Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock

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Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock

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Context Septic shock may be associated with relative adrenal insufficiency. Thus, a replacement therapy of low doses of corticosteroids has been proposed to treat septic shock.

Objective To assess whether low doses of corticosteroids improve 28-day survival in patients with septic shock and relative adrenal insufficiency.

Design and Setting Placebo-controlled, randomized, double-blind, parallel-group trial performed in 19 intensive care units in France from October 9, 1995, to February 23, 1999.

Patients Three hundred adult patients who fulfilled usual criteria for septic shock were enrolled after undergoing a short corticotropin test.

Intervention Patients were randomly assigned to receive either hydrocortisone (50-mg intravenous bolus every 6 hours) and fludrocortisone (50-µg tablet once daily) (n=151) or matching placebos (n=149) for 7 days.

Main Outcome Measure Twenty-eight-day survival distribution in patients with relative adrenal insufficiency (nonresponders to the corticotropin test).

Results One patient from the corticosteroid group was excluded from analyses because of consent withdrawal. There were 229 nonresponders to the corticotropin test (placebo, 115; corticosteroids, 114) and 70 responders to the corticotropin test (placebo, 34; corticosteroids, 36). In nonresponders, there were 73 deaths (63%) in the placebo group and 60 deaths (53%) in the corticosteroid group (hazard ratio, 0.67; 95% confidence interval, 0.47-0.95; $P=.02$). Vasopressor therapy was withdrawn within 28 days in 46 patients (40%) in the placebo group and in 65 patients (57%) in the corticosteroid group (hazard ratio, 1.91; 95% confidence interval, 1.29-2.84; $P=.001$). There was no significant difference between groups in responders. Adverse events rates were similar in the 2 groups.

Conclusion In our trial, a 7-day treatment with low doses of hydrocortisone and fludrocortisone significantly reduced the risk of death in patients with septic shock and relative adrenal insufficiency without increasing adverse events.

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SEVERE SEPSIS REMAINS AN IMPORTANT cause of death, accounting for 9.3% of all deaths in the United States in 1995.[1] If our understanding of the mechanisms of host response to stress has strongly progressed during the last 2 decades,[2] the various drugs developed for specific targets of the cytokine cascade have failed to improve patient survival.[3,4]

Corticosteroids were the first anti-inflammatory drugs tested in randomized trials. At high doses during short courses, they did not induce favorable effects.[5,6] However, the observation that severe sepsis may be associated with relative adrenal insufficiency[7,8] or systemic inflammation-induced glucocorticoid receptor resistance[9] prompted renewed interest of a replacement therapy

For editorial comment see p 886.

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with low doses of corticosteroids during longer periods.[10,11]

The interest of this new approach was confirmed by the demonstration that a single intravenous administration of 50 mg of hydrocortisone strongly improved norepinephrine and phenylephrine mean arterial pressure dose-response relationships in patients with septic shock,[12,13] particularly in those with relative adrenal insufficiency.[12] Moreover, 2 small placebo-controlled randomized trials also showed that prolonged treatment (≥5 days) with low doses of hydrocortisone (about 300 mg daily) significantly improved the time to vasopressor therapy withdrawal in septic shock.[14,15] Thus, we designed this placebo-controlled study to assess whether a replacement therapy with hydrocortisone and fludrocortisone (assuming the possibility of a primary adrenal insufficiency)[16] could improve 28-day survival in patients with septic shock, with particular interest in patients with relative adrenal insufficiency.

METHODS

Experimental Design and Study Organization

This placebo-controlled, randomized, double-blind study was performed on 2 parallel groups at 19 intensive care units (ICUs) in France (FIGURE 1). It was supported by Groupe d'Etude et de Recherche sur le Médicament (GERMED), which awarded a grant from publicly funded resources. The protocol was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale of Saint-Germain en Laye, France, on February 9, 1995. Inclusions were authorized from September 11, 1995. Two interim analyses were planned. An independent main end point and safety monitoring board met after each interim analysis to decide whether the study should be continued or stopped. Enrollment ended March 15, 1999. At the end of the study, an independent diagnosis validation committee blindly classified each patient as being unquestionable, probable, or nonprobable for having had septic shock.

Patients

All patients 18 years or older and hospitalized in participating ICUs were prospectively enrolled in the study if they met all the following criteria: (1) documented site (or at least strong suspicion) of infection, as evidenced by one or more of the following: presence of polymorphs in a normally sterile body fluid (except blood), positive culture or Gram stain of a normally sterile body fluid, clinical focus of infection (eg, fecal peritonitis), wound with purulent discharge, pneumonia or other clinical evidence of systemic infection (eg, purpura fulminans); (2) temperature higher than 38.3°C or lower than 35.6°C; (3) heart rate greater than 90 beats per minute; (4) systolic arterial pressure lower than 90 mm Hg for at least 1 hour despite adequate fluid replacement and more than 5 µg/kg of body weight of dopamine or current treatment with epinephrine or norepinephrine; (5) urinary output of less than 0.5 mL/kg of body weight for at least 1 hour or ratio of arterial oxygen tension to the fraction of inspired oxygen (PaO_2/FIO_2) of less than 280 mm Hg; (6) arterial lactate levels higher than 2 mmol/L; and (7) need for mechanical ventilation. Written informed consent had to be obtained from the patients themselves or their relatives and a short corticotropin test had to be performed before randomization. Finally, patients had to be randomized within 3 hours of the onset of shock.

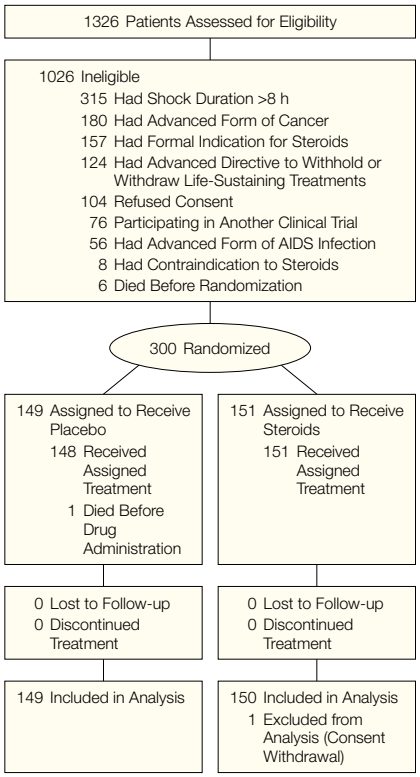
Patients were excluded if they were pregnant or had evidence for acute myocardial infarction or pulmonary embolism, advanced form of cancer or acquired immunodeficiency syndrome (AIDS) infection, and contraindication or formal indication for corticosteroids.

