To assess the consistency of the treatment effect on the primary outcome across prespecified or post hoc subgroups, we assessed differences in percentages and 95% confidence intervals across subgroups by using linear models with identity-link functions, including interaction terms.

We compared the length of ICU stay in the framework of a Fine and Gray model,[24] with death considered as a competing event. A competing-risk approach (with death and end of ICU stay as competing events) was also used to compare the percentages of patients who received the following treatments: the initiation of noninvasive ventilation or endotracheal intubation among those who had not undergone any mechanical ventilation at baseline, endotracheal intubation among those who had received only noninvasive ventilation at baseline, vasopressor therapy by day 28, and secondary infection or gastrointestinal bleeding by day 28. For competing-risk models, we assessed proportionality assumptions, including a time interaction term with the Fine and Gray models. We estimated the median of differences and 95% confidence intervals for ventilator-free days and vasopressor-free days by day 28, responses on the SF-36 Health Survey by day 90, the daily amount of insulin administered by day 7, and weight gain by day 7. We analyzed changes in the PaO_2:FIO_2 ratio and SOFA scores in the framework of a mixed model. All data were analyzed with SAS software, version 9.4 (SAS Institute), and R software, version 3.3.1 (R Foundation for Statistical Computing).

RESULTS

CHARACTERISTICS OF THE PATIENTS

From October 28, 2015, to March 11, 2020, a total of 5948 patients were assessed for eligibility; of these patients, 800 were enrolled in the trial. Reasons for noninclusion are detailed in Figure 1. The distribution of the numbers of patients who were enrolled at each site is detailed in Table S1, and the recruitment curve is shown in Figure S2.

The data and safety monitoring board met on July 2, 2018, for a first interim analysis involving 398 patients and recommended that the trial continue. The board met again on July 2, 2021, for the planned second interim analysis and recommended discontinuation of enrollment. Details regarding these analyses are provided in the Supplementary Appendix.

Of the 401 patients who were assigned to the hydrocortisone group, 1 died before receiving any treatment. Of the 399 patients who were assigned to the placebo group, 2 patients withdrew their consent and 2 patients who were under legal protection gave their consent without having the legal capacity to do so. Thus, 795 patients were included in the primary analysis. Table 1 and Table S2 show the baseline characteristics of the patients, including infections with documented pathogens. The representativeness of the trial patients is shown in Table S3, which suggests that the population was representative of patients with severe community-acquired pneumonia in a high-income country. Only 54 patients (6.8%) were included on the sole criterion of a score of more than 130 on the Pneumonia Severity Index. The actual duration of the administration of hydrocortisone and placebo and the reasons for their premature discontinuation are provided in Table S4.

PRIMARY OUTCOME

By day 28, death had occurred in 25 of 400 patients (6.2%; 95% confidence interval [CI], 3.9 to 8.6) in the hydrocortisone group and in 47 of 395 patients (11.9%; 95% CI, 8.7 to 15.1) in the placebo group (absolute difference, −5.6 percentage points; 95% CI, −9.6 to −1.7; P=0.006) (Table 2).

SECONDARY OUTCOMES

The subgroup analysis of death from any cause by day 28 is shown in Figure S3. By day 90, mortality was 9.3% in the hydrocortisone group and 14.7% in the placebo group (absolute difference, −5.4 percentage points; 95% CI, −9.9 to −0.8). The cumulative percentage of patients who were

