Corticosteroid Treatment and Intensive Insulin Therapy for Septic Shock in Adults
A Randomized Controlled Trial

The COIITSS Study Investigators*

Septic shock is a major complication of infectious diseases with a mortality rate of 60% within a short period. The characterization of the cross talk between the immune, coagulation, and neuroendocrine systems has been an important step in understanding the molecular and cellular basis of sepsis. In particular, disruption of the hypothalamic-pituitary-adrenal axis is considered a key factor of progression from septic shock. In addition, the benefit of adding fludrocortisone in this setting is unclear.

Objectives To test the efficacy of intensive insulin therapy in patients whose septic shock was treated with hydrocortisone and to assess, as a secondary objective, the benefit of fludrocortisone.

Design, Setting, and Patients A multicenter, 2 × 2 factorial, randomized trial, involving 509 adults with septic shock who presented with multiple organ dysfunction, as defined by a Sequential Organ Failure Assessment score of 8 or more, and who had received hydrocortisone treatment was conducted from January 2006 to January 2009 in 11 intensive care units in France.

Interventions Patients were randomly assigned to 1 of 4 groups: continuous intravenous insulin infusion with hydrocortisone alone, continuous intravenous insulin infusion with hydrocortisone plus fludrocortisone, conventional insulin therapy with hydrocortisone alone, or conventional insulin therapy with intravenous hydrocortisone plus fludrocortisone. Hydrocortisone was administered in a 50-mg bolus every 6 hours, and fludrocortisone was administered orally in 50-µg tablets once a day, each for 7 days.

Main Outcome Measure In-hospital mortality.

Results Of the 255 patients treated with intensive insulin, 117 (45.9%), and 109 of 254 (42.9%) treated with conventional insulin therapy died (relative risk [RR], 1.07; 95% confidence interval [CI], 0.88-1.30; P = .50). Patients treated with intensive insulin experienced significantly more episodes of severe hypoglycemia (<40 mg/dL) than those in the conventional-treatment group, with a difference in mean number of episodes per patient of 0.15 (95% CI, 0.02-0.28; P = .003). At hospital discharge, 105 of 245 patients treated with fludrocortisone (42.9%) died and 121 of 264 (45.8%) in the control group died (RR, 0.94; 95% CI, 0.77-1.14; P = .50).

Conclusions Compared with conventional insulin therapy, intensive insulin therapy did not improve in-hospital mortality among patients who were treated with hydrocortisone for septic shock. The addition of oral fludrocortisone did not result in a statistically significant improvement in in-hospital mortality.

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For editorial comment see p 365.
mg/dL (to convert to millimoles per liter, multiply by 0.0555). These levels have clearly been associated with marked increase in the risk of dying.

Thus, we hypothesized that normalization of blood glucose levels with intensive insulin treatment may improve the outcome of adults with septic shock who are treated with hydrocortisone. We examined, as a secondary objective, the benefit of adding fludrocortisone to hydrocortisone therapy.

METHODS

Study Design

The Corticosteroids and Intensive Insulin Therapy for Septic Shock (COHITSS) trial was a multicenter, randomized, 2 × 2 factorial, open-label trial comparing intensive insulin therapy with conventional blood glucose control among patients with septic shock who were treated with corticosteroids. The secondary objective was to compare hydrocortisone plus fludrocortisone with hydrocortisone alone. We did not expect any interaction between insulin and fludrocortisone. The study protocol was approved by the Comité de Protection des Personnes de Saint Germain en Laye on May 24, 2005. Written informed consent was obtained from the patients or their next of kin.

Study Population

All adults admitted to 1 of the 11 participating intensive care units in France (eTable, available at http://www.jama.com) were recruited if they or their next of kin gave consent and they had (1) criteria for severe sepsis as defined by the American College of Chest Physicians/Society of Critical Care Medicine, (2) multiple organ dysfunction as defined by a Sequential Organ Failure Assessment (SOFA) score of 8 or more, (3) need for vasopressor therapy (any dose of dopamine, adrenaline, noradrenaline, or any other vasoconstrictor agent) to maintain systolic blood pressure higher than 90 mm Hg or mean blood pressure higher than 60 mm Hg, and (4) were receiving 50 mg of hydrocortisone intravenously every 6 hours as an adjunct therapy for septic shock. We excluded pregnant women and moribund patients (those expected to die within the day of their ICU admission).

