ORIGINAL ARTICLE

# Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

D. Annane, A. Renault, C. Brun-Buisson, B. Megarbane, J.-P. Quenot, S. Siami, A. Cariou, X. Forceville, C. Schwebel, C. Martin, J.-F. Timsit, B. Misset, M. Ali Benali, G. Colin, B. Souweine, K. Asehnoune, E. Mercier, L. Chimot, C. Charpentier, B. François, T. Boulain, F. Petitpas, J.-M. Constantin, G. Dhonneur, F. Baudin, A. Combes, J. Bohé, J.-F. Loriferne, R. Amathieu, F. Cook, M. Slama, O. Leroy, G. Capellier, A. Dargent, T. Hissem, V. Maxime, and E. Bellissant, for the CRICS-TRIGGERSEP Network*

## ABSTRACT

### BACKGROUND

Septic shock is characterized by dysregulation of the host response to infection, with circulatory, cellular, and metabolic abnormalities. We hypothesized that therapy with hydrocortisone plus fludrocortisone or with drotrecogin alfa (activated), which can modulate the host response, would improve the clinical outcomes of patients with septic shock.

### METHODS

In this multicenter, double-blind, randomized trial with a 2-by-2 factorial design, we evaluated the effect of hydrocortisone-plus-fludrocortisone therapy, drotrecogin alfa (activated), the combination of the three drugs, or their respective placebos. The primary outcome was 90-day all-cause mortality. Secondary outcomes included mortality at intensive care unit (ICU) discharge and hospital discharge and at day 28 and day 180 and the number of days alive and free of vasopressors, mechanical ventilation, or organ failure. After drotrecogin alfa (activated) was withdrawn from the market, the trial continued with a two-group parallel design. The analysis compared patients who received hydrocortisone plus fludrocortisone with those who did not (placebo group).

### RESULTS

Among the 1241 patients included in the trial, the 90-day mortality was 43.0% (264 of 614 patients) in the hydrocortisone-plus-fludrocortisone group and 49.1% (308 of 627 patients) in the placebo group (P=0.03). The relative risk of death in the hydrocortisone-plus-fludrocortisone group was 0.88 (95% confidence interval, 0.78 to 0.99). Mortality was significantly lower in the hydrocortisone-plus-fludrocortisone group than in the placebo group at ICU discharge (35.4% vs. 41.0%, P=0.04), hospital discharge (39.0% vs. 45.3%, P=0.02), and day 180 (46.6% vs. 52.5%, P=0.04) but not at day 28 (33.7% and 38.9%, respectively; P=0.06). The number of vasopressor-free days to day 28 was significantly higher in the hydrocortisone-plus-fludrocortisone group than in the placebo group (17 vs. 15 days, P<0.001), as was the number of organ-failure–free days (14 vs. 12 days, P=0.003). The number of ventilator-free days was similar in the two groups (11 days in the hydrocortisone-plus-fludrocortisone group and 10 in the placebo group, P=0.07). The rate of serious adverse events did not differ significantly between the two groups, but hyperglycemia was more common in hydrocortisone-plus-fludrocortisone group.

### CONCLUSIONS

In this trial involving patients with septic shock, 90-day all-cause mortality was lower among those who received hydrocortisone plus fludrocortisone than among those who received placebo. (Funded by Programme Hospitalier de Recherche Clinique 2007 of the French Ministry of Social Affairs and Health; APROCCHSS ClinicalTrials.gov number, NCT00625209.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Annane at Service de Médecine Intensive et Réanimation, Hôpital Raymond Poincaré, 104 Blvd. Raymond Poincaré, 92380 Garches, France, or at djillali.annane@aphp.fr.

*A complete list of investigators in the APROCCHSS trial is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2018;378:809-18.
DOI: 10.1056/NEJMoa1705716

Septic shock is characterized by a dysregulated host response to infection, resulting in life-threatening circulatory, cellular, and metabolic abnormalities.[1] The short-term mortality is approximately 45 to 50%,[2] and 50% of survivors of sepsis may have subsequent long-term cognitive decline.[3] Apart from early hemodynamic and respiratory resuscitation and appropriate antiinfective treatments, there is no approved adjunct therapy for sepsis.[4] A human recombinant activated protein C, drotrecogin alpha (activated), initially showed a survival benefit in sepsis; this benefit was not confirmed in subsequent trials, resulting in the withdrawal of its commercial form (Xigris) from the market.[5,6]

Experimental and clinical evidence suggests that sepsis is associated with a dysregulated response of the hypothalamic–pituitary–adrenal axis that may involve any of the steps from cortisol production to cortisol use by cells.[7] Corticosteroids have been used in the treatment of patients with severe infections since the mid-twentieth century. However, their benefit-to-risk ratio, albeit evaluated in numerous trials, remains controversial. Quantitative analysis of these trials has variably confirmed[8] or refuted[9] the survival benefit of corticosteroids in patients with sepsis. This has resulted in substantial heterogeneity in physicians' clinical practice, with approximately one third of physicians believing that corticosteroids improve survival in septic shock, one third believing that they do not, and one third being unsure.[10]

This uncertainty about the use of corticosteroids may relate to the differences in the results of the two largest trials.[11,12] Although both trials showed treatment benefits in terms of hemodynamic status and organ function, only one trial[11] showed survival benefits. The divergent findings may have resulted from differences in the design of the trials.[13] To resolve this discrepancy, we designed a trial to test the hypothesis that hydrocortisone-plus-fludrocortisone therapy or drotrecogin alfa (activated) would improve the clinical outcomes of patients with septic shock.

## Methods

### Trial Design and Oversight

Information on the design and conduct of the Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial, including the trial protocol and amendments and the statistical analysis plan, was published previously[13] and is available with the full text of this article at NEJM.org. An independent ethics committee (Comité de Protection des Personnes d'Ile de France XI, Saint-Germain-en-Laye, France) approved the trial protocol. Participants or their legally authorized next of kin provided written informed consent before inclusion whenever possible. Otherwise, deferred written informed consent was obtained from patients.