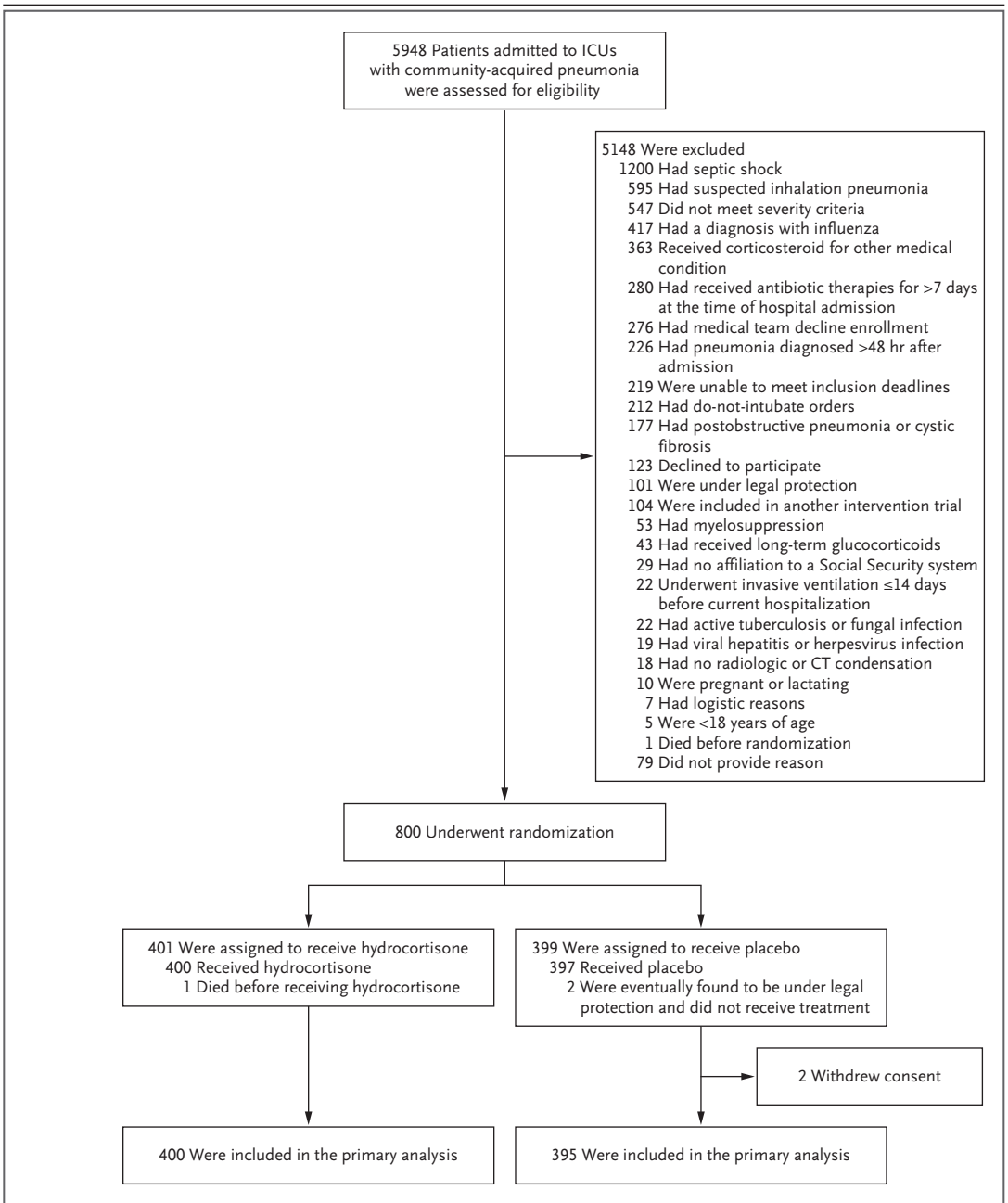


Figure 1. Screening, Randomization, and Outcomes.

Randomization was stratified according to trial center and receipt or nonreceipt of mechanical ventilation at baseline. CT denotes computed tomography, and ICU intensive care unit.