Randomization

Randomization was centralized through a secured Web site and stratified according to center, using permutation blocks, the size of which was not available to clinicians. Each patient was randomly allocated to receive 1 of the 4 following treatment combinations: intensive insulin treatment and hydrocortisone, intensive insulin treatment and hydrocortisone plus fludrocortisone, conventional glucose control and hydrocortisone, and conventional glucose control and hydrocortisone plus fludrocortisone.

Study Treatments

The treatment by hydrocortisone was standardized across the centers. Hydrocortisone was prepared in vials containing 100 mg of hydrocortisone hemisuccinate powder with ampules containing 2 mL of sterile water diluent. All patients received a 50-mg intravenous bolus of hydrocortisone every 6 hours for 7 days.

In the experimental group, the insulin (human recombinant insulin, vials of 10 mL containing 100 U/mL) titration was to follow strictly the recommendations adapted from the original study by Van den Berghe et al. The protocol is detailed in the eSupport (available at http://www.jama.com). Blood samples for glucose measurement were obtained by means of arterial catheters. Blood glucose levels were measured on arterial samples with the use of arterial blood gas analyzers or laboratory analyzers routinely used at the participating centers.

Treatment dose and route of administration—either intravenous or subcutaneous—to the patients in the control group were left to the discretion of the patient’s physician, but physicians were advised not to follow the strict control of blood glucose levels as described above. In fact, it was strongly recommended that physicians follow the 2004 Surviving Sepsis Campaign guidelines.

9-α-Fludrocortisone was prepared as 50-μg tablets. Those in the experimental group received 1 tablet via nasogas-
Data Collection at Baseline

We systematically recorded at baseline demographic and anthropometric data; time of hospital and ICU admission; patient’s location prior to ICU admission (community, hospital, long-term care facility); comorbid conditions as categorized by the Acute Physiology and Chronic Health Evaluation (APACHE)16 disability scale and McCabe class17; severity of illness as assessed by vital signs, the Simplified Acute Physiology Score (SAPS) II,18 and the SOFA score; type and dose of any antibiotics given to the patient the week preceding inclusion into the study; type and dose of vasopressors and inotropic drugs; need for renal replacement therapy; time from shock onset; time from initiation of corticosteroid therapy; and use of adjunctive treatments such as activated protein C. The following laboratory variables were also systematically recorded: arterial blood glucose and lactate levels, Gram examination and cultures of samples collected from any suspected site of infection, and total cortisol levels before and 60 min-