This investigator-led trial was publicly funded. Our placebo-controlled trial, conducted with four parallel groups that were organized in a 2-by-2 factorial design, aimed to evaluate the benefits and risks of corticosteroids and drotrecogin alfa (activated) given alone or in combination. After the withdrawal of Xigris from the market in October 2011, the trial continued with two parallel groups. The effects of drotrecogin alfa (activated) have been reported previously[14]; in the current article, we report on the effects of hydrocortisone-plus-fludrocortisone therapy. All the authors had full and independent access to all data and vouch for the integrity, accuracy, and completeness of the data and analysis and for the adherence of the trial to the protocol.

### Trial Patients

Patients in intensive care units (ICUs) were eligible for inclusion in the trial if they had indisputable or probable septic shock[15] for less than 24 hours. Septic shock was defined as the presence of a clinically or microbiologically documented infection, a Sequential Organ Failure Assessment (SOFA)[16] score of 3 or 4 (on a scale of 0 to 4 for each of six organ systems, with higher scores indicating more severe organ dysfunction) for at least two organs and at least 6 hours, and receipt of vasopressor therapy (norepinephrine, epinephrine, or any other vasopressor at a dose of ≥0.25 $\mu$g per kilogram of body weight per minute or ≥1 mg per hour) for at least 6 hours to maintain a systolic blood pressure of at least 90 mm Hg or a mean blood pressure of at least 65 mm Hg.

The exclusion criteria have been detailed elsewhere.[13] (See also the trial protocol.) Major exclusion criteria were the presence of septic shock for at least 24 hours, a high risk of bleeding,

pregnancy or lactation, underlying conditions that could affect short-term survival, known hypersensitivity to drotrecogin alfa (activated), or previous treatment with corticosteroids. After the withdrawal of Xigris from the market, the exclusion criteria that were relevant only to drotrecogin alfa (activated) were removed.[13] (Protocol amendments are detailed in the Supplementary Appendix, available at NEJM.org.)

### RANDOMIZATION AND TRIAL AGENTS

Patients were randomly assigned in permuted blocks of eight to receive hydrocortisone-plus-fludrocortisone therapy, drotrecogin alfa (activated), the combination of the three drugs, or their respective placebos. (For more details on randomization, see the protocol.) Hydrocortisone was administered as a 50-mg intravenous bolus every 6 hours, and fludrocortisone was given as a 50-$\mu$g tablet through a nasogastric tube once daily in the morning. Trial agents were administered for 7 days without tapering. Placebos of French commercial forms of hydrocortisone and fludrocortisone were manufactured for the requirements of the trial. Active agents and placebos had similar appearances (checked and certified by qualified persons for each batch) — that is, vials of white, freeze-dried powder for parenteral use of hydrocortisone hemisuccinate (100 mg) or placebo (mannitol [133.6 mg], disodium phosphate [8.73 mg], and sodium phosphate [0.92 mg]) and tablets of oral fludrocortisone or placebo (microcrystalline cellulose [59.098 mg], magnesium stearate [0.6 mg], and colloidal anhydrous silica [0.3 mg]) in blister packs of 10. The details of administration of drotrecogin alfa (activated) are available in the protocol.

### TRIAL MEASUREMENTS AND PROCEDURES

Before randomization, plasma total cortisol levels were measured before, and 30 and 60 minutes after, an intravenous bolus of 250 $\mu$g of corticotropin (Synacthen). The variables that were investigated at baseline and during the 180-day follow-up have been detailed elsewhere.[13] Nonexperimental interventions were harmonized across centers according to the 2008 Surviving Sepsis Campaign guidelines,[17] including anti-infective treatments, hemodynamic and respiratory management, and blood glucose control. Investigators followed national guidelines for the prevention of superinfection.[18] Neuromuscular-blocking agents were discouraged except in the first 24 hours in the presence of refractory hypoxemia. Investigators' adherence to guidelines was checked at each investigators' meeting.

### OUTCOMES

The primary outcome was 90-day all-cause mortality. Secondary outcomes were all-cause mortality at ICU discharge, hospital discharge, day 28, and day 180; the percentage of patients from whom care was withheld or withdrawn; the percentage of patients weaned from vasopressors at day 28 and day 90; the time to weaning from vasopressors; the number of days that patients were alive and free of vasopressors (vasopressor-free days) up to day 28 and day 90 (patients who died before day 28 or day 90 were assigned zero free days); the percentage of patients weaned from mechanical ventilation at day 28 and day 90; the time to weaning from mechanical ventilation; ventilator-free days up to day 28 and day 90; the percentage of patients with a total SOFA score below 6 (organ-failure–free) at day 28 and day 90; the time to reaching a SOFA score below 6; organ-failure–free days up to day 28 and day 90; the percentage of patients discharged from the ICU and hospital up to day 28 and day 90; the time to discharge from the ICU and hospital; and ICU-free and hospital-free days up to day 28 and day 90.

Safety outcomes included superinfection up to day 180, gastrointestinal bleeding up to day 28, episodes of hyperglycemia up to day 7, and neurologic sequelae (cognitive impairment and muscle weakness) at the time of ICU and hospital discharge, day 90, and day 180. All adverse events were recorded according to Medical Dictionary for Regulatory Activities classification (Tables S13 and S14 in the Supplementary Appendix).

### STATISTICAL ANALYSIS

We anticipated a 90-day mortality of 45% among patients with septic shock.[19] According to the 2-by-2 factorial design with a two-sided formulation, 320 patients were needed in each group (i.e., a total of 1280 patients) to detect an absolute difference of 10 percentage points in 90-day mortality ($\alpha$=0.05 and power at 95%) between

either drotrecogin alfa (activated) or corticosteroids and placebo. An intention-to-treat analysis was planned to be performed after all the participants had completed the 180-day follow-up and according to the 2-by-2 factorial design.[13] Owing to the withdrawal of Xigris from the market in 2011, the trial continued with two parallel groups (see the protocol) and was underpowered to assess the effect of drotrecogin alfa (activated). The sponsor terminated the trial when the expiration dates of the trial agents were reached and 1241 patients (97% of the expected sample size) had been enrolled.