discharged from the ICU by day 28 is shown in Figure 2. Among 442 patients who had not received any mechanical ventilation at baseline, endotracheal intubation was performed in 18.0% in the hydrocortisone group and in 29.5% in the placebo group (hazard ratio, 0.59; 95% CI, 0.40 to 0.86) (Fig. 3A). Among 618 patients who had received no invasive ventilation at baseline, the cumulative incidence of invasive mechanical ventilation before day 28 was 19.5% in the hydro-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Hydrocortisone (N = 400)	Placebo (N = 395)
Median age (IQR) — yr	67 (58–77)	67 (58–78)
Sex — no. (%)		
Male	281 (70.2)	271 (68.6)
Female	119 (29.8)	124 (31.4)
Coexisting condition — no. (%)		
COPD	86 (21.5)	105 (26.6)
Asthma	22 (5.5)	17 (4.3)
Diabetes	95 (23.8)	86 (21.8)
Immunosuppression	24 (6.0)	27 (6.8)
Type of respiratory support — no. (%)		
Mechanical ventilation	178 (44.5)	175 (44.3)
Invasive	92 (23.0)	85 (21.5)
Noninvasive	86 (21.5)	90 (22.8)
High-flow nasal cannula	169 (42.2)	162 (41.0)
Nonrebreathing mask	53 (13.2)	58 (14.7)
Median Pulmonary Severity Index (IQR)†	127 (102–153)	130 (103–150)
Distribution — no./total no. (%)		
Class I	5/396 (1.3)	4/392 (1.0)
Class II	15/396 (3.8)	15/392 (3.8)
Class III	45/396 (11.4)	47/392 (12.0)
Class IV	150/396 (37.9)	133/392 (33.9)
Class V	181/396 (45.7)	193/392 (49.2)
Median SAPS II score (IQR)‡	37 (30–45)	38 (31–47)
Median SOFA score (IQR)§	4 (3–6)	4 (3–6)
Treatment with vasopressors — no. (%)	41 (10.2)	51 (12.9)
Laboratory data		
C-reactive protein		
Median (IQR) — mg/dl	26.3 (11.7–35.6)	23.8 (11.7–35.0)
Value of >15 mg/dl — no./total no. (%)	208/298 (69.8)	215/312 (68.9)
Median procalcitonin (IQR) — ng/ml	3.2 (0.5–16.4)	4.1 (0.6–16.0)
Median cortisol (IQR) — nmol/liter	302 (24–785)	307 (25–697)
Timing of treatment		
Median interval from hospital admission to ICU admission (IQR) — hr	5.5 (2.8–10.9)	5.2 (2.4–10.9)
Median interval from ICU admission to initiation of trial agent (IQR) — hr	15.3 (7.0–20.5)	14.6 (5.9–20.5)

* COPD denotes chronic obstructive pulmonary disease, and IQR interquartile range.
† The Pneumonia Severity Index classifies patients with community-acquired pneumonia into five groups according to increasing severity, with a score of more than 130 defining group V, which is associated with the highest mortality.
‡ The Simplified Acute Physiology Score, version II (SAPS II), was calculated during the first 24 hours after admission to the intensive care unit (ICU). It is an overall severity score that ranges from 0 to 163, with higher scores indicating greater severity of illness.
§ The Sequential Organ Failure Assessment (SOFA) evaluates the functions of six major physiological systems, with each evaluated from 0 (no failure) to 4 (most severe failure).