Table 1. Baseline Characteristics of Randomized Groups

<table>
<thead>
<tr>
<th></th>
<th>Intensive Insulin Therapy (n = 255)</th>
<th>Conventional Glucose Control (n = 254)</th>
<th>Hydrocortisone + Fludrocortisone (n = 245)</th>
<th>Hydrocortisone Alone (n = 264)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (95% CI), y</td>
<td>63.7 (61.9-65.4)</td>
<td>64.3 (62.4-66.1)</td>
<td>64.0 (62.2-65.8)</td>
<td>63.9 (62.1-65.7)</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>170 (66.7)</td>
<td>160 (63.0)</td>
<td>167 (68.2)</td>
<td>163 (61.7)</td>
</tr>
<tr>
<td>Admission days, median (IQR)</td>
<td>170 (0-1)</td>
<td>160 (0-2)</td>
<td>167 (0-1)</td>
<td>163 (0-1)</td>
</tr>
<tr>
<td>In hospital before ICU admission</td>
<td>0 (0-1)</td>
<td>0 (0-2)</td>
<td>0 (0-1)</td>
<td>0 (0-2)</td>
</tr>
<tr>
<td>Physiole score, mean (95% CI)</td>
<td>58.9 (56.9-60.9)</td>
<td>60.4 (58.2-62.6)</td>
<td>58.9 (56.7-61.0)</td>
<td>60.4 (58.3-62.5)</td>
</tr>
<tr>
<td>SAPS II</td>
<td>10.4 (10.0-10.8)</td>
<td>10.8 (10.3-11.2)</td>
<td>10.6 (10.2-11.1)</td>
<td>10.1 (10.1-11.0)</td>
</tr>
<tr>
<td>Type of patients, No. %</td>
<td>218</td>
<td>220</td>
<td>207</td>
<td>231</td>
</tr>
<tr>
<td>Medical</td>
<td>193 (85.5)</td>
<td>189 (85.9)</td>
<td>186 (89.9)</td>
<td>196 (84.9)</td>
</tr>
<tr>
<td>Unscheduled surgery</td>
<td>22 (10.1)</td>
<td>26 (11.8)</td>
<td>17 (8.2)</td>
<td>31 (13.4)</td>
</tr>
<tr>
<td>Scheduled surgery</td>
<td>3 (1.4)</td>
<td>5 (2.3)</td>
<td>4 (1.9)</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Type of infection, No./total (%)</td>
<td>134/246 (54.5)</td>
<td>115/247 (46.6)</td>
<td>120/234 (51.3)</td>
<td>129/259 (49.8)</td>
</tr>
<tr>
<td>Community acquired</td>
<td>112/246 (45.5)</td>
<td>132/247 (53.4)</td>
<td>114/234 (48.7)</td>
<td>130/259 (50.2)</td>
</tr>
<tr>
<td>Infected patient, No.</td>
<td>245</td>
<td>246</td>
<td>233</td>
<td>258</td>
</tr>
<tr>
<td>Infection per patient, mean (95% CI)</td>
<td>1.5 (1.4-1.8)</td>
<td>1.6 (1.5-1.8)</td>
<td>1.6 (1.4-1.7)</td>
<td>1.5 (1.4-1.7)</td>
</tr>
<tr>
<td>Sites of infection, No.</td>
<td>173</td>
<td>180</td>
<td>168</td>
<td>185</td>
</tr>
<tr>
<td>Pathogens</td>
<td>Gram negative</td>
<td>107</td>
<td>97</td>
<td>96</td>
</tr>
<tr>
<td>Blood glucose levels, mean (95% CI), mg/dL, No. of patients</td>
<td>12.0 (11.0-13.0)</td>
<td>11.3 (10.7-11.9)</td>
<td>11.8 (11.0-12.6)</td>
<td>11.5 (10.7-12.4)</td>
</tr>
<tr>
<td>Lactate levels, mean (95% CI), mg/dL</td>
<td>44.2 (33.3-55.0) [248]</td>
<td>35.1 (30.6-38.7) [244]</td>
<td>36.7 (27.0-45.1) [236]</td>
<td>42.1 (36.0-54.1) [256]</td>
</tr>
<tr>
<td>Cortisol levels, mean (SD), µg/dL, No. of patients</td>
<td>39.8 (34.0-45.7) [227]</td>
<td>36.7 (35.6-43.8) [230]</td>
<td>41.1 (34.9-47.4) [215]</td>
<td>38.5 (34.7-42.4) [242]</td>
</tr>
<tr>
<td>Peak</td>
<td>50.7 (45.0-56.3) [223]</td>
<td>50.1 (45.1-55.1) [225]</td>
<td>50.1 (45.8-55.4) [211]</td>
<td>50.7 (46.3-58.0) [33]</td>
</tr>
<tr>
<td>Nonresponders, No. (%)</td>
<td>173</td>
<td>169</td>
<td>167</td>
<td>175</td>
</tr>
<tr>
<td>Mechanical ventilation, No.</td>
<td>218 (85.5)</td>
<td>220 (86.6)</td>
<td>213 (86.9)</td>
<td>225 (85.2)</td>
</tr>
<tr>
<td>Renal replacement therapy, No.</td>
<td>46 (18.7) [246]</td>
<td>53 (21.5) [246]</td>
<td>41 (17.2)</td>
<td>58 (22.9)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; SAPS, Simplified Acute Physiology Score; St conversion factors: To convert blood glucose levels from mg/dL to mmol/L, multiply by 0.0555; cortisol levels from µg/dL to nmol/L, multiply by 27.588; lactate levels from mg/dL to mmol/L, multiply by 0.111. Each statistic was computed on the nonmissing value, ie, the whole sample unless specifically indicated.
and to Conventional Glucose Control

Glucose According to Intensive Insulin Therapy

term health status included the Impact
90 and 180. Assessment of patients' long-
tus were obtained at discharge from the
was sedated, the score was assessed at
7, 14, 21, 28, or up to ICU discharge (de-
was recorded at study entry and at days
8 AM for 3 patients receiving intensive insulin and for

tivation−free days; time to reach a
SOFa score of less than 8; ICU and hos-
length of stay; and serious adverse
vents, including any episode in
which arterial blood glucose levels de-
creased to less than 40 mg/dL; super-
infection; presence of muscle weak-
ness at ICU discharge or at the 90- or
180-day follow-up; or the presence
posttraumatic stress disorders at the
180-day follow-up.

