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# Effect of Hydrocortisone on Development of Shock Among Patients With Severe Sepsis
## The HYPRESS Randomized Clinical Trial

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**IMPORTANCE** Adjunctive hydrocortisone therapy is suggested by the Surviving Sepsis Campaign in refractory septic shock only. The efficacy of hydrocortisone in patients with severe sepsis without shock remains controversial.

**OBJECTIVE** To determine whether hydrocortisone therapy in patients with severe sepsis prevents the development of septic shock.

**DESIGN, SETTING, AND PARTICIPANTS** Double-blind, randomized clinical trial conducted from January 13, 2009, to August 27, 2013, with a follow-up of 180 days until February 23, 2014. The trial was performed in 34 intermediate or intensive care units of university and community hospitals in Germany, and it included 380 adult patients with severe sepsis who were not in septic shock.

**INTERVENTIONS** Patients were randomly allocated 1:1 either to receive a continuous infusion of 200 mg of hydrocortisone for 5 days followed by dose tapering until day 11 (n = 190) or to receive placebo (n = 190).

**MAIN OUTCOMES AND MEASURES** The primary outcome was development of septic shock within 14 days. Secondary outcomes were time until septic shock, mortality in the intensive care unit or hospital, survival up to 180 days, and assessment of secondary infections, weaning failure, muscle weakness, and hyperglycemia (blood glucose level >150 mg/dL [to convert to millimoles per liter, multiply by 0.0555]).

**RESULTS** The intention-to-treat population consisted of 353 patients (64.9% male; mean [SD] age, 65.0 [14.4] years). Septic shock occurred in 36 of 170 patients (21.2%) in the hydrocortisone group and 39 of 170 patients (22.9%) in the placebo group (difference, −1.8%; 95% CI, −10.7% to 7.2%; $P = .70$). No significant differences were observed between the hydrocortisone and placebo groups for time until septic shock; mortality in the intensive care unit or in the hospital; or mortality at 28 days (15 of 171 patients [8.8%] vs 14 of 170 patients [8.2%], respectively; difference, 0.5%; 95% CI, −5.6% to 6.7%; $P = .86$), 90 days (34 of 171 patients [19.9%] vs 28 of 168 patients [16.7%]; difference, 3.2%; 95% CI, −5.1% to 11.4%; $P = .44$), and 180 days (45 of 168 patients [26.8%] vs 37 of 167 patients [22.2%], respectively; difference, 4.6%; 95% CI, −4.6% to 13.7%; $P = .32$). In the hydrocortisone vs placebo groups, 21.5% vs 16.9% had secondary infections, 8.6% vs 8.5% had weaning failure, 30.7% vs 23.8% had muscle weakness, and 90.9% vs 81.5% had hyperglycemia.

**CONCLUSIONS AND RELEVANCE** Among adults with severe sepsis not in septic shock, use of hydrocortisone compared with placebo did not reduce the risk of septic shock within 14 days. These findings do not support the use of hydrocortisone in these patients.

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Despite decades of study and debate, the role of adjunctive "low-dose" hydrocortisone treatment (200-300 mg/d) in patients with severe sepsis and septic shock remains controversial.[1] The current recommendation for hydrocortisone use is mainly based on 2 randomized clinical trials (RCTs).[2] In the study by Annane et al,[3] hydrocortisone improved survival and reversal of septic shock in patients with relative adrenal insufficiency. In the CORTICUS study,[4] septic shock was reversed more quickly but mortality was not significantly reduced. The higher risk of mortality and septic shock severity in the study by Annane and colleagues resulted in more restrictive recommendations for hydrocortisone use only in patients with inadequate response to fluid and vasopressor resuscitation.[2] However, septic shock reversal in the CORTICUS study was reported to be significantly accelerated by the administration of hydrocortisone irrespective of the adrenal response to corticotropin. An international consensus statement recommended replacing the terms *relative* or *absolute adrenal insufficiency*, which reflect only adrenal cortisol release, by the critical illness-related corticosteroid insufficiency (CIRCI) concept.[5]

Although meta-analyses report controversial results on mortality reduction by administration of corticosteroids,[6,7] there is consistency regarding shock reversal irrespective of disease severity or the presence of CIRCI.[5-7] In a smaller RCT in patients with community-acquired pneumonia (CAP), hydrocortisone significantly improved survival and prevented progression to shock.[8] Furthermore, 2 recent RCTs[9,10] and a meta-analysis[11] revealed positive effects of steroids in patients with CAP. Assuming that severe sepsis and septic shock reflect a disease continuum, it was hypothesized that early hydrocortisone administration might prevent shock development owing to the attenuation of an exaggerated inflammatory response. To our knowledge, this is the first RCT investigating the effects of hydrocortisone to prevent progression to shock in patients with severe sepsis presenting without shock.

### Key Points

**Question** Does adjunctive early hydrocortisone therapy prevent the development of septic shock in patients with severe sepsis who are not in shock?

**Findings** In this randomized clinical trial that included 380 adults, occurrence of septic shock was not significantly different between patients who received hydrocortisone or placebo (21.2% vs 22.9%, respectively).

**Meaning** Administration of hydrocortisone did not prevent the development of shock in patients with severe sepsis.

## Methods

### Study Design

The Hydrocortisone for Prevention of Septic Shock (HYPRESS) study is an investigator-initiated, multicenter, placebo-controlled, double-blind RCT supported by the German Federal Ministry of Education and Research. The study was conducted in cooperation with the German Sepsis Competence Network (SepNet) and the Clinical Trial Centre Leipzig, which provided internet-based randomization and data capture, assurance of accuracy and completeness of data, biostatistical analysis, and pharmacovigilance. Monitoring of sites was performed on defined intervals. The protocol was approved by the responsible ethics committees of all 34 participating sites. The trial protocol is available in Supplement 2.