Table 2. Primary and Secondary Outcomes.*

Outcome	Hydrocortisone	Placebo	Treatment Effect (95% CI)	P Value
Primary outcome				
Death by day 28 — no./total no. (%)	25/400 (6.2)	47/395 (11.9)	Difference, –5.6	0.006
95% CI — percentage points	3.9 to 8.6	8.7 to 15.1	–9.6 to –1.7	
Secondary outcomes†				
Death by day 90 — no./total no.	36/388 (9.3)	57/389 (14.7)	Difference, –5.4	
95% CI — percentage points	6.4 to 12.2	11.1 to 18.2	–9.9 to –0.8	
Patients not receiving any mechanical ventilation at baseline — no./total no. (%)				
Cumulative incidence of endotracheal intubation by day 28	40/222 (18.0)	65/220 (29.5)	HR, 0.59 (0.40 to 0.86)	
Cumulative incidence of noninvasive ventilation by day 28	15/222 (6.8)	24/220 (10.9)	HR, 0.60 (0.32 to 1.15)	
Cumulative incidence of endotracheal intubation by day 28 in patients not receiving endotracheal intubation at baseline — no./total no. (%)	60/308 (19.5)	86/310 (27.7)	HR, 0.69 (0.50 to 0.94)	
Cumulative incidence of initiation of vasopressors by day 28 in patients not receiving vasopressor at baseline — no./total no. (%)	55/359 (15.3)	86/344 (25.0)	HR, 0.59 (0.43 to 0.82)	
Safety outcomes‡				
Cumulative incidence of hospital-acquired infection by day 28 — no./total no. (%)§	39/400 (9.8)	44/395 (11.1)	HR, 0.87 (0.57 to 1.34)	0.54
Ventilator-associated pneumonia	32/152 (21.0)	38/171 (22.2)		
Bloodstream infection	5/400 (1.2)	9/395 (2.3)		
Cumulative incidence of gastrointestinal bleeding by day 28	9/400 (2.2)	13/395 (3.3)	HR, 0.68 (0.29 to 1.59)	0.38
Median daily dose of insulin by day 7 in patients receiving insulin therapy (IQR) — IU/day¶	35.5 (15.0 to 57.5)	20.5 (9.4 to 48.5)	Median difference, 8.7 (4.0 to 13.8)	>0.001
Median weight change from baseline to day 7 (IQR) — kg‖	2.0 (–0.5 to 5.0)	1.0 (–3.0 to 6.0)	Median difference, 1.0 (0 to 2.0)	0.18

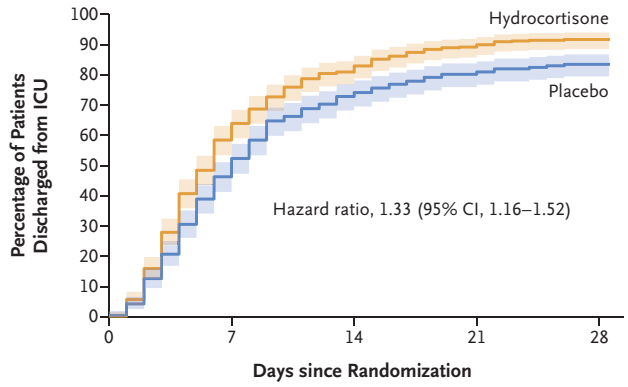
* HR denotes hazard ratio.
† For secondary outcomes, the widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing. Other secondary outcomes are reported in Table S5.
‡ Safety outcomes are detailed in Table S6.
§ Some patients had both ventilator-associated pneumonia and bloodstream infection. Other infections were not detailed if they involved fewer than 5 patients.
¶ Insulin was administered to 231 patients in the hydrocortisone group and to 177 patients in the placebo group.
‖ Data on weight change were available for 168 patients in the hydrocortisone group and 193 patients in the placebo group.

cortisone group and 27.7% in the placebo group (hazard ratio, 0.69; 95% CI, 0.50 to 0.94) (Fig. 3B). Among the 703 patients who had not received vasopressors at baseline, the cumulative incidence of vasopressor initiation was 15.3% in the hydrocortisone group and 25.0% in the placebo group (hazard ratio, 0.59; 95% CI, 0.43 to 0.82) (Fig. 3C).

Changes in the PaO_2:FIO_2 ratio and the SOFA score are shown in Figures S3 and S4, respectively. Ventilator- and vasopressor-free days by day 28, length of ICU stay, and SF-36 scores are shown in Table S5.

ADVERSE EVENTS

During the first 28 days after randomization, 169 serious adverse events occurred in 151 of 795 patients (19.0%): 70 in the hydrocortisone



No. at Risk

Hydrocortisone	400	160	67	31	17
Placebo	395	198	85	48	27

Figure 2. Discharge from ICU by Day 28.

Shown is the cumulative percentage of patients who were discharged from the ICU by day 28 (a secondary outcome in the trial). The length of ICU stay was compared in the framework of a competing-risk model, with death considered as a competing event. For secondary outcomes, the widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

group and 99 in the placebo group (Table S6). ICU-acquired infections occurred in 9.8% of patients in the hydrocortisone group and in 11.1% in the placebo group (hazard ratio, 0.87; 95% CI, 0.57 to 1.34) (Fig. S6). The occurrence of gastrointestinal bleeding was rare in the two groups (Fig. S7). By day 7, patients who were receiving insulin therapy during the first week of the trial were administered a median of 35.5 IU (interquartile range, 15.0 to 57.5) per day in the hydrocortisone group and 20.5 IU (interquartile range, 9.4 to 48.5) per day in the placebo group.