The analysis compared all the patients assigned to receive hydrocortisone plus fludrocortisone with those assigned to receive corresponding placebos. Continuous variables are presented as means and standard deviations. Categorical variables are presented as the number of patients in each category and the corresponding percentages. Missing data were not replaced. The effects of trial agents on the frequency of fatal events (mortality at day 28, at day 90, at discharge from the ICU or hospital, and at day 180) and safety outcomes were compared with the use of logistic-regression models and the chi-square test. Continuous variables were compared with the use of analyses of variance and t-tests. Cumulative event curves (censored end points) were estimated with the Kaplan–Meier procedure, and Cox models and the log-rank test were used to compare the effects of trial agents (time to ICU and hospital discharge). The Fine and Gray subdistribution hazard regression models, which extend the Cox model to competing risk data by considering the hazard function associated with the cumulative incidence function, were used to compare the effects of trial agents (time to weaning from vasopressors, to weaning from mechanical ventilation, and to reaching a SOFA score <6). No adjustment for multiple testing was made. All analyses were conducted with SAS statistical software, version 9.4 (SAS Institute).

## RESULTS

### BASELINE PATIENT CHARACTERISTICS

There were 34 participating centers. The first and last patients were recruited on September 2, 2008, and June 23, 2015, respectively. The trial was suspended twice: first, from October 25, 2011, to May 12, 2012, after the withdrawal of Xigris from the market, and second, at the request of the data and safety monitoring board, from July 22, 2014, to October 7, 2014, to check the quality of the trial agents and the distribution of serious adverse events.[13] On October 1, 2014, the data and safety monitoring board confirmed the conformity of the trial to the marketing-authorization application for fludrocortisone and hydrocortisone and the quality of their placebos; the board also confirmed that the distribution of serious adverse events between the groups did not justify halting the trial. The trial was completed on December 23, 2015 (Fig. S1 in the Supplementary Appendix). Table 1 shows the primary baseline characteristics of the patients. (See also Tables S1 through S7 in the Supplementary Appendix.) Patient demographic data, severity-of-illness scores, characteristics of infection, and treatments at baseline were similar in the two groups. Most patients were admitted from a medical ward and had severe septic shock, as evidenced by high Simplified Acute Physiology Score II (SAPS II) values (range, 0 to 163, with higher scores indicating greater severity of illness), high lactate levels, and a high degree of vasopressor dependency (mean dose of norepinephrine, 1 $\mu$g per kilogram per minute). Most patients had community-acquired infection, and the lung was the most common site of infection. The initial antimicrobial treatment was judged adequate (by the steering committee, according to the site of infection and the sensitivity of the pathogens) in 96.2% of the patients who received placebo and 96.9% of those who received corticosteroids (Tables S2, S5, and S7 in the Supplementary Appendix).

### OUTCOMES

#### *90-Day All-Cause Mortality*

At day 90, death had occurred in 264 of 614 patients (43.0%; 95% confidence interval [CI], 39.0 to 47.0) in the hydrocortisone-plus-fludrocortisone group and in 308 of 627 patients (49.1%; 95% CI, 45.1 to 53.1) in the placebo group (P=0.03) (Table 2 and Fig. 1). The relative risk of death was 0.88 (95% CI, 0.78 to 0.99) in favor of hydrocortisone-plus-fludrocortisone therapy.

#### *Secondary Outcomes*

Mortality was significantly lower in the hydrocortisone-plus-fludrocortisone group than in the

**Table 1. Baseline Characteristics of the Patients.***

| Characteristic | Placebo (N=627) | Hydrocortisone plus Fludrocortisone (N=614) | All Patients (N=1241) |
|---|---|---|---|
| Male sex — no./total no. (%) | 424/626 (67.7) | 402/614 (65.5) | 826/1240 (66.6) |
| Age — yr† | 66±15 | 66±14 | 66±14 |
| Admission from a medical ward — no./total no. (%) | 499/616 (81.0) | 495/601 (82.4) | 994/1217 (81.7) |
| SAPS II‡ | 56±19 | 56±19 | 56±19 |
| SOFA score§ | 11±3 | 12±3 | 12±3 |
| Community-acquired infection — no./total no. (%) | 459/608 (75.5) | 468/602 (77.7) | 927/1210 (76.6) |
| Site of infection — no./total no. (%)¶ | | | |
| Unknown | 18/626 (2.9) | 11/614 (1.8) | 29/1240 (2.3) |
| Lung | 363/626 (58.0) | 373/614 (60.7) | 736/1240 (59.4) |
| Abdomen | 68/626 (10.9) | 74/614 (12.1) | 142/1240 (11.5) |
| Urinary tract | 118/626 (18.8) | 102/614 (16.6) | 220/1240 (17.7) |
| Positive blood culture — no./total no. (%) | 229/626 (36.6) | 225/614 (36.6) | 454/1240 (36.6) |
| Documented pathogen — no./total no. (%) | 441/626 (70.4) | 450/614 (73.3) | 891/1240 (71.9) |
| Gram-positive bacteria — no./total no. (%) | 228/626 (36.4) | 235/614 (38.3) | 463/1240 (37.3) |
| Gram-negative bacteria — no./total no. (%) | 264/626 (42.2) | 261/614 (42.5) | 525/1240 (42.3) |
| Adequate antimicrobial therapy — no./total no. (%) | 602/626 (96.2) | 595/614 (96.9) | 1197/1240 (96.5) |
| Vasopressor administration | | | |
| Epinephrine | | | |
| No. of patients | 58 | 53 | 111 |
| Dose — μg/kg/min | 1.74±2.41 | 2.31±6.62 | 2.01±4.88 |
| Norepinephrine | | | |
| No. of patients | 552 | 534 | 1086 |
| Dose — μg/kg/min | 1.14±1.66 | 1.02±1.61 | 1.08±1.63 |
| Mechanical ventilation — no./total no. (%) | 569/623 (91.3) | 567/614 (92.3) | 1136/1237 (91.8) |
| Renal-replacement therapy — no./total no. (%) | 168/598 (28.1) | 161/596 (27.0) | 329/1194 (27.6) |