### Study Patients

Patients were screened in intermediate care units or intensive care units (ICUs) of university and community hospitals for eligibility, and written informed consent was obtained from patients, patient-authorized representatives, or legal representatives. Patients were enrolled if they met all inclusion criteria (for details, see eAppendix 2 in Supplement 1): (1) provided informed consent; (2) had evidence of infection; (3) had evidence of a systemic response to infection, defined as at least 2 systemic inflammatory response syndrome criteria[12]; and (4) had evidence of organ dysfunction present for not longer than 48 hours. The main exclusion criterion was septic shock. Other exclusion criteria were being younger than 18 years, having known hypersensitivity to hydrocortisone or mannitol (placebo), or having a history of glucocorticoid medication with indication for continuation of therapy or other indications for treatment with glucocorticoids. Patients were not excluded for using etomidate within 72 hours before enrollment, using a short course of glucocorticoids within 72 hours before enrollment, or using topical or inhaled glucocorticoids.

### Definitions

Septic shock was defined as sepsis-induced hypotension despite adequate volume status for longer than 4 hours (ie, mean arterial pressure <65 mm Hg, systolic arterial pressure <90 mm Hg, or the use of vasopressors to keep mean arterial pressure ≥65 mm Hg or systolic arterial pressure ≥90 mm Hg). Patients who had a transient need for vasopressors during initial resuscitation but were not hypotensive and did not use vasopressors for at least 2 hours were eligible for enrollment when septic shock was not present at the time of randomization. Adequate volume status was defined as a central venous pressure of 8 mm Hg or greater (≥12 mm Hg in ventilated patients) and a central venous oxygen saturation greater than 70%. For fluid replacement, patients were to receive at least 500 to 1000 mL of crystalloids or 300 to 500 mL of colloids over 30 minutes. The use of hydroxyethyl starch preparations was discouraged owing to possible harmful effects on kidney function.[13,14] Use of vasopressors was defined as therapy with dopamine at a dosage of at least 5 µg/kg/min or with any dose of epinephrine, norepinephrine, vasopressin, or other vasopressors. For further details and definitions, see eAppendix 2 in Supplement 1.

### Randomization

Randomization was stratified by participating center and sex. It was performed with an internet-based computerized randomization tool that uses a modified version of the Pocock minimization algorithm[15] with a random component to generate balanced 1:1 randomization in the strata at any time. All



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patients, study personnel, sponsors, medical staff, and nursing staff were blinded regarding the allocation of study medication throughout the entire study period.

### Study Medication

The study medication (hydrocortisone and placebo) was produced and released by BAG Health Care GmbH. The medication was delivered in boxes, each containing 17 brown glass vials for 1 patient. Each vial contained 100 mg of lyophilized hydrocortisone hydrogen succinate or the same amount of lyophilized mannitol as placebo, which was indistinguishable from hydrocortisone. The medication was administered as an intravenous bolus of 50 mg, followed by a 24-hour continuous infusion of 200 mg on 5 days, 100 mg on days 6 and 7, 50 mg on days 8 and 9, and 25 mg on days 10 and 11. Hydrocortisone dose corresponded to those used in the 2 major RCTs performed earlier,[3,4] which had shown significant effects on septic shock resolution. A continuous infusion was preferred to avoid possible undulation of the blood cortisol concentrations by bolus administration, which had been reported to complicate blood glucose control.[16] A continuous infusion was also recommended in the recent Surviving Sepsis Campaign guidelines.[2] To reduce possible hemodynamic and immunological rebound effects,[17] hydrocortisone was tapered over several days as in the CORTICUS study.[4] Study medication was discontinued for safety reasons or when patients were discharged from the ICU or reached the primary end point.

### End Points

The primary end point was the occurrence of septic shock within 14 days, which was assessed daily until day 14, or discharge from the ICU. Secondary end points were time until development of septic shock or death (whichever came first), mortality in the ICU and hospital, vital status at 28, 90, and 180 days, duration of stay in the ICU and hospital, organ dysfunctions (Sequential Organ Failure Assessment [SOFA] score, ranging from 0-24 with higher values indicating greater severity), duration of mechanical ventilation, and renal replacement therapy. In the subgroup of patients who underwent a corticotropin test at baseline, the occurrence of septic shock, mortality, length of stay (LOS) in the ICU or hospital, mechanical ventilation, organ dysfunctions (SOFA score), renal replacement therapy, and secondary infection were evaluated. Critical illness-related corticosteroid insufficiency was defined as an increase of cortisol of 9 µg/dL or less (to convert to nanomoles per liter, multiply by 27.588) 1 hour after stimulation with 250 µg of corticotropin (Synacthen). Frequency of delirium was assessed daily until ICU discharge by the Richmond Agitation-Sedation Scale[18,19] (ranging from −5 [unarousable; no response to voice or physical stimulation] to 4 [combative; overly combative or violent; immediate danger to staff]) to quantify the level of sedation and by the Confusion Assessment Method for the ICU for detection of delirium. Adverse events were assessed until day 28, with special emphasis on muscle weakness, weaning failure, secondary infection, and gastrointestinal bleeding. All events not typically associated with the course of disease had to be reported (eAppendix 2 in Supplement 1).

### Data Acquisition, Cortisol Measurement, and Patient Treatment

Disease severity was assessed by the SOFA score,[20] Simplified Acute Physiology Score II (ranging from 0-163),[21] Acute Physiology and Chronic Health Evaluation II (ranging from 0-71),[22] and Simplified Acute Physiology Score 3 (ranging from 0-217) (with higher scores indicating greater severity on all instruments).[23] Serum cortisol concentration was batch analyzed by mass spectrometry in a reference laboratory in blood samples stored at −80°C and taken before and 60 minutes after administration of 250 µg of corticotropin at baseline. All patients had to be treated according to guidelines of the German Sepsis Society[13] (eAppendix 2 in Supplement 1).