DISCUSSION

In this large, multicenter trial, early hydrocortisone therapy reduced the rate of death by day 28 among patients who had been admitted to the ICU for severe community-acquired pneumonia. The results appeared to be consistent across important subgroups. Our data do not indicate any particular safety issues, including no between-group difference in the occurrence of hospital-acquired infections.

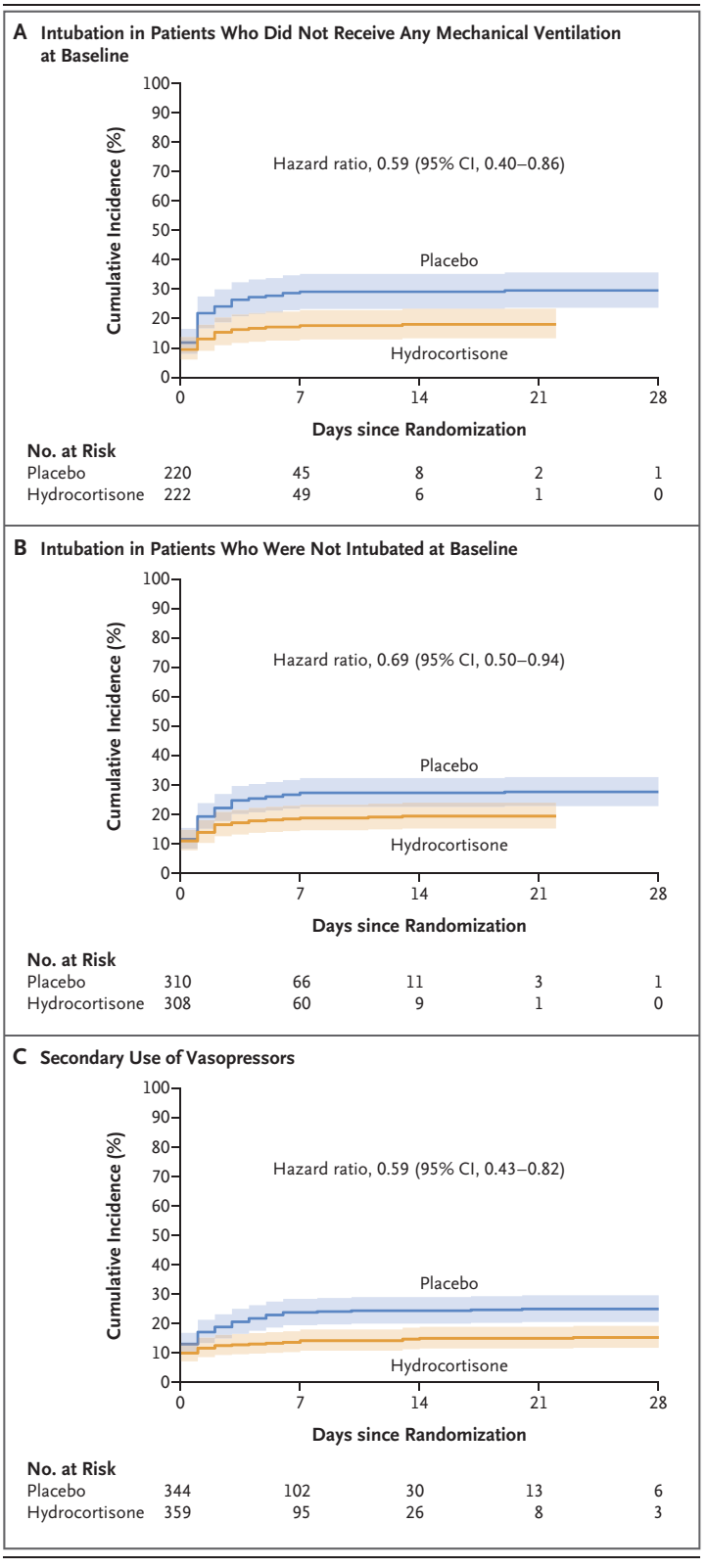
Few large, multicenter trials have evaluated glucocorticoids in patients with severe community-acquired pneumonia who have been admitted to the ICU. In a trial involving 120 critically ill patients with community-acquired pneumonia and a C-reactive protein level of more than 15 mg per deciliter, treatment with methylprednisolone reduced a composite outcome of treatment failure but did not alter in-hospital mortality.[12] The results of a recently published trial showed no benefit of methylprednisolone in 584 patients hospitalized in the ICU for community-acquired pneumonia, with mortality on day 60 of 16% as compared with 18% in the placebo group.[25]