* Plus–minus values are means ±SD. There were no significant differences between the two groups.
† One patient in the placebo group had a missing value for age.
‡ The Simplified Acute Physiology Score II (SAPS II) ranges from 0 to 163, with higher scores indicating greater severity of illness. SAPS II values were missing for one patient in the placebo group and two patients in the hydrocortisone-plus-fludrocortisone group.
§ Scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating greater severity of illness. The SOFA score was calculated from admission data and was missing for one patient in the placebo group.
¶ Not all sites of infection are listed here, and patients could have had more than one site of infection.

placebo group at ICU discharge (35.4% [217 of 613 patients] vs. 41.0% [257 of 627 patients], P=0.04), hospital discharge (39.0% [239 of 613 patients] vs. 45.3% [284 of 627 patients], P=0.02), and day 180 (46.6% [285 of 611 patients] vs. 52.5% [328 of 625 patients], P=0.04) (Table 2, and Fig. S2 in the Supplementary Appendix). Patients in the hydrocortisone-plus-fludrocortisone group had a significantly shorter time than those in the placebo group to weaning from mechanical ventilation (P=0.006), to weaning from vasopressor therapy (P<0.001), and to reaching a SOFA score below 6 (P<0.001) (Fig. 2, and Figs. S3 through S5 in the Supplementary Appendix). Similarly, patients in the hydrocortisone-plus-fludrocortisone group had significantly more

**Table 2. Trial Outcomes.***

| Outcome | Placebo (N=627) | Hydrocortisone plus Fludrocortisone (N=614) | All Patients (N=1241) | Relative Risk (95% CI)† | P Value |
|---|---|---|---|---|---|
| Primary outcome: death from any cause at day 90 — no. (%) | 308 (49.1) | 264 (43.0) | 572 (46.1) | 0.88 (0.78–0.99) | 0.03 |
| Secondary outcomes | | | | | |
| Death from any cause | | | | | |
| At day 28 — no. (%) | 244 (38.9) | 207 (33.7) | 451 (36.3) | 0.87 (0.75–1.01) | 0.06 |
| At ICU discharge — no./total no. (%) | 257/627 (41.0) | 217/613 (35.4) | 474/1240 (38.2) | 0.86 (0.75–0.99) | 0.04 |
| At hospital discharge — no./total no. (%) | 284/627 (45.3) | 239/613 (39.0) | 523/1240 (42.2) | 0.86 (0.76–0.98) | 0.02 |
| At day 180 — no./total no. (%) | 328/625 (52.5) | 285/611 (46.6) | 613/1236 (49.6) | 0.89 (0.79–0.99) | 0.04 |
| Decision to withhold or withdraw active treatment by day 90 — no./total no. (%) | 61/626 (9.7) | 64/614 (10.4) | 125/1240 (10.1) | 1.07 (0.77–1.49) | 0.69 |
| Vasopressor-free days to day 28‡ | | | | | |
| Mean | 15±11 | 17±11 | 16±11 | — | <0.001 |
| Median (IQR) | 19 (1–26) | 23 (5–26) | 21 (2–26) | | |
| Ventilator-free days to day 28‡ | | | | | |
| Mean | 10±11 | 11±11 | 11±11 | — | 0.07 |
| Median (IQR) | 4 (0–21) | 10 (0–22) | 8 (0–21) | | |
| Organ-failure–free days to day 28‡ | | | | | |
| Mean | 12±11 | 14±11 | 13±11 | — | 0.003 |
| Median (IQR) | 12 (0–24) | 19 (0–25) | 15 (0–24) | | |

* Plus–minus values are means ±SD. IQR denotes interquartile range.
† Shown is the relative risk for hydrocortisone plus fludrocortisone versus placebo.
‡ Patients who died before day 28 were assigned zero free days.

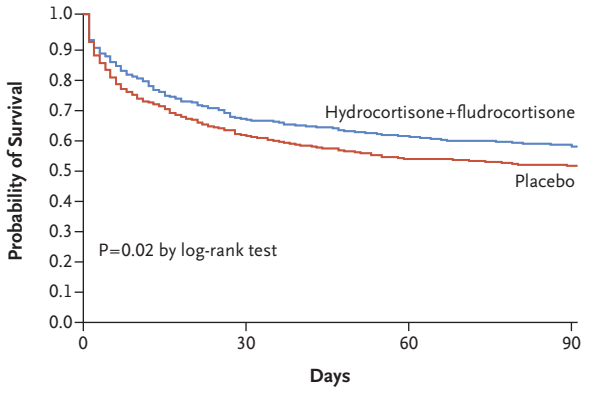


**Figure 1. 90-Day Survival Distributions.**
Shown are survival curves from randomization up to 90 days. The survival rate was significantly higher in the hydrocortisone-plus-fludrocortisone group than in the placebo group.

vasopressor-free days to day 28 than those in the placebo group (P<0.001) and significantly more organ-failure–free days to day 28 (P=0.003) (Table 2, and Tables S8 and S9 in the Supplementary Appendix).

### *Serious Adverse Events*

A total of 326 of 614 patients (53.1%) in the hydrocortisone-plus-fludrocortisone group and 363 of 626 patients (58.0%) in the placebo group had at least one serious adverse event by day 180 (P=0.08) (Table 3). The risk of gastroduodenal bleeding was not significantly higher with hydrocortisone plus fludrocortisone than with placebo (relative risk, 0.88; 95% CI, 0.58 to 1.34; P=0.56), nor was the risk of superinfection (relative risk, 1.09; 95% CI, 0.92 to 1.30; P=0.30). However, the risk of hyperglycemia was significantly higher with hydrocortisone plus fludrocortisone (relative risk, 1.07; 95% CI, 1.03 to 1.12; P=0.002).