### Statistical Analysis

The study was planned to detect an absolute difference of 15% in the proportion of patients with septic shock within 14 days with a significance level of .05 and a power of 0.8. The difference of 15% was postulated to be a meaningful difference that could change clinical practice, and was supported by similar differences of hydrocortisone on 7-day septic shock resolution in patients with septic shock,[24] assuming that hydrocortisone might be as effective in preventing septic shock as in resolving it.

Assuming 40% of patients in the placebo group had septic shock,[8,25-27] 169 evaluable patients per arm were required. Accounting for an expected dropout rate of about 10%, 190 patients per arm (380 in total) had to be included. The statistical analysis was conducted consistent with the intention-to-treat (ITT) principle. The primary end point was assessed by $\chi^2$ test; heterogeneity between centers with more than 10 recruited patients was assessed by $I^2$. Secondary end points were analyzed by $\chi^2$ test, Fisher exact test, *t* test, Mann-Whitney *U* test, or log-rank test, as appropriate. All reported *P* values are 2-sided, and $P < .05$ was regarded as statistically significant. Secondary analyses were not adjusted for multiple testing because these statistical comparisons were performed with exploratory rather than confirmatory intention. Planned subgroup analyses included the ITT population and the per-protocol (PP) population, administration of study medication for at least 48 hours, medical and surgical patients, and patients with pneumonia. Post hoc subgroup analyses were performed for CIRCI, delirium, and CAP. A multivariable logistic regression model was performed to investigate adjusted treatment effects. Two interim analyses were performed after recruitment of one-third and two-thirds of the planned sample size. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc), R version 3.1.0 (R Foundation), and SPSS version 22.0 (IBM Corp) statistical software. For details of the statistical analyses, see eAppendix 2 in Supplement 1.

## Results

### Patient Population

From January 13, 2009, to August 27, 2013, 9953 patients with severe sepsis or septic shock were screened at 34 study sites for eligibility. A total of 380 patients were randomized to receive



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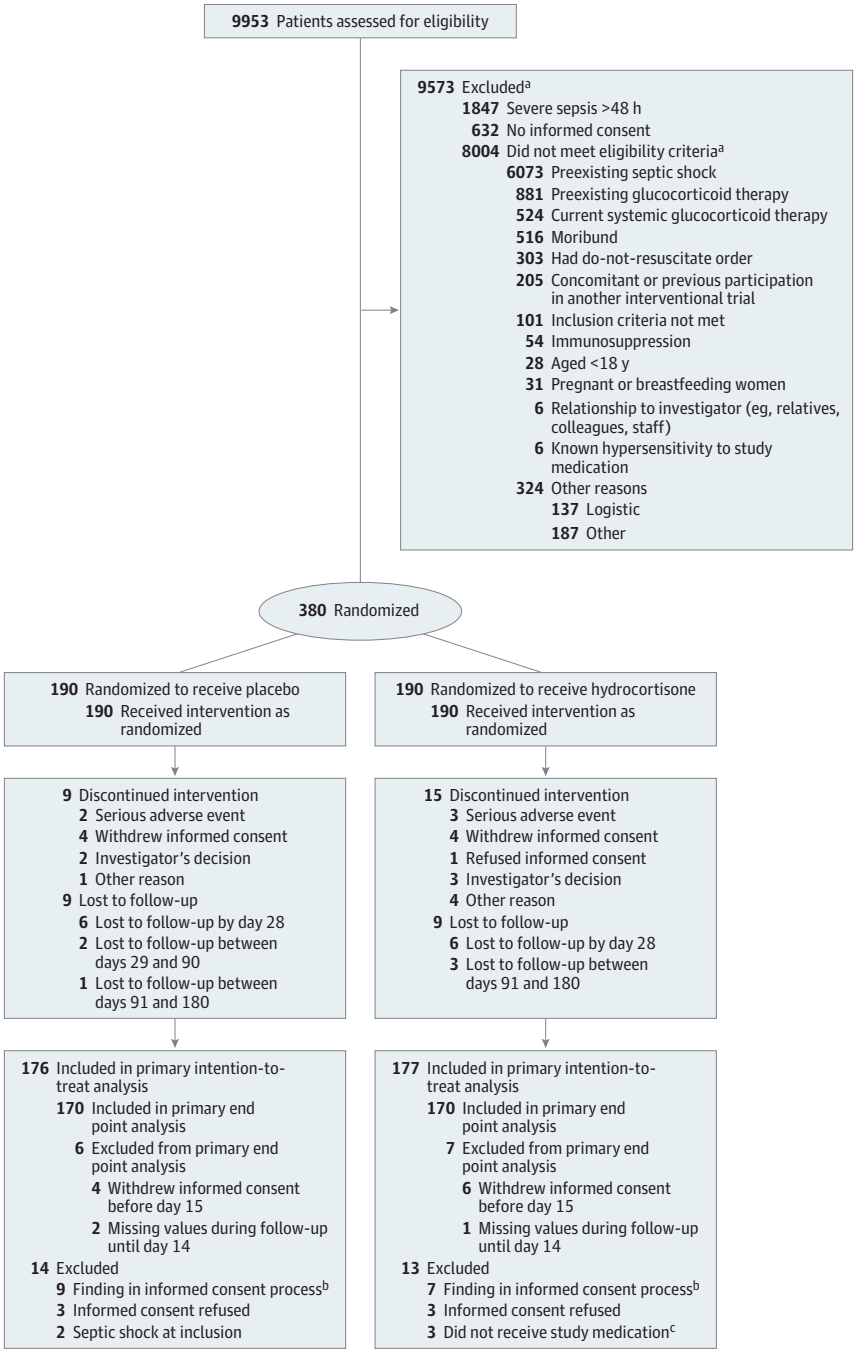
Figure 1. CONSORT Flow Diagram




[a] Multiple reasons possible.

