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

The COIITSS Study Investigators*

S EPTIC SHOCK IS A MAJOR COMPLICATION of infectious diseases with a mortality rate of 60% within a short period.1 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 infection to septic shock.1

Subsequently, the role of corticosteroids in the treatment of septic shock has gained a renewed interest in the past decade. A recent meta-analysis of randomized controlled trials suggested some survival benefit to prolonged low-dose corticosteroid therapy.2 However, the 2 largest trials included in this meta-analysis yielded different treatment effects on mortality in short periods.3,4 The first trial found a 10% absolute reduction in 28-day mortality in patients with septic shock and a cortisol increment after receiving corticotrophin of 9 µg/dL or less,3 whereas the second trial found no evidence of a beneficial treatment effect.4 Because the first trial included the sickest patients, international guidelines suggested that prolonged low-dose corticosteroid therapy should be considered for adults with septic shock who respond poorly to fluids and vasopressors.3

Corticosteroids are associated with hyperglycemia, a complication that may per se affect patient outcomes while they are in the intensive care unit [ICU].6,7 The first large randomized trial assessing intensive insulin therapy8 found a survival benefit of normalization of blood glucose levels in surgical ICU patients that could not be confirmed in subsequent multicenter studies involving patients with severe sepsis8 or in a general ICU population.10 Nevertheless, patients whose septic shock is treated with hydrocortisone commonly have blood glucose levels higher than 180

Context Corticosteroid therapy induces potentially detrimental hyperglycemia in 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 fludrocortisone plus hydrocortisone, 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.

Trial Registration clinicaltrials.gov Identifier: NCT00320099

For editorial comment see p 365.

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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.

## METHODS

### Study Design

The Corticosteroids and Intensive Insulin Therapy for Septic Shock (COIITSS) trial was a multicenter, randomized, $2 \times 2$ factorial, open-label trial comparing intensive insulin therapy with conventional blood glucose control among patients with septic shock who were treated with hydrocortisone. We examined, as a secondary objective, the benefit of adding fludrocortisone to hydrocortisone therapy.

### Study Treatments

The treatment by hydrocortisone was standardized across the centers. Hydrocortisone was prepared as 50-µg tablets. Those in the experimental group received 1 tablet via nasogastric tube every 6 hours for 7 days.

### 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 Population

All adults admitted to 1 of the 11 participating intensive care units in France 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 vasoressor 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).

9-α-Fludrocortisone was prepared as 50-µg tablets. Those in the experimental group received 1 tablet via nasogastric tube every 6 hours.
tric tube every morning at 8 AM for 7 days. Patients in the control group received hydrocortisone therapy alone.

Concomitant therapies should have followed the 2004 Surviving Sepsis Campaign guidelines. Compliance to these guidelines was ensured at each investigators’ meeting.14

**Definitions**

Organ *system failure* was defined for each of the 6 major organ systems as a SOFA score of 3 or 4 points (on a scale of 0-4 for each organ system, for an aggregate score of 0-24, with higher scores indicating more severe organ dysfunction).13 *Reversal of shock* was defined as the maintenance of a systolic blood pressure of at least 90 mm Hg without vasopressor support for at least 24 hours. *Superinfection* was defined as a new infection occurring 48 hours or more after the initiation of a study drug. New sepsis was defined as a new septic episode with microbiologic confirmation. New *septic shock* was defined as a new episode of septic shock after reversal of the initial episode. Nonresponders to a corticotropin test were patients whose cortisol level failed to increase by more than 9 µg/dL.15 (to convert to nanomoles per liter, multiply by 27.88).

**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 inotropics; 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 = 244)</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></td>
<td></td>
<td></td>
<td></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>In ICU before randomization</td>
<td>1 (0-1)</td>
<td>1 (0-1)</td>
<td>1 (0-1)</td>
<td>1 (0-1)</td>
</tr>
<tr>
<td>Physiology scores, mean (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFA</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 (88.5)</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></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community acquired</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>Hospital 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 (1.4-1.6)</td>
<td>1.6 (1.5-1.6)</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></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest</td>
<td>173</td>
<td>180</td>
<td>168</td>
<td>185</td>
</tr>
<tr>
<td>Urogenital</td>
<td>41</td>
<td>35</td>
<td>36</td>
<td>40</td>
</tr>
<tr>
<td>Septicemia</td>
<td>32</td>
<td>36</td>
<td>37</td>
<td>31</td>
</tr>
<tr>
<td>Pathogens</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram negative</td>
<td>107</td>
<td>97</td>
<td>98</td>
<td>106</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 (37.0-45.1) [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 (44.8-55.4) [211]</td>
<td>50.7 (45.3-56.6) [237]</td>
</tr>
<tr>
<td>Nonresponders, No. (%)</td>
<td>173 (67.8)</td>
<td>166 (65.5)</td>
<td>167 (68.2)</td>
<td>175 (66.3)</td>
</tr>
<tr>
<td>Mechanical ventilation, No. (%)</td>
<td>218 (85.8)</td>
<td>220 (86.8)</td>
<td>213 (88.9)</td>
<td>225 (85.2)</td>
</tr>
<tr>
<td>Renal replacement therapy, No. (%)</td>
<td>46 (18.7)</td>
<td>53 (21.5)</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; SD, standard deviation; mg/dL, milligrams per deciliter; mmol/L, millimoles per liter. Use of an additives was not intended to reflect the outpatient setting. Data were not available for patients who died or were discharged on hospital day 0.