Several factors may explain these discrepancies. First, the pharmacodynamic properties of glucocorticoids may differ, including the balance between mineralocorticoid and glucocorticoid effects. In a previous small trial that suggested a decrease in mortality,[7] the patients also received hydrocortisone. Second, we excluded patients with septic shock at baseline because the pathophysiological processes and role for glucocorticoids may differ.[26,27] Third, the very short median time between admission to the ICU and the first administration of hydrocortisone or placebo in our trial (<15 hours) may have promoted an early effect. Fourth, our trial population included a larger proportion of women (30.6%) than another trial in which glucocorticoid treatment did not alter mortality,[25] and potential differences in response to glucocorticoids according to sex have been suggested.[28]

Hydrocortisone was not associated with an increase in hospital-acquired infections or gastrointestinal bleeding. However, patients in the hydrocortisone group received higher doses of insulin during the first 7 days of treatment. An increased incidence of hyperglycemia, which is consistent with the pharmacodynamic effects of glucocorticoids, has been reported in trials[9,11] and in meta-analyses.[15,29,30] Such increases are usually transient,[11] which we did not verify in the trial.

Our trial has several limitations. First, the observed mortality of 11.9% in the control group was lower than anticipated (27%), which may indicate a lower severity of illness than expected. However, the enrollment of a high-risk popula-

Figure 3. Intubation and Initiation of Vasopressor Therapy.
Several secondary outcomes focused on the incidence of intubation and the initiation of vasopressor therapy according to the treatment that patients were receiving at baseline. Panel A shows the cumulative incidence of intubation among the 442 patients who did not undergo any type of mechanical ventilation at baseline. Panel B shows the cumulative incidence of intubation among the 618 patients who were not intubated at baseline. Panel C shows the cumulative incidence of the initiation of vasopressor therapy among the 703 patients who were not receiving a vasopressor at baseline.



tion is suggested by the percentage of patients who underwent mechanical ventilation, the distribution of the score on the Pneumonia Severity Index, and the PaO_2:FIO_2 ratio at baseline. However, we excluded patients with septic shock at the time of enrollment. Second, a standardized microbiologic investigation was not mandated, and no pathogen was isolated in 357 of 795 patients (44.9%). Even in studies with exhaustive microbiologic evaluations, no pathogen is detected in up to 62% of patients with community-acquired pneumonia.[31] Third, we included a small percentage of immunocompromised patients, and the results should be applied with caution in this population. Fourth, we did not evaluate the reversibility of glucocorticoid-induced hyperglycemia. Likewise, we did not specifically assess the potential neuropsychological and neuromuscular side effects of glucocorticoids. Fifth, the administration of hydrocortisone by continuous infusion and with tapering doses as compared with other potential regimens is not itself supported by a high level of evidence.

We found that early treatment with hydrocortisone reduced 28-day mortality among patients who had been admitted to the ICU with severe community-acquired pneumonia.

Supported by the French Ministry of Health (Programme Hospitalier de Recherche Clinique 2014).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients who participated in the trial and their families and the members of the data and safety monitoring board — Drs. Jean Chastre, Béatrice Guyomarch, and Sylvain Marchand-Adam — for their commitment and responsiveness.

APPENDIX

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