[b] The informed consent process could not be completed as defined in the protocol.

[c] Septic shock occurred soon after randomization but before administration of study medication.

hydrocortisone (n = 190) or placebo (n = 190). The median time from screening to enrollment was 12.5 hours (interquartile range [IQR], 6-21 hours) in the placebo group and 14 hours (IQR, 6.5-23 hours) in the hydrocortisone group ($P$ = .49). The ITT population excluded 27 patients and included 353 patients (64.9% male; mean [SD] age, 65.0 [14.4] years) (**Figure 1**). The PP population consisted of 322 patients, and the safety analysis set included 375 patients. Six patients (2 in the placebo group, 4 in the hydrocortisone group) received a reduced dose (<80% of total dose according to protocol). Ten patients (5 in the placebo group, 5 in the hydrocortisone group) received an increased dose (quotient of applied dose and expected dose >1.2). These patients were excluded from the PP analysis. Follow-up was conducted until February 23, 2014.

## Baseline Characteristics and Treatment During Study

Treatment arms were comparable regarding age, type of admission to the ICU, severity of disease or organ dysfunction, use of glucocorticoids or etomidate within 72 hours before randomization, initial treatment and vital signs within 6 hours



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Table 1. Baseline Characteristics[a]

| Characteristic | Placebo (n = 176) | Hydrocortisone (n = 177) | Total (N = 353) |
|---|---|---|---|
| Male, No./total No. (%) | 111/176 (63.1) | 118/177 (66.7) | 229/353 (64.9) |
| Age, mean (SD), y | 64.6 (14.6) | 65.5 (14.2) | 65.0 (14.4) |
| Type of admission, No./total No. (%) | | | |
| Surgery, elective | 42/176 (23.9) | 27/176 (15.3) | 69/352 (19.6) |
| Surgery, emergency | 32/176 (18.2) | 44/176 (25.0) | 76/352 (21.6) |
| Nonsurgery, elective | 4/176 (2.3) | 5/176 (2.8) | 9/352 (2.6) |
| Nonsurgery, emergency | 98/176 (55.7) | 100/176 (56.8) | 198/352 (56.3) |
| SOFA score, mean (SD)[b,c] | 6.2 (2.4) | 6.4 (2.6) | 6.3 (2.5) |
| APACHE II score, mean (SD)[b,d] | 18.5 (6.0) | 19.5 (6.9) | 19.0 (6.5) |
| SAPS II score, mean (SD)[b,e] | 52.2 (9.9) | 56.1 (13.3) | 54.1 (11.8) |
| SAPS 3 score, mean (SD)[b,f] | 58.4 (11.0) | 58.5 (11.9) | 58.4 (11.4) |
| SIRS criteria, No./total No. (%) | | | |
| Temperature ≤36°C or ≥38°C | 141/176 (80.1) | 129/177 (72.9) | 270/353 (76.5) |
| Heart rate ≥90 beats/min | 164/176 (93.2) | 158/177 (89.3) | 322/353 (91.2) |
| Tachypnea, hypocapnia, or mechanical ventilation | 157/176 (89.2) | 145/176 (82.4) | 302/352 (85.8) |
| Leukocytosis, leukopenia, or left shift | 132/176 (75.0) | 131/177 (74.0) | 263/353 (74.5) |
| Organ dysfunction, No./total No. (%) | | | |
| Central nervous system | 47/176 (26.7) | 41/175 (23.4) | 88/351 (25.1) |
| Coagulation | 26/176 (14.8) | 35/177 (19.8) | 61/353 (17.3) |
| Pulmonary | 119/175 (68.0) | 117/177 (66.1) | 236/352 (67.0) |
| Renal | 73/176 (41.5) | 70/177 (39.5) | 143/353 (40.5) |
| Microcirculatory | 53/176 (30.1) | 61/176 (34.7) | 114/352 (32.4) |
| Source of infection, No./total No. (%) | | | |
| Community | 83/176 (47.2) | 82/177 (46.3) | 165/353 (46.7) |
| Nosocomial, ICU | 52/176 (29.5) | 41/177 (23.2) | 93/353 (26.3) |
| Nosocomial, ward | 41/176 (23.3) | 54/177 (30.5) | 95/353 (26.9) |
| Focus of primary infection, No./total No. (%) | | | |
| Known focus | 146/176 (83.0) | 149/176 (84.7) | 295/352 (83.8) |
| Pneumonia | 78/146 (53.4) | 56/149 (37.6) | 134/295 (45.4) |
| Respiratory tract, other | 10/146 (6.8) | 8/149 (5.4) | 18/295 (6.1) |
| Thoracic | 2/146 (1.4) | 9/149 (6.0) | 11/295 (3.7) |
| Gastrointestinal | 7/146 (4.8) | 10/149 (6.7) | 17/295 (5.8) |
| Intra-abdominal | 24/146 (16.4) | 37/149 (24.8) | 61/295 (20.7) |
| Primary bacteremia | 2/146 (1.4) | 2/149 (1.3) | 4/295 (1.4) |
| Bones or soft tissue | 14/146 (9.6) | 15/149 (10.1) | 29/295 (9.8) |
| Surgical wound | 3/146 (2.1) | 4/149 (2.7) | 7/295 (2.4) |
| Urogenital | 21/146 (14.4) | 24/149 (16.1) | 45/295 (15.3) |
| Catheter | 3/146 (2.1) | 6/149 (4.0) | 9/295 (3.1) |
| Medication within 72 h before randomization | | | |
| Intravenous glucocorticoids, No./total No. (%) | 6/176 (3.4) | 3/177 (1.7) | 9/353 (2.5) |
| Hydrocortisone equivalent, median (range), mg | 600 (392-1000) | 200 (200-400) | 400 (200-1000) |
| Etomidate, No. (%) | | | |
| No./total No. (%) | 11/176 (6.3) | 12/176 (6.8) | 23/352 (6.5) |
| Mean (SD), mg | 33.0 (13.8) | 23.8 (10.4) | 28.2 (12.8) |

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score II; SAPS 3, Simplified Acute Physiology Score 3; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment.