During recruitment, we refined the eligibility criteria by not making the arterial lactate requirement mandatory (the 6th criterion) but adding it as an option to the 5th criterion. We also increased the maximum delay from the onset of septic shock and randomization from 3 to 8 hours (amendment of July 18, 1996); and we excluded patients who received etomidate during the 6 hours preceding randomization because it is a selective inhibitor of the 11 β-hydroxylase and therefore could interfere with cortisol response to corticotropin (amendment of June 19, 1997).

Randomization

Randomization was centrally performed, concealed, and stratified by center in blocks of 4 according to a computer-generated random number table. In each center, sequentially numbered boxes containing the whole treatment for each patient were delivered to the investigator by the pharmacist following the order of the randomization list. All patients, medical and nursing staffs, and pharmacists remained blinded throughout the study period.

Figure 1. Study Flow Chart



We included the patient in the placebo group who died before treatment in our intent-to-treat analysis. Of the 1026 ineligible patients, 65% were men, and had a mean (SD) age of 59 (16) years and a Simplified Acute Physiology Score II (SAPS II) score of 60 (23). Of those randomized, 67% were men and had a mean (SD) age of 61 (16) years and a SAPS II score of 59 (19).

Treatments

Hydrocortisone came in vials containing 100 mg of hydrocortisone hemisuccinate powder and ampoules containing 2 mL of glucose solution solvent, which was administered intravenously every 6 hours as a 50-mg bolus (Roussel-Uclaf, Romainville, France). One tablet containing 50 µg of 9-α-fludrocortisone was administered daily through a nasogastric tube with 10 to 40 mL of water over 30 seconds (Pharmacie Centrale des Hôpitaux, Paris, France). Placebos were indiscernible from active treatments. Treatment duration was 7 days.

Data Collection at Inclusion

Clinical Evaluation. The following data were recorded: (1) general characteristics including estimated prognosis of any underlying disease[17] and level of activity limitation[18]; (2) severity of illness assessed by vital signs, Simplified Acute Physiology Score II (SAPS II),[19] and Logistic Organ Dysfunction (LOD) score[20]; and (3) interventions including the volume of fluid infusion and the type and doses of vasopressors and antibiotics.

Laboratory Variables. Hematological and chemistry data, arterial lactate and blood gas determinations, and blood cultures and cultures of specimen drawn from the site of infection were done systematically. The short corticotropin test was performed using a 250-µg intravenous bolus of tetracosactrin (Synacthène Ciba, Rueil-Malmaison, France). Blood samples were taken immediately before the test and 30 and 60 minutes after the test. After centrifugation, plasma samples were stored at –80°C until assayed. Cortisol was measured blindly and serially before interim and final statistical analyses using Immunotech radioimmunoassay.[21] To reduce heterogeneity in cortisol determination, all plasma samples were measured at a central laboratory. Cortisol response was defined as the difference between the highest of the concentrations taken after the test and those taken before the test. Relative adrenal insufficiency (ie, nonresponders) was defined by a response of 9 µg/dL or less.[7,8]

Table 1. General Characteristics of 299 Patients With Septic Shock*

Characteristic	Nonresponders		Responders		All	
	Placebo (n = 115)	Steroids (n = 114)	Placebo (n = 34)	Steroids (n = 36)	Placebo (n = 149)	Steroids (n = 150)
Age, mean (SD), y	60 (17)	63 (15)	60 (18)	59 (16)	60 (17)	62 (15)
Sex						
Men	78 (68)	72 (63)	26 (76)	24 (67)	104 (70)	96 (64)
Women	37 (32)	42 (37)	8 (24)	12 (33)	45 (30)	54 (36)
White race	110 (96)	105 (93)	29 (88)	32 (89)	139 (95)	137 (92)
McCabe classification						
Nonfatal disease	82 (71)	74 (65)	21 (62)	24 (67)	103 (69)	98 (65)
Ultimately fatal disease	32 (28)	40 (35)	13 (38)	12 (33)	45 (30)	52 (35)
Rapidly fatal disease	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Level of activity limitation†						
A	36 (31)	25 (22)	9 (26)	8 (22)	45 (30)	33 (22)
B	48 (42)	51 (45)	8 (24)	19 (53)	56 (38)	70 (47)
C	17 (15)	24 (21)	10 (29)	6 (17)	27 (18)	30 (20)
D	14 (12)	14 (12)	7 (21)	3 (8)	21 (14)	17 (11)
Prior or preexisting disease						
Hypertension	31 (27)	35 (31)	9 (26)	9 (25)	40 (27)	44 (29)
Coronary artery disease	8 (7)	15 (13)	3 (9)	5 (14)	11 (7)	20 (13)
Congestive heart failure	7 (6)	10 (9)	4 (12)	5 (14)	11 (7)	15 (10)
Neurological disease	13 (11)	16 (14)	15 (44)	11 (31)	28 (19)	27 (18)
Chronic pulmonary disease	17 (15)	14 (12)	7 (21)	3 (8)	24 (16)	17 (11)
Cancer	16 (14)	15 (13)	2 (6)	8 (22)	18 (12)	23 (15)
Diabetes	15 (13)	18 (16)	2 (6)	2 (6)	17 (11)	20 (13)
Liver disease	12 (10)	8 (7)	0 (0)	5 (14)	12 (8)	13 (9)
Admission category						
Medical	62 (54)	65 (57)	28 (82)	24 (67)	90 (60)	89 (59)
Emergency surgery	49 (43)	43 (38)	6 (18)	12 (33)	55 (37)	55 (37)
Elective surgery	4 (3)	6 (5)	0 (0)	0 (0)	4 (3)	6 (4)

*Results are based on patient responses to a short corticotropin test. Data are presented as number (percentage) unless otherwise indicated.
†Levels of activity limitation are defined as follows: A, prior good health, no functional limitations; B, mild to moderate limitation of activity because of chronic medical problem; C, chronic disease producing serious but not incapacitating restriction of activity; and D, severe restriction of activity due to disease, includes persons bedridden or institutionalized due to illness.

Follow-up

The following data were recorded daily during the 28-day period following randomization: vital signs, results from standard laboratory tests and cultures of specimen drawn from any new site of infection, and interventions. In addition, the patient's status at discharge from ICU and hospital and 1 year after randomization was recorded.

End Points

The main end point was the 28-day survival distribution from randomization in nonresponders to the short corticotropin test. Secondary end points were 28-day survival distributions from randomization in responders to the short corticotropin test and in all patients; 28-day, ICU, hospital, and 1-year mortality rates; and time to vasopressor therapy withdrawal during the 28 days from randomization in the 2 subsets of patients and in all patients.

Adverse events were carefully monitored and classified as being possibly related to corticosteroids (superinfection, gastrointestinal bleeding, psychiatric disorders), possibly related to vasopressors (life-threatening arrhythmia, myocardial infarction, limb or cerebral ischemia), related to ICU invasive procedures, and not related to 1 of the 3 previous categories.