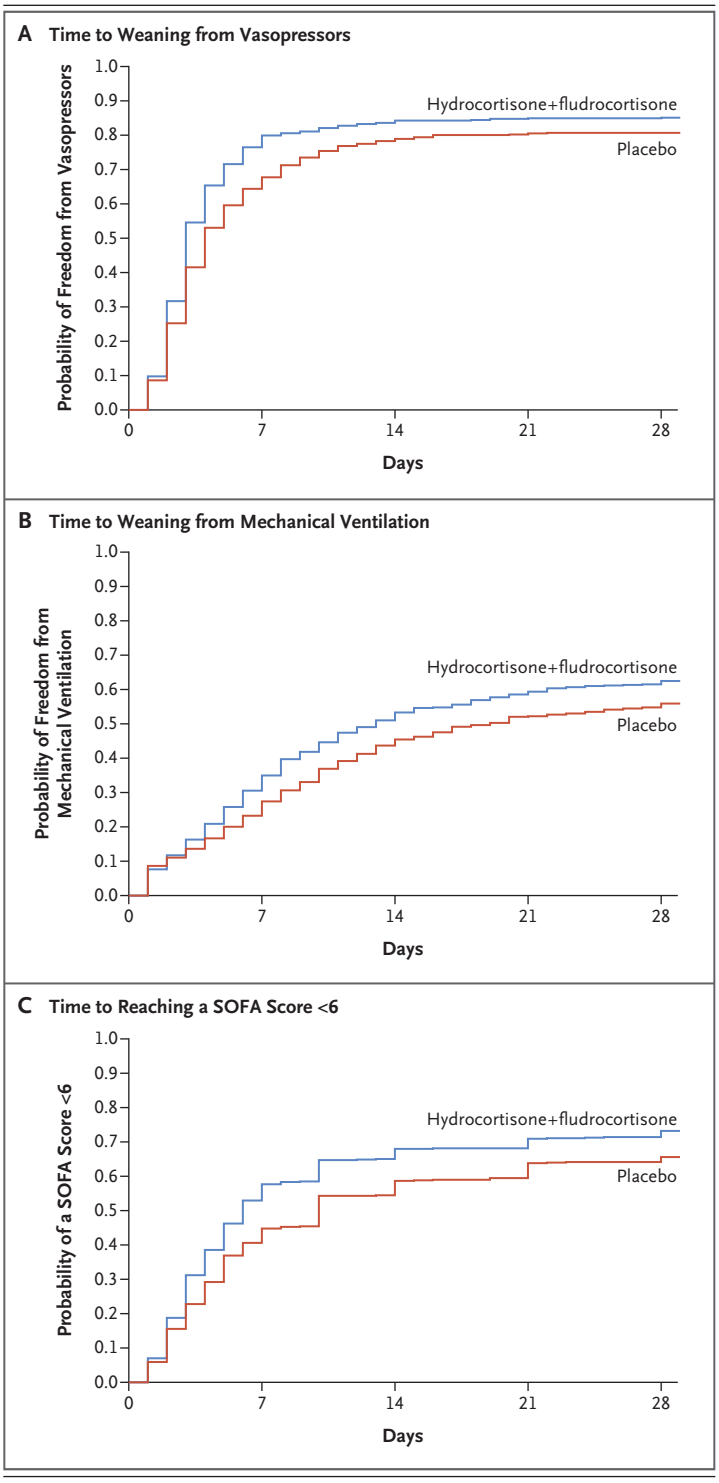


**Figure 2. Time to Weaning from Vasopressors, to Weaning from Mechanical Ventilation, and to Reaching a SOFA Score below 6.**

Shown are cumulative incidence functions from randomization up to 28 days. The time to weaning from vasopressor therapy (Panel A) was significantly shorter in the hydrocortisone-plus-fludrocortisone group than in the placebo group (P<0.001 by Gray test), as was the time to weaning from mechanical ventilation (Panel B) (P=0.006 by Gray test). In addition, the time to reaching a Sequential Organ Failure Assessment (SOFA) score below 6 (on a scale of 0 to 24, with higher scores indicating greater severity of illness) (Panel C) was significantly shorter in the hydrocortisone-plus-fludrocortisone group than in the placebo group (P<0.001 by Gray test).

## DISCUSSION

In this trial involving adults with septic shock, all-cause mortality was lower with hydrocortisone plus fludrocortisone than with placebo at day 90, at discharge from the ICU and hospital, and at day 180. The time to weaning from vasopressors, to weaning from mechanical ventilation, and to reaching a SOFA score below 6 was shorter with hydrocortisone plus fludrocortisone than with placebo. The number of days alive and free of vasopressors and organ failure was higher with hydrocortisone plus fludrocortisone than with placebo. The risk of secondary infections, gastroduodenal bleeding, or neurologic sequelae was not significantly higher with hydrocortisone plus fludrocortisone than with placebo, but the risk of hyperglycemia was significantly higher with hydrocortisone plus fludrocortisone. There was some imbalance between the two groups in the distribution of pathogens, with slightly more viral infections in the hydrocortisone-plus-fludrocortisone group than in the placebo group.

The mechanisms by which corticosteroids may favorably affect the outcome of patients with septic shock have been detailed recently.[7] In brief, corticosteroids improve cardiovascular function by restoring effective blood volume through increased mineralocorticoid activity and by increasing systemic vascular resistance, an effect that is partly related to endothelial glucocorticoid receptors.[20] This might explain why in our trial there was less need for vasopressors with hydrocortisone plus fludrocortisone than with placebo. Corticosteroids attenuate inflammation in various organs in both animals and humans with sepsis, an effect partly related to inhibition of nuclear factor κB (NF-κB).[21] In our trial, hydrocortisone-plus-fludrocortisone therapy accelerated the resolution of organ failure in adults with septic shock.