[a] For a list of concomitant diseases, see eTable 1 in Supplement 1.

[b] Higher scores indicate greater disease severity.

[c] Possible scores range from 0 to 24.

[d] Possible scores range from 0 to 71.

[e] Possible scores range from 0 to 163.

[f] Possible scores range from 0 to 217.

after diagnosis of severe sepsis, administration of study medication, antibiotic therapy, and treatment characteristics during the study. Pneumonia was slightly more frequent in patients who received placebo (**Table 1** and eTables 1, 2, and 3 in Supplement 1).

## Primary End Point

There was no significant difference in the proportion of septic shock after 14 days between patients who received hydrocortisone or placebo in the ITT or PP population (**Table 2**). In the ITT population, septic shock occurred in 36 of 170



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Table 2. Primary and Secondary End Points[a]

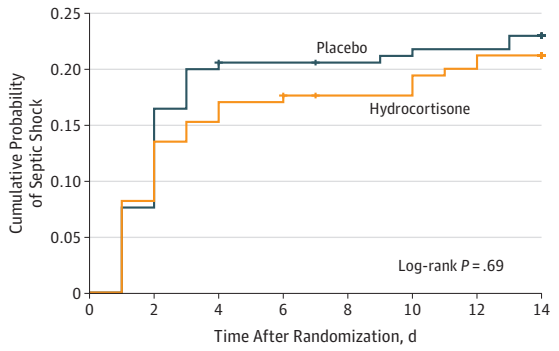
| End Point | Placebo (n = 176) | Hydrocortisone (n = 177) | Total (N = 353) | *P* Value |
|---|---|---|---|---|
| Primary | | | | |
| Septic shock, No./total No. (%) [95% CI] | | | | |
| ITT population | 39/170 (22.9) [17.2-30.0] | 36/170 (21.2) [15.6-28.1] | 75/340 (22.1) [17.9-26.9] | .70 |
| PP population | 33/156 (21.2) [15.4-28.4] | 29/155 (18.7) [13.3-25.7] | 62/311 (19.9) [15.8-24.8] | .59 |
| Secondary | | | | |
| Mortality, No./total No. (%) [95% CI] | | | | |
| 28 d | 14/170 (8.2) [5.0-13.4] | 15/171 (8.8) [5.4-14.0] | 29/341 (8.5) [6.0-12.0] | .86 |
| 90 d | 28/168 (16.7) [11.8-23.0] | 34/171 (19.9) [14.6-26.5] | 62/339 (18.3) [14.5-22.8] | .44 |
| 180 d | 37/167 (22.2) [16.5-29.0] | 45/168 (26.8) [20.7-34.0] | 82/335 (24.5) [20.2-29.4] | .32 |
| ICU | 14/172 (8.1) [4.9-13.2] | 13/171 (7.6) [4.5-12.6] | 27/343 (7.9) [5.5-11.2] | .85 |
| Hospital | 22/172 (12.8) [8.6-18.6] | 23/171 (13.5) [9.1-19.4] | 45/343 (13.1) [10.0-17.1] | .86 |
| LOS, median (IQR), d | | | | |
| ICU | 9 (6-17) | 8 (5-15) | 8 (5-16) | .23 |
| Hospital | 25 (16-40) | 26 (16-46) | 26 (16-43) | .36 |
| Mechanical ventilation, No./total No. (%) [95% CI] | 103/172 (59.9) [52.4-66.9] | 91/171 (53.2) [45.8-60.5] | 194/343 (56.6) [51.3-61.7] | .21 |
| MV-free time, median (IQR), d | 5 (2-7) | 4 (2-7) | 4 (2-7) | .34 |
| RRT, No./total No. (%) [95%CI] | 21/172 (12.2) [8.1-17.9] | 21/171 (12.3) [8.2-18.0] | 42/343 (12.2) [9.2-16.1] | .98 |
| RRT-free time, median (IQR), d | 7 (4-14) | 6 (4-12) | 7 (4-13) | .35 |
| SOFA score until day 14, median (IQR)[b] | 5.0 (3.5-6.8) | 4.7 (3.5-6.5) | 4.8 (3.5-6.6) | .69 |
| Delirium, No./total No. (%) [95% CI] | 25/102 (24.5) [17.2-33.7] | 11/98 (11.2) [6.4-19.0] | 36/200 (18.0) [13.3-23.9] | .01 |

Abbreviations: ICU, intensive care unit; IQR, interquartile range; ITT, intention-to-treat; LOS, length of stay; MV, mechanical ventilation; PP, per-protocol; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment.

[a] For rows including number/total number, the total number refers to the number of patients with valid data. Data are missing in up to 5% in the ITT population, except for SOFA (data missing in 25%) and delirium (data missing in 43%).

[b] The SOFA score for each patient was calculated by the sum of daily SOFA scores divided by the observation time.