Sample Size and Statistical Analysis

A total of 270 patients was the calculated sample size needed to detect, in

a 1-sided test performed with a 0.05 type I error, a difference between the 2 groups of nonresponders on the 28-day mortality rate of 20% with a 90% probability, assuming a mortality rate of 95% in the nonresponder placebo subgroup[7,22] and a frequency of nonresponders of 40% in the population of patients with septic shock.[7] A 1-sided formulation was chosen to compute the sample size because the trial was designed to test whether low doses of corticosteroids were more effective than placebo, and we had no interest in formally demonstrating the opposite alternative hypothesis (a deleterious effect of corticosteroids).[22,23]

The 2 interim analyses were planned using an O'Brien and Fleming stopping boundary.[24] With this procedure, the differences between the 2 groups were considered significant if the critical z values were higher than 3.471, 2.454, and 2.004 at the first, second, and final analyses, respectively (corresponding to nominal 2-sided P values $<.0005$, $<.0141$ and $<.0451$, respectively).

The statistical analysis, prospectively defined, was performed according to the intent-to-treat principle (in

Table 2. Severity of Illness of 299 Patients With Septic Shock*

	Nonresponders		Responders		All Patients	
Characteristic	Placebo (n = 115)	Steroids (n = 114)	Placebo (n = 34)	Steroids (n = 36)	Placebo (n = 149)	Steroids (n = 150)
Temperature, °C	37.9 (2.1)	38.0 (2.0)	38.0 (2.6)	38.0 (2.0)	37.9 (2.2)	38.0 (2.0)
Temperature <35.6 °C, No. (%)	28 (24)	28 (25)	5 (15)	9 (25)	33 (22)	37 (25)
Heart rate, beats/min	119 (21)	119 (20)	117 (21)	115 (23)	118 (21)	118 (21)
Mean arterial pressure, mm Hg	55 (9)	54 (10)	53 (12)	53 (11)	55 (10)	54 (10)
SAPS II	58 (18)	60 (18)	54 (20)	59 (22)	57 (19)	60 (19)
LOD score	9 (3)	9 (3)	9 (3)	9 (4)	9 (3)	9 (3)
Hemoglobin, g/dL	10.1 (2.2)†	10.0 (2.2)	10.3 (2.7)	10.3 (2.3)	10.2 (2.3)†	10.0 (2.3)
Leukocytes, $\times 10^3/\mu L$	12.6 (8.9)†	12.7 (9.8)	14.4 (6.4)	14.5 (11.1)	13.0 (8.4)†	13.1 (10.1)
Platelets, $\times 10^3/\mu L$	165 (132)†	153 (108)†	209 (112)	159 (153)	175 (129)†	155 (120)†
Arterial lactate, mmol/L	4.8 (4.6)	4.8 (4.7)	2.6 (2.4)	3.7 (3.0)	4.3 (4.3)	4.6 (4.4)
Pao_2/Fio_2, mm Hg	178 (134)	181 (126)	146 (81)	158 (96)	171 (124)	176 (120)
Cortisol concentration, µg/dL						
Before corticotropin test	24 (35)	18 (12)	31 (56)	30 (23)	26 (41)	21 (16)
30 min after corticotropin test	22 (16)	19 (12)	41 (60)	45 (31)	26 (33)	26 (21)
60 min after corticotropin test	23 (17)	20 (12)	46 (57)	55 (45)	28 (32)	28 (28)
Response to corticotropin test	0 (26)	2 (3)	16 (6)	28 (36)	3 (24)	9 (21)§
Three-level prognostic classification, No. (%)‡						
Good	0 (0)	0 (0)	28 (82)	27 (75)	28 (19)	27 (18)
Intermediate	99 (86)	105 (92)	6 (18)	9 (25)	105 (70)	114 (76)
Poor	16 (14)	9 (8)	0 (0)	0 (0)	16 (11)	9 (6)
Fluid loading, mL/kg	34 (29)	32 (28)	29 (33)	27 (22)	33 (30)	30 (27)
Vasopressors, µg/kg per min						
Dopamine	11.6 (6.0) [n = 107]	11.5 (6.2) [n = 101]	11.4 (4.6) [n = 30]	10.3 (5.2) [n = 35]	11.5 (5.7) [n = 137]	11.2 (6.0) [n = 136]
Dobutamine	8.2 (4.4) [n = 40]	10.2 (6.5) [n = 40]	9.2 (4.1) [n = 11]	7.4 (4.7) [n = 13]	8.4 (4.3) [n = 51]	9.5 (6.2) [n = 53]
Epinephrine	1.0 (0.9) [n = 29]	0.8 (0.6) [n = 34]	1.0 (0.0) [n = 2]	1.0 (1.1) [n = 7]	1.0 (0.9) [n = 31]	0.8 (0.7) [n = 41]
Norepinephrine	1.1 (1.1) [n = 41]	1.1 (1.1) [n = 38]	0.6 (0.4) [n = 7]	0.7 (0.6) [n = 8]	1.0 (1.1) [n = 48]	1.1 (1.1) [n = 46]
Time to a pressor from shock onset, h	3.3 (4.1)	3.4 (4.3)	3.9 (4.8)	4.6 (5.9)†	3.5 (4.3)	3.7 (4.7)†
Time on a pressor before study drugs, h	4.0 (3.2)	4.3 (3.6)	4.4 (2.3)†	3.5 (2.9)	4.1 (3.0)†	4.1 (3.4)
Ventilatory support						
Tidal Volume, mL/kg	8.8 (2.0)‖	8.6 (2.3)¶	9.1 (2.2)	9.0 (2.6)	8.9 (2.1)‖	8.7 (2.4)¶
Fio_2, %	78 (24)	80 (23)	79 (22)	80 (23)	78 (24)	80 (23)
PEEP, cm Ho_2	6.9 (3.1) [n = 59]	6.3 (2.8) [n = 69]	7.1 (2.5) [n = 16]	6.8 (2.5) [n = 18]	6.9 (3.0) [n = 75]	6.4 (2.7) [n = 87]

*Results are based on patient responses to a short corticotropin test. Data are presented as mean (SD) unless otherwise indicated. SAPS II indicates Simplified Acute Physiology Score II; LOD, Logistic Organ Dysfunction; Pao_2, arterial oxygen pressure; Fio_2, inspired oxygen fraction; and PEEP, positive end-expiratory pressure.
†One value is missing.
‡Three-level prognostic classifications are defined as good, cortisol concentrations before corticotropin test ≤34 µg/dL and response to corticotropin test >9 µg/dL; intermediate, cortisol concentrations before corticotropin test ≤34 µg/dL and response to corticotropin test ≤9 µg/dL, or cortisol concentrations before corticotropin test >34 µg/dL and response to corticotropin test >9 µg/dL; poor, cortisol concentrations before corticotropin test >34 µg/dL and response to corticotropin test ≤9 µg/dL.
§$P = .04$ for comparison with the placebo group using t test.
‖Two values are missing.
¶Three values are missing.

all analyses, patients were grouped according to their original randomized treatment) with SAS statistical software (SAS Institute, Cary, NC). For continuous variables, the mean (SDs) are reported whereas, for categorical variables, the number of patients in each category and the corresponding percentages are given.