**Table 3. Adverse Events.***

| Event | Placebo (N=627) | Hydrocortisone plus Fludrocortisone (N=614) | Relative Risk (95% CI)† | P Value |
|---|---|---|---|---|
| ≥1 Serious event by day 180 — no./total no. (%) | 363/626 (58.0) | 326/614 (53.1) | 0.92 (0.83–1.01) | 0.08 |
| ≥1 Serious bleeding event by day 28 — no./total no. (%) | 119/626 (19.0) | 127/614 (20.7) | 1.09 (0.87–1.36) | 0.46 |
| Gastroduodenal bleeding — no./total no. (%) | 45/626 (7.2) | 39/614 (6.4) | 0.88 (0.58–1.34) | 0.56 |
| ≥1 Episode of superinfection by day 180 — no./total no. (%) | 178/626 (28.4) | 191/614 (31.1) | 1.09 (0.92–1.30) | 0.30 |
| Site of superinfection — no./total no. (%) | | | | |
| Lung | 116/626 (18.5) | 127/614 (20.7) | 1.12 (0.89–1.40) | 0.34 |
| Blood | 48/626 (7.7) | 49/614 (8.0) | 1.04 (0.71–1.53) | 0.84 |
| Catheter-related | 37/626 (5.9) | 40/614 (6.5) | 1.10 (0.71–1.70) | 0.66 |
| Urinary tract | 33/626 (5.3) | 40/614 (6.5) | 1.24 (0.79–1.93) | 0.35 |
| Other | 57/626 (9.1) | 70/614 (11.4) | 1.25 (0.90–1.74) | 0.18 |
| New sepsis — no./total no. (%) | 122/626 (19.5) | 134/614 (21.8) | 1.12 (0.90–1.39) | 0.31 |
| New septic shock — no./total no. (%) | 103/626 (16.5) | 109/614 (17.8) | 1.08 (0.84–1.38) | 0.54 |
| Hyperglycemia | | | | |
| ≥1 Episode of blood glucose levels ≥150 mg/dl by day 7 — no./total no. (%) | 520/626 (83.1) | 547/614 (89.1) | 1.07 (1.03–1.12) | 0.002 |
| No. of days with ≥1 episode of blood glucose levels ≥150 mg/dl by day 7 | | | | |
| Mean | 3.4±2.5 | 4.3±2.5 | — | <0.001 |
| Median (IQR) | 3 (1–6) | 5 (2–6) | | |
| Neurologic sequelae by day 28 — no./total no. (%)‡ | | | | |
| Last MDRS score >1 | 130/626 (20.8) | 153/614 (24.9) | 1.20 (0.98–1.47) | 0.08 |
| Last MDRS score >3 | 92/626 (14.7) | 108/614 (17.6) | 1.20 (0.93–1.54) | 0.17 |
| Last MDRS score =5 | 65/626 (10.4) | 73/614 (11.9) | 1.15 (0.84–1.57) | 0.40 |

* Plus–minus values are means ±SD.
† Shown is the relative risk for hydrocortisone plus fludrocortisone versus placebo.
‡ Neurologic sequelae were assessed according to the score on the Muscular Disability Rating Scale (MDRS), with a score of 1 indicating no deficit, 2 minor deficit with no functional disability, 3 distal motor deficit, 4 mild-to-moderate proximal motor deficit, and 5 severe proximal motor deficit.

With respect to 90-day all-cause mortality, there was an absolute difference of 6 percentage points and a relative difference of 12% that favored hydrocortisone plus fludrocortisone over placebo; these findings are in keeping with those of a recent Cochrane review.[8] In this systematic review, only 2 of 33 trials were powered to address the effects of a long (≥5 days) course of low-dose corticosteroids on mortality.[8] The first trial (Ger-Inf-05), in which patients received hydrocortisone plus fludrocortisone or matching placebos for 7 days, showed an absolute difference of 6 percentage points in 28-day mortality in favor of hydrocortisone plus fludrocortisone.[11] The second trial (Corticosteroid Therapy of Septic Shock [CORTICUS]) showed no significant survival benefit from an 11-day course of hydrocortisone alone.[12] In a more recent trial involving 380 adults with severe sepsis (Hydrocortisone for Prevention of Septic Shock [HYPRESS]),[22] hydrocortisone alone failed to prevent septic shock. That trial was not powered to address the effects of hydrocortisone on mortality and excluded patients with shock.

There are two main differences between trials that showed a survival benefit from corticosteroid therapy (APROCCHSS and Ger-Inf-05) and those that did not (CORTICUS and HYPRESS). First, in the APROCCHSS and Ger-Inf-05 trials, fludrocortisone was added to hydrocortisone to pro-

vide additional mineralocorticoid potency. It was administered enterally in the absence of an intravenous formulation of this drug. The rationale for adding mineralocorticoid treatment is that an experimental sepsis study showed marked NF-$\kappa$B–mediated down-regulation of vascular mineralocorticoid receptors.[23] Treatment with aldosterone, a mineralocorticoid-receptor agonist, restored $\alpha$1-adrenoceptor expression, improved contractile response to phenylephrine, and improved survival in mice with endotoxic shock. In a recent pharmacokinetic study involving adults with septic shock, enteral administration of 50 $\mu$g of fludrocortisone resulted in plasma concentrations of the drug that exerted significant mineralocorticoid effects, with some interindividual variability.[24]

Second, the APROCCHSS and Ger-Inf-05 trials focused on patients with septic shock whose condition did not improve after initial resuscitation according to the 6-hour bundle of care outlined in the Surviving Sepsis Campaign guidelines.[17] For these patients, norepinephrine at a dose of more than 0.25 $\mu$g per kilogram per minute for more than 6 hours was required in order for hemodynamic stabilization to be achieved. This group of patients was selected because they may be at high risk for death, which makes them the best target group for adjunct therapy.[15] The crude in-hospital mortality of 45.3% that was observed in the placebo group of the APROCCHSS trial is close to that reported by the Sepsis-3 task force.[1,2] Patients in the APROCCHSS trial were sicker than those in the CORTICUS trial, as evidenced by higher SOFA scores (by approximately 1.5 points) and higher SAPS II values (by approximately 7 points), and were more likely to be admitted from medical wards. Hence, the Ger-Inf-05 and APROCCHSS trials independently showed a survival benefit with hydrocortisone plus fludrocortisone in adults with septic shock and persistent vasopressor dependency and organ failures.