Outcomes were investigated in the
subgroup of patients who did not re-

Follow-up

Randomized patients were followed up
for 180 days. Data collected during their
ICU stays included vital signs, results
from laboratory tests and cultures of
specimens drawn from any new site of
infection, and any major interventions
that were performed. In addition, muscle
weakness—a muscular disability rating
score (MDRs) of 1 was no deficit; 2, mini-
mal deficit or atrophy; 3, mild to
moderate distal deficit; 4, mild to
moderate proximal deficit; and 5, se-
vere proximal deficit or atrophy19—
was recorded at study entry and at days
7, 14, 21, 28, or up to ICU discharge (de-
pending on which occurred first) and
then at days 90 and 180. If the patient
was sedated, the score was assessed at
least 6 hours after interruption of seda-
tion. Vital status and neurological sta-
tus were obtained at discharge from the
ICU and from the hospital, and at days
90 and 180. Assessment of patients’ long-
term health status included the Impact
of Event Scale20,21 with a score of 30 or
more indicating the presence of post-
traumatic stress disorders;22-24 the Short-
Form General Health Survey,25-27 and the
Hospital Anxiety and Depression scale
in that order. The latter tool includes 2
scales evaluating depression (7 items) and
anxiety (7 items).28-30 Patients scor-
ing 10 or more for each of these scales is
at risk of major psychological dis-

Study Outcomes

The primary outcome measure was in-
hospital mortality (or 90-day mortal-
ity, whichever occurred first).

Secondary outcomes included 28-, 90-, and 180-day mortality rates; num-
ber of vasopressor and mechanical
ventilation−free days; time to reach a
SOFa score of less than 8; ICU and hos-

Statistical Analysis

We estimated 50% in-hospital mortal-
ity among patients with septic shock who
became dependent on vasopressor and
were treated with hydrocortisone.1 Using
a bilateral formulation, we calculated that
254 patients per group were needed to
detect an absolute reduction of 12.5% of
in-hospital mortality (α = .05 and study
power at 80%) with intensive insulin
therapy, corresponding to 25% relative
risk (RR) reduction, ie, less than the 32%
RR reduction suggested by the trial of
Van den Berghe et al.8 The comparison
of hydrocortisone to hydrocortisone plus
fludrocortisone was a secondary objec-
tive and was not taken into account in
the sample-size computation.

The statistical analysis involved only
1 statistical analysis, an intent-to-treat
analysis, performed by an independent
statistician after all patients had com-
pleted the study follow-up sessions. Ac-
tive tracing of patients was performed
using hospital administrative data, which
prevented patients from being lost to
follow-up. Categorical variables were
compared by Fisher exact tests and con-
tinuous variables by nonparametric
Kruskal-Wallis tests or regression mixed-
effects models whenever appropriate.
The cumulative incidence of in-
hospital death was compared using the
Gray test,31 and adjusted comparison
using predictors identified among base-
line characteristics was performed by
the Fine and Gray regression model.32 Over-
all survival was estimated using the
Kaplan-Meier method, and benefit of
each randomization was estimated by
using Cox models stratified on the other
randomization group. Interaction be-
 tween both randomizations and be-
tween-treatments effect and response to
corticotrophin tests were assessed using
the Gail and Simon33 heterogeneity test.
Assumption of proportionality for the
Cox model was checked.34 Finally, to as-
 sess the difference in the control of blood
glucose across randomized groups, we
fitted a linear mixed-effects model.15 This
allowed modeling observational hetero-
genrety incurred by repeated measure-
ments of glucose levels and insulin doses
over time in the same patient and ac-
counted for the fixed and random na-
ture of the study factors.

All tests were 2-sided. A P value
of .05 was considered statistically signifi-
cant. The only comparisons that were
performed are those reported in the ar-
ticle. All were prefixed and scheduled
in the protocol, and none of them were
performed post hoc. All statistical analy-
ses were performed using the SAS 9.1
(SAS Institute Inc, Cary, North Caro-
lina) and R (http://www.R-project.
org) software packages.