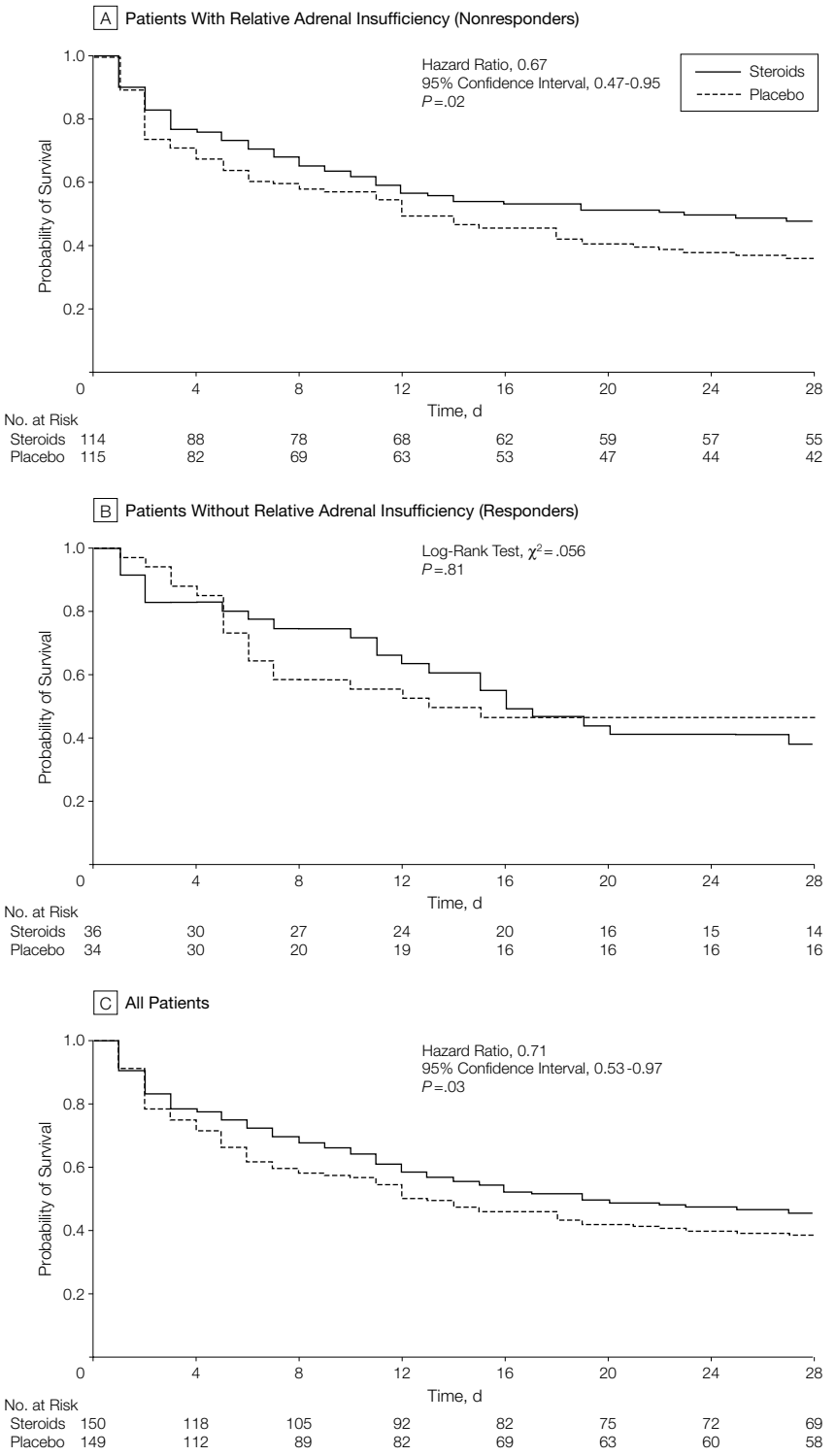
Table 3. Type and Site of Infection, Type of Organism, and Type of Antibiotics Used in 299 Patients With Septic Shock*