Although this trial could not assess the potential interaction between drotrecogin alfa (activated) and corticosteroids, this question is no longer relevant since the withdrawal of Xigris from the market in 2011. In conclusion, 7-day treatment with a 50-mg intravenous bolus of hydrocortisone every 6 hours and a daily dose of 50 $\mu$g of oral fludrocortisone resulted in lower mortality at day 90 and at ICU and hospital discharge than placebo among adults with septic shock.

Supported by Programme Hospitalier de Recherche Clinique 2007 of the French Ministry of Social Affairs and Health (contract P070128).

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

We thank Jean Carlet and Jean-François Dhainaut for their helpful contribution at the time of designing this trial.

## APPENDIX

The authors' full names and academic degrees are as follows: Djillali Annane, M.D., Ph.D., Alain Renault, M.Sc., Christian Brun-Buisson, M.D., Bruno Megarbane, M.D., Jean-Pierre Quenot, M.D., Shidasp Siami, M.D., Alain Cariou, M.D., Xavier Forceville, M.D., Ph.D., Carole Schwebel, M.D., Claude Martin, M.D., Jean-François Timsit, M.D., Benoît Misset, M.D., Mohamed Ali Benali, M.D., Gwenhael Colin, M.D., Bertrand Souweine, M.D., Karim Asehnoune, M.D., Emmanuelle Mercier, M.D., Loïc Chimot, M.D., Claire Charpentier, M.D., Bruno François, M.D., Thierry Boulain, M.D., Franck Petitpas, M.D., Jean-Michel Constantin, M.D., Gilles Dhonneur, M.D., François Baudin, M.D., Alain Combes, M.D., Julien Bohé, M.D., Jean-François Loriferne, M.D., Roland Amathieu, M.D., Fabrice Cook, M.D., Michel Slama, M.D., Olivier Leroy, M.D., Gilles Capellier, M.D., Auguste Dargent, M.D., Tarik Hissem, M.D., Virginie Maxime, M.D., and Eric Bellissant, M.D., Ph.D.

The authors' affiliations are as follows: Service de Médecine Intensive et Réanimation, Hôpital Raymond Poincaré, Garches (D.A., V.M.), Laboratory of Infection and Inflammation Unité 1173, University of Versailles Saint-Quentin-en-Yvelines, INSERM, Montigny-le-Bretonneux (D.A.), Service de Pharmacologie Clinique–Centre d'Investigation Clinique (CIC) INSERM 1414, Centre Hospitalier Universitaire (CHU) de Rennes–Université de Rennes 1, Hôpital Pontchaillou, Rennes (A.R., E.B.), Service de Réanimation Médicale (C.B.-B.) and Service d'Anesthésie et des Réanimations Chirurgicales (G.D., F.C.), Hôpital Henri-Mondor (Assistance Publique–Hôpitaux de Paris [AP-HP]), Créteil, Réanimation Médicale et Toxicologique, Hôpital Lariboisière (AP-HP), Université Paris-Diderot, INSERM Unité Mixte de Recherche Scientifique (UMRS) 1144 (B. Megarbane), Réanimation Médicale–Hôpitaux Universitaires Paris Centre–Site Cochin (AP-HP) and Université Paris Descartes (A. Cariou), Médecine Intensive et Réanimation, Pôle 2i, Infection et Immunité, Hôpital Bichat–Claude Bernard, AP-HP, Infection, Antimicrobiens, Modélisation, Evolution (IAME) Unité 1137, Université Paris Diderot, INSERM (J.-F.T.), Service d'Anesthésie et Réanimations Chirurgicales, Hôpitaux Universitaires Paris Centre–Site Cochin (AP-HP) (F.B.), and Service de Réanimation Médicale, Hôpital Pitié-Salpêtrière (AP-HP), and Université Paris Sorbonne INSERM, UMRS 1166–Institute of Cardiometabolism and Nutrition (A. Combes), Paris, Service de Réanimation Médicale, Hôpital Universitaire François Mitterrand, Lipness Team, INSERM Research Center Lipids, Nutrition, Cancer–Unité Mixte de Recherche (UMR) 1231 and Laboratoire d'Excellence LipSTIC, and CIC 1432, Epidémiologie Clinique, Université de Burgundy, Dijon (J.-P.Q., A.D.), Service d'Anesthésie–Réanimation, Centre Hospitalier d'Etampes, Etampes (S.S., T.H.), Réanimation Médico-Chirurgicale, CIC INSERM 1414, Grand Hôpital de l'Est Francilien Site de Meaux, Hôpital Saint Faron, Meaux (X.F.), Service de Réanimation Médicale, CHU de Grenoble, Grenoble (C.S.), Service d'Anesthésie et de Réanimation, Assistance Publique–Hôpitaux de Marseille, Hôpital Nord, Aix Marseille Université, CIC 1409, and CIC 9502, Marseille (C.M.), Service de Réanimation Polyvalente, Groupe Hospitalier Paris Saint Joseph, and Service de Réanimation Médicale, CHU de Rouen–Hôpital Charles Nicolle, Rouen (B. Misset), Service de Réanimation Polyvalente, Centre Hospitalier de Valenciennes,