Figure 2. Time to Septic Shock




No. at risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo | 176 | 161 | 139 | 136 | 134 | 131 | 130 | 128 |
| Hydrocortisone | 177 | 163 | 146 | 142 | 138 | 138 | 134 | 130 |

Tick marks on curves indicate censored data.

patients (21.2%) in the hydrocortisone group vs 39 of 170 patients (22.9%) in the placebo group (difference, −1.8%; 95% CI, −10.7% to 7.2%; *P* = .70). In the PP population, septic shock occurred in 29 of 155 patients (18.7%) in the hydrocortisone group vs 33 of 156 patients (21.2%) in the placebo group (difference, −2.4%; 95% CI, −11.5% to 6.6%; *P* = .59). In addition, no significant difference between the groups was observed regarding time to septic shock development (**Figure 2**), or in time to septic shock in those patients who developed septic shock (eFigure 1 in Supplement 1). Subgroup analysis of medical or surgical patients, patients with pneumonia, or study medication treatment for at least 48 hours did not reveal a benefit for shock prevention (eFigure 2 in Supplement 1). To exclude a center effect, 11 sites that recruited at least 10 patients (n = 279) were analyzed; there was no heterogeneity for the primary end point ($I^2$ = 0%; *P* = .74).

## Secondary End Points

There were no significant differences in 28-day, 90-day, 180-day, ICU, or hospital all-cause mortality; LOS in the ICU or hospital; ventilation- or renal replacement-free days; or median SOFA score until day 14 between patients treated with placebo or hydrocortisone (Table 2 and eFigure 3 in Supplement 1). At 28 days, mortality occurred in 15 of 171 patients (8.8%) in the hydrocortisone group and 14 of 170 patients (8.2%) in the placebo group (difference, 0.5%; 95% CI, −5.6% to 6.7%; *P* = .86). At 90 days, mortality occurred in 34 of 171 patients (19.9%) in the hydrocortisone group vs 28 of 168 patients (16.7%) in the placebo group (difference, 3.2%; 95% CI, −5.1%



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Table 3. Adverse Events in Safety Analysis Set

| Adverse Event | Placebo (n = 189) | Hydrocortisone (n = 186) | Total (N = 375) | *P* Value[a] |
|---|---|---|---|---|
| Secondary infections, No. (%) | 32 (16.9) | 40 (21.5) | 72 (19.2) | .26 |
| MRC Scale for Muscle Strength score available, No. (%) | 151 (79.9) | 150 (80.6) | 301 (80.3) | .86 |
| Muscle weakness, No. (%)[b] | 36 (23.8) | 46 (30.7) | 82 (27.2) | .18 |
| Respiratory, No. (%) | 24 (12.7) | 24 (12.9) | 48 (12.8) | .95 |
| Weaning failure | 16 (8.5) | 16 (8.6) | 32 (8.5) | .96 |
| Respiratory failure | 7 (3.7) | 3 (1.6) | 10 (2.7) | .34 |
| Other | 9 (4.8) | 6 (3.2) | 15 (4.0) | .45 |
| Cardiovascular, No. (%) | 19 (10.1) | 17 (9.1) | 36 (9.6) | .76 |
| Arterial hypertension | 1 (0.5) | 5 (2.7) | 6 (1.6) | .12 |
| Other | 18 (9.5) | 14 (7.5) | 32 (8.5) | .49 |
| Abdominal, No. (%) | 6 (3.2) | 7 (3.8) | 13 (3.5) | .76 |
| Gastrointestinal bleeding | 2 (1.1) | 3 (1.6) | 5 (1.3) | .68 |
| Gastrointestinal ulcer | 1 (0.5) | 0 | 1 (0.3) | .99 |
| Other | 4 (2.1) | 7 (3.8) | 11 (2.9) | .35 |
| Impaired wound healing, No. (%) | 3 (1.6) | 5 (2.7) | 8 (2.1) | .50 |
| Central nervous system, No. (%) | 9 (4.8) | 8 (4.3) | 17 (4.5) | .83 |
| Stroke, TIA, or convulsion | 5 (2.6) | 2 (1.1) | 7 (1.9) | .45 |
| Delirium | 4 (2.1) | 5 (2.7) | 9 (2.4) | .75 |
| Other | 0 | 1 (0.5) | 1 (0.3) | .50 |
| Hypernatremia, No. (%)[c] | 10 (5.3) | 10 (5.4) | 20 (5.3) | .97 |
| Maximum sodium concentration, mean (SD), mEq/L | 141 (6) | 141 (5) | 141 (6) | .29 |
| Sodium concentration during study medication administration, mean (SD), mEq/L | 140 (6) | 141 (5) | 141 (6) | .15 |
| Hyperglycemia, No. (%)[d] | 154 (81.5) | 169 (90.9) | 323 (86.1) | .009 |
| Maximum glucose concentration, median (IQR), mg/dL | 160 (134-196) | 164 (145-204) | 161 (140-201) | .04 |
| Hyperglycemia during study medication administration, No. (%) | 145 (76.7) | 164 (88.2) | 309 (82.4) | .004 |
| Maximum glucose concentration during study medication administration, median (IQR), mg/dL | 157 (133-198) | 170 (147-208) | 163 (141-201) | .006 |
| Other, No. (%) | 18 (9.5) | 12 (6.5) | 30 (8.0) | .27 |

Abbreviations: IQR, interquartile range; MRC, Medical Research Council; TIA, transient ischemic attack.

SI conversion factors: To convert sodium to millimoles per liter, multiply by 1.0; glucose to millimoles per liter, multiply by 0.0555.

[a] Calculated by $\chi^2$ test, Fisher exact test, Mann-Whitney *U* test, or *t* test, as appropriate.

[b] The MRC Scale for Muscle Strength scores range from 0 to 60; a score less than 48 indicates muscle weakness.

[c] Defined as a sodium concentration greater than 155 mEq/L.

[d] Defined as a glucose concentration greater than 150 mg/dL.

to 11.4%; *P* = .44). At 180 days, mortality occurred in 45 of 168 patients (26.8%) in the hydrocortisone group vs 37 of 167 patients (22.2%) in the placebo group (difference, 4.6%; 95% CI, −4.6% to 13.7%; *P* = .32). Analysis of the PP population revealed no significant differences for secondary end points between the treatment arms. A post hoc analysis of 54 patients with CAP did not reveal significant differences for the primary or secondary end points between patients treated with hydrocortisone (n = 24) or placebo (n = 30).