	Nonresponders		Responders		All Patients	
Characteristic	Placebo (n = 115)	Steroids (n = 114)	Placebo (n = 34)	Steroids (n = 36)	Placebo (n = 149)	Steroids (n = 150)
Type of infection						
Community-acquired	74 (64)	70 (61)	19 (56)	24 (67)	93 (62)	94 (63)
Postsurgery	19 (17)	23 (20)	3 (9)	3 (8)	22 (15)	26 (17)
Other (hospital-acquired)	22 (19)	21 (18)	12 (35)	9 (25)	34 (23)	30 (20)
Site of infection						
Lung only	46 (40)	42 (37)	24 (71)	19 (53)	70 (47)	61 (41)
Abdominoperitoneal only	22 (19)	22 (19)	1 (3)	4 (11)	23 (15)	26 (17)
Urinary tract only	5 (4)	6 (5)	2 (6)	1 (3)	7 (5)	7 (5)
Cellulitis only	11 (10)	7 (6)	1 (3)	1 (3)	12 (8)	8 (5)
Other (1 site only)	6 (5)	6 (5)	0 (0)	2 (6)	6 (4)	8 (5)
>1 site	25 (22)	29 (25)	6 (18)	9 (25)	31 (21)	38 (25)
Unknown	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	2 (1)
Positive culture						
At any site	96 (83)	92 (81)	30 (88)	29 (81)	126 (85)	121 (81)
Gram-positive only	26 (23)	34 (30)	11 (32)	12 (33)	37 (25)	46 (31)
Gram-negative only	34 (30)	31 (27)	11 (32)	6 (17)	45 (30)	37 (25)
Fungus only	1 (1)	0 (0)	3 (9)	1 (3)	4 (3)	1 (1)
Mixed	35 (30)	27 (24)	5 (15)	10 (28)	40 (27)	37 (25)
Culture not obtained	3 (3)	3 (3)	1 (3)	1 (3)	4 (3)	4 (3)
Of blood	24 (21)	32 (28)	7 (21)	7 (19)	31 (21)	39 (26)
Gram-positive only	11 (10)	21 (18)	6 (18)	5 (14)	17 (11)	26 (17)
Gram-negative only	8 (7)	10 (9)	1 (3)	2 (6)	9 (6)	12 (8)
Fungus only	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mixed	5 (4)	1 (1)	0 (0)	0 (0)	5 (3)	1 (1)
Type of organism						
Gram-positive						
MSSA	16 (14)	17 (15)	8 (24)	7 (19)	24 (16)	24 (16)
MRSA	7 (6)	8 (7)	0 (0)	6 (17)†	7 (5)	14 (9)
Other *Staphylococcus* species	2 (2)	2 (2)	1 (3)	0 (0)	3 (2)	2 (1)
Streptococcus pneumoniae	10 (9)	12 (11)	4 (12)	4 (11)	14 (9)	16 (11)
Other *Streptococcus* species	11 (10)	13 (11)	2 (6)	4 (11)	13 (9)	17 (11)
Enterococcus species	15 (13)	10 (9)	1 (3)	3 (8)	16 (11)	13 (9)
Clostridium species	2 (2)	1 (1)	0 (0)	0 (0)	2 (1)	1 (1)
Other gram-positive	4 (3)	2 (2)	0 (0)	1 (3)	4 (3)	3 (2)
Gram-negative						
Escherichia coli	31 (27)	24 (21)	3 (9)	6 (17)	34 (23)	30 (20)
Pseudomonas aeruginosa	14 (12)	9 (8)	5 (15)	3 (8)	19 (13)	12 (8)
Klebsiella pneumoniae	8 (7)	2 (2)	0 (0)	1 (3)	8 (5)	3 (2)
Other *Enterobacter* species	18 (16)	14 (12)	2 (6)	2 (6)	20 (13)	16 (11)
Haemophilus influenzae	12 (10)	6 (5)	1 (3)	2 (6)	13 (9)	8 (5)
Bacteroides species	5 (4)	8 (7)	0 (0)	0 (0)	5 (3)	8 (5)
Other gram negative	6 (5)	5 (4)	4 (12)	3 (8)	10 (7)	8 (5)
Fungus						
Candida albicans	0 (0)	1 (1)	2 (6)	2 (6)	2 (1)	3 (2)
Other *Candida* species	2 (2)	0 (0)	2 (6)	1 (3)	4 (3)	1 (1)
Yeast	1 (1)	1 (1)	0 (0)	0 (0)	1 (1)	1 (1)
Appropriate antibiotics‡	109 (95)	104 (91)	32 (94)	33 (92)	141 (95)	137 (91)
Time to appropriate antibiotics, mean (SD), h§	5.0 (9.9)	6.3 (9.4)	9.2 (17.4)	9.3 (16.2)	6.0 (12.1)	7.1 (11.4)

*Results are based on patient responses to a short corticotropin test. Data are presented as number (percentage) unless otherwise indicated. MRSA indicates methicillin-resistant *Staphyloccus aureus*; MSSA, methicillin-susceptible *S aureus*.
†P = .03 using Fisher exact test.
‡Appropriate antibiotics are based on the site of infection and available cultures.
§Time to appropriate antibiotics indicates delay from diagnosis of severe sepsis and administration of first dose of antibiotics.

Analyses were similarly performed in nonresponders, in responders, and in all patients. Pretreatment characteristics were compared between groups using the *t* test (for continuous variables) or χ^2 or Fisher exact tests when appropriate (for categorical variables). Cumulative event curves (28-day survival and time-to-vasopressor therapy withdrawal end points) were estimated with the Kaplan-Meier procedure and median times to event were reported. The effects of treatments on these end points were estimated from adjusted Cox proportional hazards regression models[25] using baseline cortisol, cortisol response, McCabe classification, LOD score, arterial lactate levels, and PaO_2/FIO_2 results for the adjustment.[8] Corresponding hazard ratios (HRs) along with their 95% confidence intervals (CIs) were reported. Proportionality among the event rates in the Cox models was assessed by the plot of the log (–log [survival function]) vs time. When the proportionality assumption was not upheld, Cox models were not used and only the Kaplan-Meier curves were reported along with log-rank tests. For 28-day survival, patients who were still alive at 28 days were treated as censored. For this end point, the number needed to treat at 28 days was estimated.[26] For time-to-vasopressor-therapy withdrawal, among patients who had more than 1 outcome event during the 28 days from randomization, time to the first event was used in the analyses. For this end point, the patients who died before vasopressor therapy could be withdrawn and those for whom vasopressor therapy could not be withdrawn during the 28 days from randomization were treated as censored. The effects of treatments on the frequency of fatal events (28-day, ICU, hospital and 1-year mortality rates) were estimated from logistic regression analysis using the same variables for the adjustment as the Cox models. Corresponding adjusted odds ratios (ORs) along with their 95% CIs were reported. We also computed the 28-day, ICU, hospital, and 1-year relative risks (RRs)

Figure 2. Kaplan-Meier Analysis of the Probability of Survival of Patients With Septic Shock



Results are according to the response to the short corticotropin test. In nonresponders, the median time to death was 12 days in the placebo and 24 days in the corticosteroid groups; in responders, 14 days in the placebo and 16.5 days in the corticosteroid groups; and in all patients, 13 days in the placebo and 19.5 in the corticosteroid groups.

Table 4. Frequency of Fatal Events in 299 Patients with Septic Shock*

Variable	No. (%) Placebo	No. (%) Steroids	Adjusted OR (95% CI)	*P* Value
Nonresponders				
No. of patients	115	114		
28-day mortality	73 (63)	60 (53)	0.54 (0.31-0.97)	.04
ICU mortality	81 (70)	66 (58)	0.50 (0.28-0.89)	.02
Hospital mortality	83 (72)	70 (61)	0.53 (0.29-0.96)	.04
1-Year mortality	88 (77)	77 (68)	0.57 (0.31-1.04)	.07
Responders				
No. of patients	34	36		
28-Day mortality	18 (53)	22 (61)	0.97 (0.32-2.99)	.96
ICU mortality	20 (59)	24 (67)	0.99 (0.31-3.16)	.99
Hospital mortality	20 (59)	25 (69)	1.20 (0.38-3.76)	.75
1-Year mortality	24 (71)	25 (69)	0.70 (0.20-2.40)	.57
All Patients				
No. of patients	149	150		
28-Day mortality	91 (61)	82 (55)	0.65 (0.39-1.07)	.09
ICU mortality	101 (68)	90 (60)	0.61 (0.37-1.02)	.06
Hospital mortality	103 (69)	95 (63)	0.67 (0.40-1.12)	.12
1-Year mortality	112 (75)	102 (68)	0.62 (0.36-1.05)	.08

*Results are based on patient responses to a short corticotropin test. Using baseline cortisol, cortisol response, McCabe classification, Logistic Organ Dysfunction score, arterial lactate levels and PaO_2/FIO_2 results for adjustment, analyses were performed with use of logistic models. OR indicates, odds ratios; CI, confidence intervals; and ICU, intensive care unit.

of death along with their 95% CIs. The frequency of adverse events was compared between groups using the χ^2 or Fisher exact tests when appropriate. All reported *P* values are 2-sided.