RESULTS

From January 2006 to January 2009, 946
patients were assessed for eligibility, and
509 were included (FIGURE I). The treat-
ment groups were well balanced at base-
line (TABLE I). None of the patients re-
ceived etomidate. There was no missing
data on the primary outcome variable.
Twenty-five patients (4.9%) were lost to follow-up after hospital discharge.

**Glucose Control Trial**

Patients in the intensive insulin therapy group had markedly lower blood glucose from the first day through their last day in the ICU than those in the control group ($P<10^{-5}$; **Figure 2**). The median dose of insulin in the experimental group was 71 UI (IQR, 43–96) per day vs 46 UI (IQR, 30–65) in the control group ($P<.001$). The time spent with glucose levels in the range of 80 to 110 mg/dL was significantly greater in the intensive insulin therapy group than in the control group ($P<10^{-5}$).

At hospital discharge, 117 of 255 patients (45.9%) in the experimental group died (95% confidence interval [CI], 39.9%–52.0%) and 109 of 254 patients (42.9%) in the control group died (95% CI, 37.0%–49.1%; $P=.50$; **Table 2**). The RR of dying while in the hospital was 1.07 (95% CI, 0.88–1.30). There was no evidence for interaction with fludrocortisone treatment (RR, 0.89; 95% CI, 0.65–1.21 in the hydrocortisone plus fludrocortisone group; RR, 0.91; 95% CI, 0.66–1.26 in the hydrocortisone group; $P=.31$).

No significant difference existed between treatment groups for any of the secondary outcome measures (**Table 2**). The hazard ratio of death was 1.04 (95% CI, 0.8–1.34; $P=.003$). Patients receiving intensive insulin therapy had markedly lower blood glucose than in the control group ($P<.001$). The median number of days that surviving patients spent in the ICU was 10 for those in the experimental group vs 9 for those in control group ($P=.68$); the median length of stay in the hospital was 24 days for the experimental group vs 22 days for those in the control group ($P=.87$); the median vasopressor-free days for each group was 4 days ($P=.58$); and the median mechanical ventilation-free days was 10 for the experimental group vs 13 days for the control group ($P=.51$; **Table 2**). The cumulative incidence of a SOFA score of less than 8 did not differ between groups (64.3% for the experimental group vs 60.6% for the control group; $P=.38$). The proportion of superinfections ($P=.66$) and the MDRS score ($P=.06$) were also similar between the 2 groups. Forty-two of 255 patients (16.4%) receiving intensive insulin experienced severe hypoglycemic episodes vs 20 of 254 (7.8%) in the control group ($P=.003$). Patients receiving intensive insulin has a mean (SD) number of hypoglycemic episodes of 0.29