Valenciennes (M.A.B.), Service de Réanimation Médico-Chirurgicale, Centre Hospitalier Départemental de Vendée, Site de La Roche-sur-Yon, Les Oudairies, La Roche-sur-Yon (G. Colin), Réanimation Médicale Polyvalente, CHU Gabriel Montpied (B.S.), and Pôle de Médecine Péri-Opératoire, Génétique, Reproduction, et Développement, UMR–Centre National de la Recherche Scientifique 6293, Université Clermont-Auvergne, INSERM Unité 1103, CHU Clermont-Ferrand (J.-M.C.), Clermont-Ferrand, Service d'Anesthésie, Réanimation Chirurgicale, Hôtel Dieu–Hôpital Mère–Enfant, CHU Nantes, Laboratoire EA3826 Thérapeutiques et Expérimentales des Infections, Nantes (K.A.), Réanimation Polyvalente, Centre Hospitalier Régional Universitaire Bretonneau, Tours (E.M.), Service d'Anesthésie-Réanimation, Centre Hospitalier de Périgueux, Périgueux (L.C.), Service de Réanimation Chirurgicale, Hôpital Central, CHU de Nancy, Nancy (C.C.), Service de Réanimation Polyvalente, INSERM CIC 1435–CHU Dupuytren, Limoges (B.F.), Service Réanimation Médicale Polyvalente et Unité de Surveillance Continue, Centre Hospitalier Régional d'Orléans, Orléans (T.B.), Réanimation Chirurgicale, Département d'Anesthésie-Réanimations–Urgences, Service d'Assistance Médicale d'Urgence (SAMU) 86, Hôpital de la Miletrie, CHU, Poitiers (F.P.), Service de Réanimation Médicale, Centre Hospitalier Lyon-Sud (Hospices Civils de Lyon), Pierre-Bénite (J.B.), Service d'Anesthésie-Réanimation, Hôpital Saint Camille, Bry-sur-Marne (J.-F.L.), Réanimation Polyvalente, Hôpital Jean Verdier (AP-HP), Bondy (R.A.), Service de Réanimation Médicale, CHU Amiens–Picardie–Site Sud, Amiens (M.S.), Service de Réanimation Médicale et Maladies Infectieuses, Centre Hospitalier Tourcoing Gustave Dron, Tourcoing (O.L.), and Service de Réanimation Médicale–SAMU 25, Hôpital Jean Minjoz–CHU de Besançon, Besançon (G. Capellier) — all in France.

## REFERENCES

**1.** Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801-10.
**2.** Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a new definition and assessing new clinical criteria for septic shock: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:775-87.
**3.** Annane D, Sharshar T. Cognitive decline after sepsis. Lancet Respir Med 2015; 3:61-9.
**4.** Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017;43:304-77.
**5.** Lilly announces withdrawal of Xigris following recent clinical trial results. Indianapolis: Eli Lilly, October 25, 2011 (https://investor.lilly.com/releasedetail2.cfm?ReleaseID=617602).
**6.** Sherkow JS. Patent law's reproducibility paradox. Duke Law J 2017;66:845-911.
**7.** Annane D. The role of ACTH and corticosteroids for sepsis and septic shock: an update. Front Endocrinol (Lausanne) 2016;7:70.
**8.** Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for treating sepsis. Cochrane Database Syst Rev 2015;12:CD002243.
**9.** Volbeda M, Wetterslev J, Gluud C, Zijlstra JG, van der Horst IC, Keus F. Glucocorticosteroids for sepsis: systematic review with meta-analysis and trial sequential analysis. Intensive Care Med 2015;41: 1220-34.
**10.** Bruno JJ, Dee BM, Anderegg BA, Hernandez M, Pravinkumar SE. US practitioner opinions and prescribing practices regarding corticosteroid therapy for severe sepsis and septic shock. J Crit Care 2012;27:351-61.
**11.** Annane D, Sébille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002;288:862-71.
**12.** Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008;358:111-24.
**13.** Annane D, Buisson CB, Cariou A, et al. Design and conduct of the Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial. Ann Intensive Care 2016;6:43.
**14.** Annane D, Timsit JF, Megarbane B, et al. Recombinant human activated protein C for adults with septic shock: a randomized controlled trial. Am J Respir Crit Care Med 2013;187:1091-7.
**15.** Annane D, Bellissant E, Cavaillon JM. Septic shock. Lancet 2005;365:63-78.
**16.** Vincent JL, de Mendonça A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Crit Care Med 1998;26:1793-800.
**17.** Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36:296-327.
**18.** Guide "100 recommandations pour la surveillance et la préventions des infections nosocomiales." Bulletin Epidémiologique Hebdomadaire. No. 48. November 30, 1992 (http://invs.santepubliquefrance.fr/beh/1992/48/index.html).
**19.** Annane D, Vignon P, Renault A, et al. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. Lancet 2007;370:676-84.
**20.** Goodwin JE, Feng Y, Velazquez H, Sessa WC. Endothelial glucocorticoid receptor is required for protection against sepsis. Proc Natl Acad Sci U S A 2013;110: 306-11.
**21.** Meduri GU, Muthiah MP, Carratu P, Eltorky M, Chrousos GP. Nuclear factor-kappaB- and glucocorticoid receptor alpha-mediated mechanisms in the regulation of systemic and pulmonary inflammation during sepsis and acute respiratory distress syndrome: evidence for inflammation-induced target tissue resistance to glucocorticoids. Neuroimmunomodulation 2005; 12:321-38.
**22.** Keh D, Trips E, Marx G, et al. Effect of hydrocortisone on development of shock among patients with severe sepsis: the HYPRESS randomized clinical trial. JAMA 2016;316:1775-85.
**23.** Fadel F, André-Grégoire G, Gravez B, et al. Aldosterone and vascular mineralocorticoid receptors in murine endotoxic and human septic shock. Crit Care Med 2017;45(9):e954-e962.
**24.** Polito A, Hamitouche N, Ribot M, et al. Pharmacokinetics of oral fludrocortisone in septic shock. Br J Clin Pharmacol 2016; 82:1509-16.