RESULTS

Study Description

From October 9, 1995, to February 23, 1999, 1326 patients were screened and 300 patients (placebo, 149; corticosteroids, 151) were included in the study (Figure 1). Interim analyses were performed on April 3, 1997, and April 20, 1998, after the evaluation of 114 and 220 patients, respectively. After each analysis, the independent main end point and safety monitoring board advised the study chairpersons to continue the study. We included the patient in the placebo group who died before study drugs could be administered in our intent-to-treat analysis. One patient in the corticosteroid group was excluded from the final analysis because of consent withdrawal. Among the 299 remaining patients, there were 229 nonresponders (placebo, 115; corticosteroids, 114) and 70 responders (placebo, 34; corticosteroids, 36).

Characteristics of Study Patients at Inclusion

At baseline, the 2 groups were balanced with respect to general characteristics (TABLE 1) and severity of illness (TABLE 2). Cortisol response to corticotropin was higher in the corticosteroid group than in the placebo group in the all-patients analysis, but the distribution of patients according to our 3-level prognostic classification[8] was similar in the 2 groups. The type and site of infection and the type of organism involved were also similar in the 2 groups (TABLE 3). Finally, a blinded evaluation determined that appropriate antibiotic therapy, based on the site of infection and available cultures, was promptly (<24 hours from diagnosis of severe sepsis) started and continued for at least 7 days in most cases (ie, 95% in the placebo group, 91% in the corticosteroid group).

Mortality Distribution

Nonresponders. At day 28 , there were 73 deaths (63%) in the placebo group and 60 deaths (53%) in the corticosteroid group. The median time to death was 12 days in the placebo group and 24 days in the corticosteroid group. The HR estimated using a Cox model was 0.67 (95% CI, 0.47-0.95; *P*=.02;FIGURE 2A). The number of patients needed to treat to save 1 additional life at day 28 is 7 (95% CI, 4-49).

Responders. At day 28, there were 18 deaths (53%) in the placebo group and 22 deaths (61%) in the corticosteroid group. The median time to death was 14 days in the placebo group and 16.5 days in the corticosteroid group. The proportionality assumption was not supported for the Cox model and comparison of survival distributions was performed using a log-rank test (*P*=.81) (Figure 2B).

All Patients. At day 28, there were 91 deaths (61%) in the placebo group and 82 deaths (55%) in the corticosteroid group. The median time to death was 13 days in the placebo group and 19.5 days in the corticosteroid group. The HR estimated using a Cox model was 0.71 (95% CI, 0.53-0.97; *P*=.03) (Figure 2C). The number of patients needed to treat to save 1 additional life at day 28 is 8 (95% CI, 5-81).

Mortality Rates

Nonresponders. As mentioned above, at day 28, there were 73 deaths (63%) in the placebo group and 60 deaths (53%) in the corticosteroid group (RR, 0.83; 95% CI, 0.66-1.04; adjusted OR, 0.54; 95% CI, 0.31-0.97; *P*=.04). There were 81 deaths (70%) in the placebo group and 66 deaths (58%) in the corticosteroid group at the end of ICU stay (RR, 0.82; 95% CI, 0.68-1.00; adjusted OR, 0.50; 95% CI, 0.28-0.89; *P*=.02). A similar significant difference was observed at the end of hospital stay. There were 88 deaths (77%) in the placebo group and 77 deaths (68%) in the corticosteroid group after 1 year of follow-up (RR, 0.88; 95% CI, 0.75-1.04; adjusted OR, 0.57; 95% CI, 0.31-1.04; *P*=.07) (TABLE 4).

Responders. There was no significant effect of corticosteroids on 28-day, ICU, hospital, and 1-year mortality rates in responders (Table 4).

All Patients. There was no significant effect of corticosteroids on 28-day, ICU, hospital, and 1-year mortality rates

in all patients. For example, the ICU mortality is represented by RR, 0.89 (95% CI, 0.75-1.05), adjusted OR, 0.61 (95% CI, 0.37-1.02), $P=.06$ and year of follow-up is represented by RR, 0.91 (95% CI, 0.78-1.04), adjusted OR, 0.62 (95% CI, 0.36-1.05), $P=.08$ (Table 4).

Time-to-Vasopressor-Therapy Withdrawal

Nonresponders. The median time to vasopressor therapy withdrawal was 10 days in the placebo group and 7 days in the corticosteroid group. The HR estimated using a Cox model was 1.91 (95% CI, 1.29-2.84; $P=.001$) (FIGURE 3A). At day 28, vasopressor therapy had been withdrawn in 46 patients (40%) in the placebo group and in 65 patients (57%) in the corticosteroid group.

Responders. The median time-to-vasopressor-therapy withdrawal was 7 days in the placebo group and 9 days in the corticosteroid group. The proportionality assumption was not supported for the Cox model and comparison of time-to-vasopressor-therapy withdrawal distributions was performed using a log-rank test ($P=.49$, Figure 3B). At day 28, vasopressor therapy had been withdrawn in 18 patients (53%) in the placebo group and in 18 patients (50%) in the corticosteroid group.

All Patients. The median time to vasopressor therapy withdrawal was 9 days in the placebo group and 7 days in the corticosteroid group. The HR estimated using a Cox model was 1.54 (95% CI, 1.10-2.16; $P=.01$; Figure 3C). At day 28, vasopressor therapy had been withdrawn in 64 patients (43%) in the placebo group and in 83 patients (55%) in the corticosteroid group.