### Table 2. Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Variables</th>
<th>Intensive Insulin Therapy (n = 255)</th>
<th>Conventional Glucose Control (n = 254)</th>
<th>Hydrocortisone + Fludrocortisone (n = 245)</th>
<th>Hydrocortisone Alone (n = 264)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital death, No./total (%)</td>
<td>117/255 (45.8)</td>
<td>109/254 (42.9)</td>
<td>106/249 (42.9)</td>
<td>121/264 (45.8)</td>
<td>.50</td>
</tr>
<tr>
<td>Overall survival, Deaths, No. (%)</td>
<td>122 (47.9)</td>
<td>118 (46.5)</td>
<td>118 (45.7)</td>
<td>128 (48.5)</td>
<td>.67</td>
</tr>
<tr>
<td>Kaplan-Meier estimate of survival rates, HR (95% CI), d</td>
<td>1.04 (0.80–1.34)</td>
<td>1 (Reference)</td>
<td>0.94 (0.73–1.21)</td>
<td>1 (Reference)</td>
<td>.61</td>
</tr>
<tr>
<td>28</td>
<td>62.2 (56.4–68.5)</td>
<td>61.1 (55.3–67.5)</td>
<td>62.5 (56.6–68.9)</td>
<td>60.9 (55.2–67.1)</td>
<td>.004b</td>
</tr>
<tr>
<td>90</td>
<td>51.8 (45.9–58.4)</td>
<td>54.8 (48.9–61.4)</td>
<td>54.2 (48.2–61.0)</td>
<td>52.4 (46.6–68.9)</td>
<td>.005b</td>
</tr>
<tr>
<td>180</td>
<td>50.9 (45.0–57.6)</td>
<td>52.1 (46.2–58.8)</td>
<td>52.9 (49.9–59.7)</td>
<td>50.2 (44.4–56.6)</td>
<td>.67b</td>
</tr>
<tr>
<td>No. of patients who died</td>
<td>103</td>
<td>82</td>
<td>105</td>
<td>121</td>
<td>.74b</td>
</tr>
<tr>
<td>Causes of death, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple organ failure</td>
<td>92 (78.6)</td>
<td>66 (60.6)</td>
<td>75 (71.4)</td>
<td>83 (82.6)</td>
<td>.67b</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>9 (8.7)</td>
<td>7 (6.5)</td>
<td>7 (6.7)</td>
<td>9 (7.4)</td>
<td>.74b</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (1.0)</td>
<td>2 (2.4)</td>
<td>3 (2.9)</td>
<td>0</td>
<td>.004b</td>
</tr>
<tr>
<td>Brain hemorrhage</td>
<td>0</td>
<td>2 (2.4)</td>
<td>0</td>
<td>1 (2.7)</td>
<td>.005b</td>
</tr>
<tr>
<td>Refractory hypoxia</td>
<td>1 (1.0)</td>
<td>2 (2.4)</td>
<td>2 (1.9)</td>
<td>1 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>3 (3.7)</td>
<td>3 (2.9)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No. of days, median (IQR) Vasopressor-free within the first 7 days</td>
<td>4 (1–6)</td>
<td>4 (2–5)</td>
<td>0.58</td>
<td>0.60</td>
<td>4 (2–5)</td>
</tr>
<tr>
<td>Mechanical ventilation-free within 28 days</td>
<td>10 (2–22)</td>
<td>13 (2–23)</td>
<td>51 (20–23)</td>
<td>12 (2–23)</td>
<td>.50</td>
</tr>
<tr>
<td>Cumulative incidence of SOFA &lt;8 at day 7 (95% CI)</td>
<td>64.3 (58.6–70.1)</td>
<td>60.6 (54.7–66.6)</td>
<td>63.3 (57.3–69.2)</td>
<td>61.7 (56.0–67.5)</td>
<td>.75</td>
</tr>
<tr>
<td>Length of stay, median (IQR), d ICU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>9 (4–19)</td>
<td>9 (4–15)</td>
<td>7.0 (4–14)</td>
<td>9 (4–17.5)</td>
<td>.86</td>
</tr>
<tr>
<td>Survivors</td>
<td>10 (6–19)</td>
<td>9 (5–15)</td>
<td>9 (4–16)</td>
<td>9 (5–17)</td>
<td>.52</td>
</tr>
<tr>
<td>Hospital</td>
<td>16 (5–34)</td>
<td>15 (7–30)</td>
<td>8.7 (4–14)</td>
<td>14 (6–25)</td>
<td>.95</td>
</tr>
<tr>
<td>All patients</td>
<td>24 (12–43)</td>
<td>22 (11–39)</td>
<td>8.7 (5–13)</td>
<td>19 (5–40)</td>
<td>.09</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment

*Adjusted on baseline prognostic variables, namely age, time in hospital prior to ICU admission, time in ICU prior to randomization, Simplified Acute Physiology Score II, SOFA score, lactate level and mechanical ventilation, and a random center effect.

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(0.90) vs 0.14 (0.58) for those in the control group ($P = .003$; Table 3). Patients who had hypoglycemia died at a similar rate: 45.2% receiving intensive insulin vs 50% receiving conventional glucose treatment.

### Fludrocortisone Trial

At hospital discharge, 105 of 245 patients (42.9%) died in the fludrocortisone-treated group and 121 of 264 patients (45.8%) in the control group ($P = .50$). The RR of dying in the hospital was 0.94 (95% CI, 0.77-1.14). No significant difference in overall mortality existed between the fludrocortisone-treated patients and the controls (hazard ratio, 0.94; 95% CI, 0.73-1.21; Table 2 and eFigure, available at http://www.jama.com). In the subgroup of nonresponders, no significant difference in mortality existed between treatment groups.

Nor did significant differences exist between the 2 groups for the survivors’ ICU ($P = .52$) and hospital ($P = .052$) lengths of stay, for the number of vasoressor-free days ($P = .62$), and for mechanical ventilation-free days ($P = .50$; Table 2). The cumulative incidence of a SOFA score less than 8 was not different between the treatment groups ($P = .75$). However, significantly more patients experienced superinfection in the fludrocortisone group than in the control group ($P = .02$). Patients receiving fludrocortisone experienced more urinary tract superinfection than the control group; however, the rate of lung, abdominal, or blood stream superinfection was much the same between the groups (Table 3). The proportion of deaths among patients with superinfection was also comparable (Table 3). Similarly, the MDRS scores were much the same at day 28 ($P = .10$; Table 3).