## Adverse Effects

There were more episodes of hyperglycemia (blood glucose level >150 mg/dL [to convert to millimoles per liter, multiply by 0.0555]) in the hydrocortisone group (169 of 186 patients [90.9%]) than in the placebo group (154 of 189 patients [81.5%]) (difference, 9.4%; 95% CI, 2.4% to 16.4%; *P* = .009) (**Table 3**). The total amount of administered insulin was not significantly different between the hydrocortisone and placebo groups (safety set analysis: mean [SD], 264.6 [312.2] vs 212.2 [246.8] IU, respectively; difference, 52.4 IU; 95% CI, −21.8 to 126.7 IU; *P* = .17) (eTable 3 in Supplement 1). Two patients developed severe hypertension during hydrocortisone administration, which required antihypertensive therapy. Both patients recovered without sequelae. Secondary infections, weaning failure, muscle weakness, hypernatremia, or other adverse events were not significantly different between treatment groups (Table 3).

## Critical Illness–Related Corticosteroid Insufficiency

Cortisol data from corticotropin tests were available from 206 of 353 patients (58.4%), of whom 69 (33.5%) had CIRCI. Baseline characteristics were comparable between patients with and without CIRCI (eTable 4 in Supplement 1). In the placebo group, septic shock occurred in 10 of 37 patients with CIRCI (27.0%) and in 9 of 66 patients without CIRCI (13.6%) (difference, 13.4%; 95% CI, −2.1% to 30.5%; *P* = .09). In a multivariate analysis, SOFA score (per SOFA point: odds ratio = 1.26; 95% CI, 1.07-1.49; *P* = .007) and CIRCI (odds ratio = 2.58; 95% CI, 1.13-5.91; *P* = .03) at baseline, but not age or sex, were independently prognostic for development of septic shock (eTable 5 in Supplement 1). In this subpopulation of 206 patients, there was no significant difference regarding the primary or secondary



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end points between patients with or without CIRCI who received hydrocortisone or placebo (eTable 6 in Supplement 1).

### Delirium

Delirium was assessed by the Richmond Agitation-Sedation Scale and the Confusion Assessment Method for the ICU in 286 of 353 patients (81.0%). The median number of assessments per patient was 7 (IQR, 4-12) in the placebo group and 6.5 (IQR, 4-10.5) in the hydrocortisone group (difference, 1.61 assessments; 95% CI, −0.36 to 3.58 assessments; $P$ = .21). Twenty-six patients were excluded from analysis owing to low Richmond Agitation-Sedation Scale score or incomplete data. In the remaining 260 patients, delirium was less frequent in patients who received hydrocortisone than in those who received placebo (11 of 130 patients [8.5%] vs 25 of 130 patients [19.2%], respectively; difference, −10.8%; 95% CI, −19.2% to −2.3%; $P$ = .01). The results remained significant after exclusion of another 60 patients (28 from the placebo group, 32 from the hydrocortisone group) who were diagnosed by the investigator to have no delirium but had at least 1 incomplete delirium assessment or had only 1 baseline assessment (n = 6 in the hydrocortisone group) (with delirium occurring in 11 of 98 patients [11.2%] in the hydrocortisone group vs 25 of 102 patients [24.5%] in the placebo group; difference, −13.3%; 95% CI, −23.7% to −2.6%; $P$ = .01) (Table 2).

## Discussion

In this RCT, low-dose hydrocortisone did not prevent the evolution from severe sepsis to septic shock. There were no significant differences between treatment groups with regard to mortality or LOS in the ICU or hospital, or mortality up to 180 days. Patients treated with hydrocortisone had a significantly higher risk of developing hyperglycemia and a lower risk of developing delirium in a post hoc analysis.

The rationale for this study was based on the notion that severe sepsis and septic shock reflect stages of a disease continuum with increasing mortality.[28] Occurrence of septic shock was chosen as the primary outcome variable for the following reasons. First, hydrocortisone in septic shock showed conflicting results in terms of mortality, but consistent hemodynamic effects and faster septic shock resolution.[6,24] Second, administration of hydrocortisone was associated with immunomodulatory effects including reduced inducible nitric oxide formation—a key mediator of septic shock pathophysiology.[17] Thus, it was hypothesized that attenuation of inflammation in early severe sepsis could prevent progression to shock. Third, this hypothesis was supported by data of Confalonieri et al[8] showing that septic shock was prevented by hydrocortisone in patients with CAP. Fourth, because occurrence of septic shock is associated with an increased risk of mortality,[28] it was hypothesized that prevention of septic shock leading to organ dysfunction could also affect secondary outcome variables such as LOS in the ICU or mortality. If prolonged administration of hydrocortisone was able to prevent septic shock development, this beneficial effect of hydrocortisone could outweigh adverse effects such as hyperglycemia, which can be readily treated by administration of insulin. Vasopressor-dependent (volume-resistant) septic shock in patients with sepsis is still the key indication for suggesting hydrocortisone in the current international guidelines of the Surviving Sepsis Campaign.[2] Hence, it seems plausible to take this as a primary end point if prevention of septic shock is tested. We assumed a rate of septic shock of 40% in patients with severe sepsis based on previous studies[8,25-27] and data from the SepNet Clinical Trials Group. However, owing to different study populations, effect sizes, and septic shock criteria, only a rough estimation was possible (see limitations described later). According to recommendations of the German Sepsis Society to transfer patients with severe sepsis to an intermediate care unit or ICU, only patients treated in these units were enrolled in HYPRESS. This was different from a recent retrospective cohort study of patients with sepsis and similar lactate values but lower hospital mortality (7.9% mortality in the study by Liu et al[29] vs 13.1% mortality in this study), who were treated predominantly in the general ward.[29]