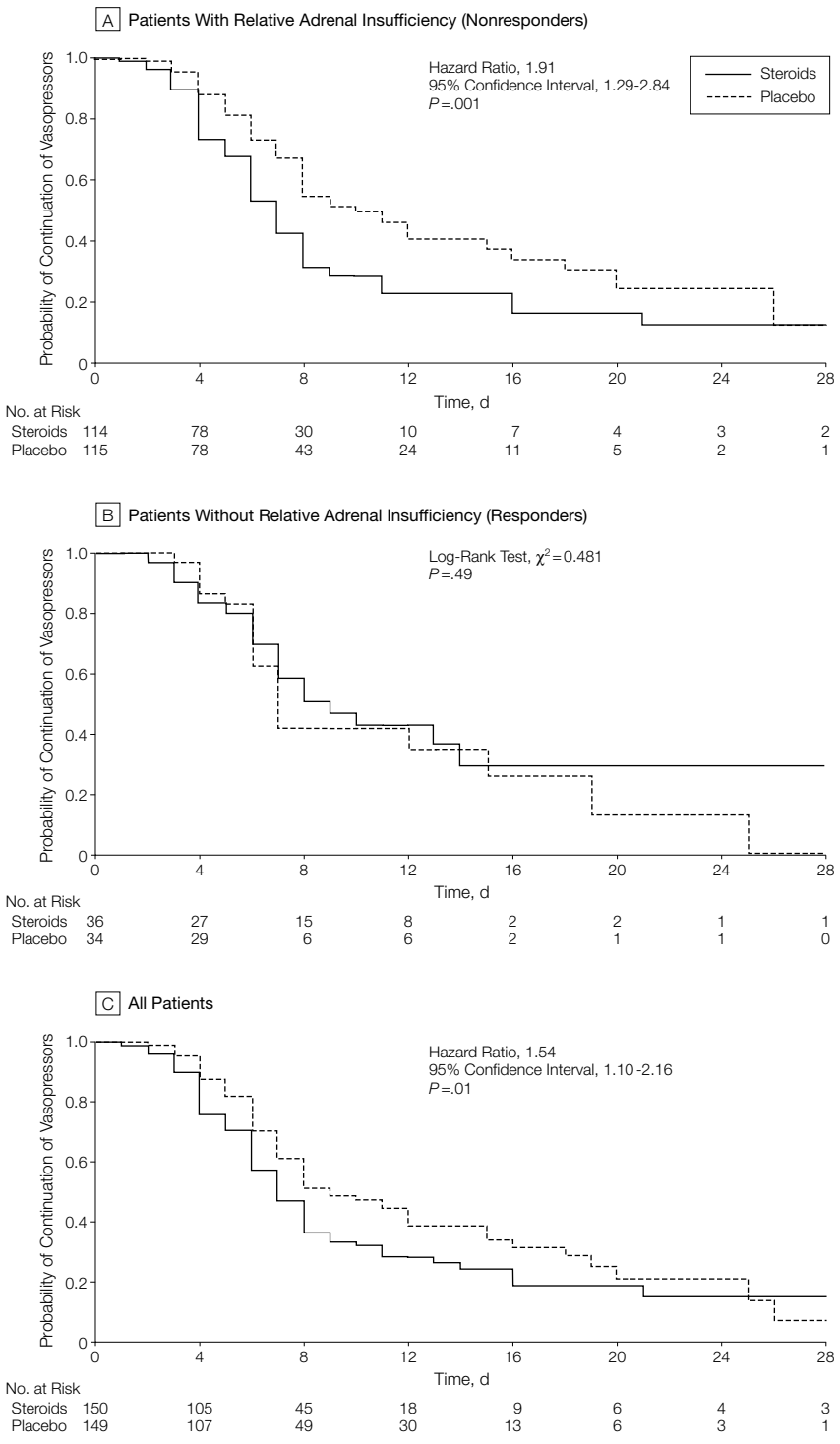
Adverse Events

There were no significant differences between the 2 groups in the rates of adverse events possibly related to corticosteroids or vasopressors, or related to ICU invasive procedures (TABLE 5).

COMMENT

We found that a 7-day replacement therapy with hydrocortisone (50 mg in-

Figure 3. Kaplan-Meier analysis of the Probability of Continuation of Vasopressor Therapy of Patients With Septic Shock



Results are according to the response to the short corticotropin test. In nonresponders, the median time to vasopressor therapy withdrawal was 10 days in the placebo and 7 days in the corticosteroid groups; in responders, 7 days in the placebo and 9 days in the corticosteroid groups; and in all patients, 9 days in the placebo and 7 days in the corticosteroid groups.

Table 5. Adverse Events in 299 Patients With Septic Shock*

Event	No. (%) Placebo (n = 149)	No. (%) Steroids (n = 150)
Possibly related to steroids	33 (22)	32 (21)
Superinfection	27 (18)	22 (15)
Catheter-related infection	10 (7)	12 (8)
Nosocomial pneumonia	11 (7)	9 (6)
Urinary tract infection	3 (2)	1 (1)
Surgical wound infection	7 (5)	0 (0)†
Other infection	2 (1)	2 (1)
Gastrointestinal bleeding	8 (5)	11 (7)
Psychiatric disorders	1 (1)	0 (0)
Possibly related to vasopressors	3 (2)	5 (3)
Arrhythmia	1 (1)	4 (3)
Myocardial infarction	1 (1)	0 (0)
Limb or cerebral ischemia	1 (1)	1 (1)
Related to ICU invasive procedures	6 (4)	3 (2)
Others	3 (2)	4 (3)

*ICU indicates intensive care unit.
†P = .007 for comparison with the placebo group using the Fisher exact test.

travenous bolus every 6 hours) and fludrocortisone (50 µg tablet once daily) significantly reduced 28-day mortality and duration of vasopressor administration in all patients with septic shock, in particular those with relative adrenal insufficiency. In addition, among the latter, corticosteroid therapy significantly reduced mortality during both ICU and hospital stays, and tended to reduce 1-year mortality. Our results indicate that, in this population, 1 additional life could be saved at day 28 for every 7 patients treated with corticosteroids. Replacement therapy had no significant effect on the same variables in patients who had septic shock without relative adrenal insufficiency. If the power to detect differences in responders was lower than that in nonresponders due to the lower proportion of responders, it should be observed that no tendency toward efficacy (or deleterious effect) was observed in responders for any of the above mentioned variables. These results confirm the hypothesis on which the study was planned that patients with septic shock with relative adrenal insufficiency could benefit from replacement therapy.

Our results are consistent with a study of healthy volunteers challenged with endotoxin[27] and with 2 studies of patients with septic shock,[12,13] that showed that low doses of hydrocortisone can restore vascular responsiveness to catecholamines. Our results are also consistent with those of 2 small trials showing that replacement therapy with hydrocortisone reduces the time-to-vasopressor-therapy withdrawal in septic shock.[14,15] Finally, our study establishes that a short corticotropin test performed at early onset of septic shock is useful for identifying patients that could most benefit from replacement therapy with corticosteroids. However, it has to be stressed that the time required to obtain the results largely depends on the method used to measure cortisol (eg, enzymatic method, radioimmunoassay) and therefore that treatment should be started as soon as the test has been completed.