### COMMENT

The current study showed no evidence to support a strategy of intensive insulin therapy aimed at maintaining blood glucose levels in the range of 80 to 110 mg/dL for treating septic shock with corticosteroids. Furthermore, no evidence supports the routine use of oral fludrocortisone.

This study enrolled patients with septic shock who were treated with low-dose corticosteroids, in accordance with the 2004 Surviving Sepsis Campaign guidelines. Of note, patients’ severity of illness, as assessed by SAPS II scores and crude mortality rate, was very similar to those of patients enrolled in the Ger-Inf-05 trial and greater than patients in the Corticosteroid Therapy of Septic Shock (CORTICUS) study. These findings suggest that in participating hospitals, physicians treated the sickest patients with corticosteroids in anticipa-

### Table 3. Serious Adverse Events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intensive Insulin Therapy (n = 255)</th>
<th>Conventional Glucose Control (n = 254)</th>
<th>P Value</th>
<th>Hydrocortisone + Fludrocortisone (n = 245)</th>
<th>Hydrocortisone Alone (n = 264)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superinfection, No. of patients/episodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Total</td>
<td>47/106</td>
<td>43/132</td>
<td>.66</td>
<td>53/144</td>
<td>37/94</td>
<td>.02</td>
</tr>
<tr>
<td>Lung</td>
<td>35/99</td>
<td>29/94</td>
<td>.43</td>
<td>36/82</td>
<td>28/71</td>
<td>.18</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>4/10</td>
<td>1/1</td>
<td>.37</td>
<td>4/10</td>
<td>1/1</td>
<td>.20</td>
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<tr>
<td>Urinary tract</td>
<td>7/8</td>
<td>13/16</td>
<td>.18</td>
<td>15/17</td>
<td>5/7</td>
<td>.02</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>0/0</td>
<td>1/1</td>
<td>.50</td>
<td>1/1</td>
<td>0/0</td>
<td>.48</td>
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<tr>
<td>Blood</td>
<td>9/10</td>
<td>4/5</td>
<td>.26</td>
<td>8/9</td>
<td>5/6</td>
<td>.40</td>
</tr>
<tr>
<td>Others</td>
<td>14/19</td>
<td>8/15</td>
<td>.28</td>
<td>15/25</td>
<td>7/9</td>
<td>.08</td>
</tr>
<tr>
<td>In-hospital death among patients with superinfection, No./total (%)</td>
<td>26/47 (55.3)</td>
<td>21/43 (48.8)</td>
<td>.67</td>
<td>27/33 (50.9)</td>
<td>20/37 (51.4)</td>
<td>.80</td>
</tr>
<tr>
<td>Hypoglycemia, glucose $&lt;40$ mg/dL, No. of measures per patient, median (IQR)</td>
<td>72 (43-110)</td>
<td>44 (32-56)</td>
<td>&lt;.001</td>
<td>51 (31-79)</td>
<td>53 (38-81)</td>
<td>.36</td>
</tr>
<tr>
<td>No. of patients/episodes</td>
<td>42/72</td>
<td>20/44</td>
<td>.003</td>
<td>32/51</td>
<td>30/53</td>
<td>.59</td>
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<tr>
<td>No. of episodes</td>
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<td>.002</td>
<td></td>
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<td>.54</td>
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<td>1</td>
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<tr>
<td>Episodes, mean (SD)</td>
<td>0.289 (0.90)</td>
<td>0.139 (0.58)</td>
<td>.003</td>
<td>0.238 (0.86)</td>
<td>0.198 (0.68)</td>
<td>.63</td>
</tr>
<tr>
<td>In-hospital death among patients with hypoglycemia, No./total (%)</td>
<td>19/42 (45.2)</td>
<td>10/20 (50.0)</td>
<td>.79</td>
<td>14/32 (43.8)</td>
<td>15/30 (50.0)</td>
<td>.80</td>
</tr>
<tr>
<td>MDRS day 28</td>
<td></td>
<td></td>
<td>.06</td>
<td></td>
<td></td>
<td>.10</td>
</tr>
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<td>9</td>
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<td>4</td>
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</tbody>
</table>

Abbreviations: IQR, interquartile range; MDRS, muscular disability rating score.