However, the current study did not show a protective effect on shock development, time to septic shock, mortality, or LOS in the ICU or hospital. The results are in contrast to a small study in 46 patients with severe CAP, in which hydrocortisone administration was associated with improved survival and significantly lower rates of septic shock. This study was prematurely stopped after an interim analysis owing to improvement of oxygenation and hospital mortality.[8] The presented data did not support that hydrocortisone was more effective with regard to the primary or secondary end points in patients with pneumonia or in the subgroup of patients with CAP. However, recent larger RCTs of steroids in patients with CAP did not reveal reduction of mortality but did show some beneficial effects on other outcomes. In 304 non-ICU patients, a 4-day treatment with 5 mg of dexamethasone reduced median hospital LOS by 1 day.[30] Another RCT enrolled 120 patients with severe CAP and a high inflammatory response who received methylprednisolone at a dosage of 0.5 mg/kg twice daily or placebo for 5 days.[10] Primary end points were parameters of early (<72 hours) or late (72-120 hours) treatment failure. Treatment failure rates were lower in patients who received steroids than in those who received placebo (13% vs 32%, respectively; $P$ = .02), with late radiographic progression as the only significantly different parameter; notably, late septic shock was rare and less frequent in patients who received steroids than in those who received placebo (0 vs 4 patients, respectively). In the largest RCT to date, with 785 patients with CAP, patients received either 50 mg of prednisone or placebo for 7 days.[9] The primary end point was time to clinical stability for at least 24 hours. Treatment with prednisone shortened time to clinical stability by 1 to 4 days irrespective of severity of CAP, and it shortened time to hospital discharge and duration of antibiotic therapy by 1 day. Thus, there is some evidence that moderate doses of steroids may be more effective in patients with CAP than other causes of sepsis.[11]

Another interesting finding in this study was that despite a higher risk of septic shock in patients with CIRCI, there was



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no detectable difference in septic shock development between treatment groups; however, sample size and event numbers were small. The results are in line with results of the CORTICUS trial, in which effects of hydrocortisone on septic shock resolution were independent from CIRCI. Moreover, in a CORTICUS subgroup analysis, etomidate administration was associated with a significantly higher risk for CIRCI and 28-day mortality. However, hydrocortisone treatment did not reduce mortality in patients with CIRCI who received etomidate.[31] Whether combined biomarkers may be more suitable to detect eligible patients needs further investigation. A subgroup analysis of patients with CAP showed most effects in patients who had low basal cortisol levels combined with high proinflammatory cytokine profiles.[32]

The results from this study do not support an increased risk for secondary infections. Reasonable concerns were amplified by results of the CORTICUS trial, which showed higher numbers of secondary infections including new sepsis and septic shock in patients who received hydrocortisone.[4] A Bayesian analysis, mainly based on CORTICUS results, of patients with septic shock reported an increased risk of infections.[33] However, other studies in patients with septic shock,[3] acute respiratory distress syndrome,[34] trauma,[35] or CAP[8-10,30] and a meta-analysis[7] did not report any increased risk.

An unexpected finding was that delirium developed less frequently in patients treated with hydrocortisone. Indeed, several observational studies reported an association between high serum cortisol concentration and delirium after noncardiac[36] and cardiac[37] surgery and severe sepsis or septic shock.[38] There is compelling evidence that systemic inflammation plays an important role in the pathogenesis of delirium, but it remains controversial whether high cortisol concentration mirrors an activation of the stress response to cope with inflammation, or whether delirium is caused by high cortisol concentration. A prospective cohort study in 330 mechanically ventilated patients with acute lung injury reported a significant dose-independent association between systemic corticosteroid administration and development of delirium.[39] However, in an RCT with 737 patients undergoing cardiac surgery who received dexamethasone, 1 mg/kg, or placebo at anesthesia induction did not reveal a significant difference of postoperative delirium between treatment groups.[40] Thus, the results question the concept of cortisol-induced delirium in critical illness and provide some evidence of protective effects of prolonged administration of low-dose hydrocortisone in early severe sepsis.

There are limitations of the study to be addressed. First, inclusion in the trial was possible only after informed consent could be obtained, so that patients who developed septic shock early may have been missed. Second, data from corticotropin tests were available in a subgroup of 206 patients only, because adrenal function assessment was not an absolute inclusion criterion and therefore was not performed at all study sites or in all patients at a single site. Analyses of CIRCI were post hoc and should be regarded as hypothesis generating only. Third, mortality in the study population was more comparable to the mortality reported in recent studies with CAP[9,10,30] than to the mortality (approximately 30%) reported in the study by Confalonieri et al[8]; thus, it cannot be excluded that hydrocortisone would have been more effective in patients with a higher risk of death. Fourth, data on delirium should be interpreted with caution because patients had to be excluded owing to incomplete data sets, only 1 daily assessment was performed in most patients, and interrater reliability was not assessed. Analyses were performed post hoc and results should therefore be regarded as hypothesis generating. Fifth, secondary analyses were not adjusted for multiple testing, as these statistical comparisons were performed with exploratory rather than confirmatory intention. Adjustment for clustering within site was not performed because site was a stratification factor for randomization. Sixth, the observed rate of septic shock in the placebo group (23%; 95% CI, 17%-30%) was lower than originally presumed for sample size calculation (40%). The point estimate of the difference of septic shock occurrences was −1.8% (ie, close to 0) with a 95% CI of −10.7% to 7.2%. Hence, the trial gives no indication of a clinically relevant major benefit of hydrocortisone treatment, which it was designed to detect.

## Conclusions

Among adults with severe sepsis not in septic shock, the use of hydrocortisone compared with placebo did not reduce the risk of septic shock within 14 days. These findings do not support the use of hydrocortisone in these patients.

ARTICLE INFORMATION

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