The sample size was calculated to detect a difference of 20% between the 2 groups of nonresponders on the 28-day mortality rate using a 1-sided formulation. Such a formulation was chosen because the preliminary reports that were available at the planning phase of the study[22,23] had shown that for several days patients tolerated well 200 to 300 mg of hydrocortisone daily, and we had no interest in formally demonstrating a hypothetical deleterious effect of corticosteroids. However, as recommended by the 9th International Conference on Harmonization, at the time of analysis, all tests were performed using a 2-sided formulation and all reported P values were 2-sided. The sample size was also computed based on the assumptions of a mortality rate of 95% in the nonresponder placebo subgroup and a frequency of nonresponders of 40% in the population of patients with septic shock. In fact, the mortality rate in the nonresponder placebo subgroup (63%) was much lower than expected compared with the reports that were available at the planning phase of the study[7,22] and with the hypothesis that patients with adrenal insufficiency would very likely die without hormone replacement. Conversely, the proportion of nonresponders (77%) was much higher than expected and the resulting increase in the sample size of nonresponders (from 108 to 229) may have favored the detection of a lower difference (10%) than expected between the 2 groups.

Several differences between the design of this positive study and previous negative studies[28-33] deserve comment. First, our trial was focused on a very specific population who were presumed to benefit from corticosteroids because of relative adrenal insufficiency. Second, low doses of a combination of the natural hormone hydrocortisone and fludrocortisone were used (as recommended to treat adrenal insufficiency)[16] rather than high doses of a synthetic glucocorticoid compound. The addition of fludrocortisone to hydrocortisone was justified because primary adrenal insufficiency could not be ruled out[16] since it has been shown that 40% to 65% of critically ill patients have high-plasma renin activity and low-plasma aldosterone concentrations.[34,35] Moreover, in situations that require high amounts of active glucocorticoid, the reduction of fludrocortisone to cortisol can serve as a second source of cortisol in addition to that of adrenal glands.[36] Third, patients were treated for a longer time (ie, 7 days) than those treated in previous trials. Indeed, recent work in healthy volunteers challenged with endotoxin[37] and in patients with septic shock[23,38] have shown that short courses of corticosteroid treatment may be followed by a rebound of the systemic inflammatory response.

In conclusion, in catecholamine-dependent septic shock patients, particularly those with relative adrenal insufficiency, a 7-day treatment with the combination of hydrocortisone and fludrocortisone is safe and associated with a significant reduction in short-term and long-term mortality. In practice, we suggest that all patients with catecholamine-dependent septic shock should be given the combination of hy-

drocortisone and fludrocortisone as soon as a short corticotropin stimulation test is performed. When the results of the test are available, treatment may be withdrawn in responders and continued up to 7 days in nonresponders. Further studies are required to better determine the optimal dose and duration of corticosteroids to be given in this setting. The interest of a replacement therapy with corticosteroids in patients with septic shock without relative adrenal insufficiency deserves additional investigation.

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Analysis and interpretation of data: Annane, Sébille, Bollaert, Bellissant
Drafting of the manuscript: Annane, Sébille, Bellissant.
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Statistical expertise: Annane, Sébille, Bellissant.
Obtained funding: Annane, Bollaert, François, Trocheé, Chaumet-Riffaut, Bellissant.
Administrative, technical, or material support: Annane, Chaumet-Riffaut.
Study supervision: Annane, Bellissant.
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Previous Presentations: Portions of this study were presented at the Society Critical Care Medicine Annual Meeting, San Francisco, Calif, February 10-14, 2001. The abstract of our presentation was published in *Crit Care Med*. 2000;28(suppl 12):A46.
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cian shortage over the next several decades will strain community hospitals' workforces. Rather than try to increase graduate medical education funding to large training programs, perhaps ways to create and expand community hospital training programs should be explored.

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1. Werner RM, Goldman LE, Dudley RA. Comparison of change in quality of care between safety-net and non–safety-net hospitals. *JAMA*. 2008;299(18):2180-2187.
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In Reply: Mr Aviles and Ms O'Connell take exception with our finding that hospitals with a higher percentage of Medicaid patients have lower baseline performance on average than other hospitals. We do not suggest that *all* safety-net hospitals have low performance, but that *on average* baseline hospital performance is lower if the percentage of patients insured by Medicaid is higher. This finding is consistent with numerous other studies that have found that a hospital's payer mix, its ownership (ie, public hospitals), and the race and socioeconomic status of its patients influence hospital performance[1-3] and suggests that safety-net hospitals face barriers to performing well on these measures.

We agree with O'Connell that safety-net hospitals are a heterogeneous group. For this reason, we did not categorize hospitals as safety-net or non–safety-net hospitals, as O'Connell suggests. Rather, we document a continuous relationship between the percentage of patients insured by Medicaid at a hospital and that hospital's baseline performance as well as improvement in performance over time. While Aviles and O'Connell cite specific safety-net hospitals and voluntary groups of safety-net hospitals (such as NAPH) that provide higher than average performance relative to other hospitals, these cited hospitals are not representative of all safety-net hospitals. However, as examples of superior performance and transparency, they are indeed laudable. We hope our observation that safety-net hospitals have lower baseline performance on average and smaller improvements in performance over time will lead to a discussion about how to structure public reporting and pay for performance so that *all* safety-net hospitals benefit.

In response to Dr Williams, numerous studies have found that care for minority patients[2,4] and poor patients[5] is concentrated in a small number of hospitals. The issue is not the absolute number of patients, but rather the quality of care at hospitals that see a disproportionate share of poor and underserved patients. This quality is often lower on average, potentially driving a large portion of documented health care disparities. In our article, Table 1 indicates that while only 3% of hospitals with a low percentage of Medicaid patients are teaching hospitals, this number increases to 12% among hospitals with a high percentage of Medicaid patients. While only 12% of teaching *hospitals* are in the high Medicaid group, because they are larger than average, these hospitals care for an even higher percentage of *patients* with Medicaid. Thus, we stand by our statement that safety-net hospitals are more likely to be larger, governmentally owned, and/or major teaching institutions. Nonetheless, there is little doubt that safety-net hospitals are varied in size, ownership, and teaching status, as Table 1 shows.

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CORRECTIONS

Incorrect Numbers in Text: In the Original Contribution entitled "Lead, Mercury, and Arsenic in US- and Indian-Manufactured Ayurvedic Medicines Sold via the Internet" published in the August 27, 2008, issue of *JAMA* (2008;300[8]:915-923), 2 numerical errors were published. On page 916 at the bottom of the first column, the power statement should have read that " . . . this sample size provided 90% power to demonstrate a 15% difference in metal prevalence ($\alpha = .05$)." On page 918 at the top of the second column, the tolerable weekly intake for mercury should have read "5 μg/kg of mercury." These errors do not affect the findings or conclusions of the article.

Incorrect City Name: In Appendix I, Table 1 of the Medical Education issues from 2007 (2007;298[9]:1071) and 2008 (2008;300[10]:1221), the location for University of Connecticut School of Medicine should be listed as Farmington.

Author Name Misspelled: In the Caring for the Critically Ill Patient article entitled "Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock" (2002;288[7]:862-871), an author's name was misspelled. The second-to-last name in the byline should be Philippe Chaumet-Riffaud.