SI conversion factor: To convert blood glucose levels from mg/dL to mmol/L, multiply by 0.0555.
tion of the updated Surviving Sepsis Campaign recommendations. The observed mortality was concordant with the benefit from corticosteroids reported in the Ger-Inf-05 trial. Otherwise, the study population mimicked common characteristics of septic shock. The study was powered to detect a 12.5% absolute risk reduction of mortality with tight glucose control, corresponding to a 25% RR reduction. This estimate was based on the best evidence available at the time the study was designed. Indeed, the trial by Van den Bergh et al suggested an RR reduction of 32%. In addition, most of the recent large clinical trials in septic shock, including the Vasopressin and Septic Shock (VASST), CORTICUS, and Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trials were designed to detect a very similar absolute difference in mortality.

As expected, hydrocortisone at a dose of 50 mg every 6 hours was associated with higher basal blood glucose levels than in the VISEP or the Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trials and more in the range of levels reported in the trial by Van den Bergh and colleagues. In the current study, blood glucose levels decreased in both treatment groups on the first day of randomization. We aimed at comparing tight glucose control to usual care rather than comparing 2 different strategies of blood glucose control. Usual care should follow the 2004 Surviving Sepsis Campaign guidelines.

Then, in the experimental group, blood glucose levels decreased markedly compared with the conventional-treatment group, in which levels were maintained at approximately 150 mg/dL in accordance with recommendations. The median doses of insulin in both groups were very similar to those observed in the Van den Bergh trial, thus, suggesting that the investigators involved in our trial likely followed the glucose control algorithm. The NICE-SUGAR trial suggested that patients who were receiving corticosteroids might benefit from tight glucose control.

In contrast, in corticosteroid-treated septic shock, this study found no evidence that intensive insulin therapy to achieve normoglycemia was superior to insulin therapy in maintaining blood glucose levels at 150 mg/dL or less. Of note, compared with the conventional-treated group in this study, during the first week after randomization in the Ger-Inf-05 study, the mean (SD) blood glucose levels were markedly higher, ranging between 186 (83) and 220 (110) mg/dL. Thus, this study cannot exclude the benefit of some glucose control compared with no control at all in corticosteroid-treated septic shock. As reported in previous studies, the intensive insulin therapy did not prevent major ICU-acquired complications such as superinfection or muscle weakness.

The use of fludrocortisone in addition to hydrocortisone was debated in recent years. On the one hand, a dose of 200 mg per day of hydrocortisone may likely provide enough mineralocorticoid activity. On the other hand, the 11β-hydroxysteroid dehydrogenase type II enzyme that inactivates cortisol to prevent its binding to mineralocorticoid receptors may be up-regulated in sepsis. The use of fludrocortisone was also suggested as a potential explanation for the differences in outcome benefits observed in the Ger-Inf-05 trial and in the CORTICUS trial. In the current study, there was no significant difference in any outcome between patients treated with or without fludrocortisone. The direction of the point estimate may favor the use of fludrocortisone, but the size of the effect was small. Physicians and nurses were not blinded when administering fludrocortisone, and a placebo was not available for technical reasons. In addition, the decision to randomly allocate the patients to fludrocortisone was because the 2004 Surviving Sepsis Campaign left this treatment as optional. Then, we thought that this was the best way to prevent heterogeneous use of fludrocortisone across participating sites. Further trials should be powered to detect a 10% RR reduction in mortality, as observed in the current exploratory trial, or they should investigate the benefits vs the risks of intravenous fludrocortisone.

In conclusion, the current study does not support the hypothesis that intensive insulin therapy to maintain blood glucose levels in the range of 80 to 110 mg/dL reduces the RR of death by 25% in patients whose septic shock is treated with hydrocortisone. The current data do not support the routine use of oral fludrocortisone in addition to hydrocortisone when physicians decide to introduce corticosteroids in the management of a patient with septic shock.

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Study supervision: Annane, Maxime, Azoulay, Wolf, Bollaert.
INTENSIVE INSULIN VS CONVENTIONAL THERAPY FOR SEPTIC SHOCK

Study Organization and Investigators are available at http://www.jama.com.

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Online-Only Material: An eTable, eFigure, and supplementary information is available at http://www.jama.com.

REFERENCES