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(Reprinted) JAMA, January 27, 2010—Vol 303, No. 4 343
and to Conventional Glucose Control

Glucose According to Intensive Insulin Therapy

of Event Scale20,21 with a score of 30 or

term health status included the Impact

90 and 180. Assessment of patients’ long-
tus were obtained at discharge from the

ation. Vital status and neurological sta-

was sedated, the score was assessed at

pending on which occurred first) and

7, 14, 21, 28, or up to ICU discharge (de-

mg/dL to mmol/L, multiply by 0.0555.

Bars indicate 95% confidence intervals. To convert

2 receiving conventional glucose therapy. The error

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 scoring

10 or more for each of these scales is at risk of major psychological dis-


ture of the study factors.

The statistical analysis involved only

patients were assessed for eligibility, and

From January 2006 to January 2009, 946

patients were assessed for eligibility, and

509 were included (FIGURE 1). The treat-

ment groups were well balanced at base-

line (TABLE 1). None of the patients re-

ceived etomidate. There was no missing

data on the primary outcome variable.

FIGURE 2. Comparison of Mean 8 AM Blood

Glucose According to Intensive Insulin Therapy

and to Conventional Glucose Control

Blood glucose measurements were not available at

8 AM for 3 patients receiving intensive insulin and for

2 receiving conventional glucose therapy. The error

bars indicate 95% confidence intervals. To convert

mg/dL to mmol/L, multiply by 0.0555.

ates after administration of a 250-µg

intravenous bolus of corticotrophin.

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, minimal deficit or atrophy; 3, mild to

moderate distal deficit; 4, mild to moderate proximal deficit; and 5, sev-

ere 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-

tatus were obtained at discharge from the

ICU and from the hospital, and at days

90 and 180. Assessment of patients’ long-
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

Complete 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-

between both randomizations and be-

between-treatments effect and response to
corticortrophin 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.35 This

allowed modeling observational hetero-

geneity 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

.05 was considered statistically signifi-
cant. The only comparisons that were

performed are those reported in the arti-
cle. All were prefixed and scheduled

in the protocol, and none of them were

performed post hoc. All statistical an-

alyses 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 1). The treat-

ment groups were well balanced at base-

line (TABLE 1). None of the patients re-

ceived etomidate. There was no missing

data on the primary outcome variable.

No. of patients

Conventional glucose therapy

252 248 234 219 203 186 174 162

Intensive insulin therapy

252 238 220 205 195 181 166 153

Mean 8 AM Blood Glucose Levels, mg/dL

100

120

140

160

180

0 1 2 3 4 5 6 7

Days

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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 (45.7%) 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; $P = .31$).

<table>
<thead>
<tr>
<th>Causes of death, No. (%)</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>In-hospital death, No./total (%)</td>
<td>117 (45.9)</td>
<td>109 (42.9)</td>
<td>.30</td>
<td>103 (42.9)</td>
<td>121 (45.8)</td>
<td>.50</td>
</tr>
<tr>
<td>Kaplan-Meier estimate of survival rates, HR (95% CI), d</td>
<td>1.04 (0.80-1.34)</td>
<td>1.00 (Reference)</td>
<td>.78</td>
<td>.04 (0.73-1.21)</td>
<td>1.00 (Reference)</td>
<td>.61</td>
</tr>
<tr>
<td>No. of patients who died</td>
<td>103</td>
<td>82</td>
<td>105</td>
<td>121</td>
<td></td>
<td></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>.38</td>
<td>.75</td>
<td>63.3 (57.3-69.2)</td>
<td>61.7 (56.0-67.5)</td>
</tr>
<tr>
<td>Length of stay, median (IQR), d</td>
<td>ICU</td>
<td>All patients</td>
<td>9 (4-19)</td>
<td>9 (4-15)</td>
<td>.70</td>
<td>.09</td>
</tr>
<tr>
<td></td>
<td>Survivors</td>
<td>10 (6-19)</td>
<td>9 (5-15)</td>
<td>.68</td>
<td>.46</td>
<td>10 (6-16)</td>
</tr>
<tr>
<td>Hospital</td>
<td>All patients</td>
<td>16 (5-34)</td>
<td>15 (7-30)</td>
<td>.87</td>
<td>.94</td>
<td>14 (6-25)</td>
</tr>
<tr>
<td></td>
<td>Survivors</td>
<td>24 (12-43)</td>
<td>21 (11-39)</td>
<td>.87</td>
<td>.57</td>
<td>19 (5-40)</td>
</tr>
</tbody>
</table>

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

Adjustment based 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, lactic acid and mechanical ventilation, and a random center effect.

Comparison of multiple organ failure vs other causes.

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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 superinfecion 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).

### Table 3. Serious Adverse Events

<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>Superinfection, No. of patients/episodes</td>
<td>47/106</td>
<td>43/132</td>
<td>.66</td>
<td>53/144</td>
<td>37/94</td>
</tr>
<tr>
<td>Total</td>
<td>35/59</td>
<td>29/94</td>
<td>.37</td>
<td>4/10</td>
<td>1/1</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>7/8</td>
<td>13/16</td>
<td>.18</td>
<td>15/17</td>
<td>5/7</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>
</tr>
<tr>
<td>Blood</td>
<td>9/10</td>
<td>4/5</td>
<td>.26</td>
<td>8/9</td>
<td>5/6</td>
</tr>
<tr>
<td>Others</td>
<td>14/19</td>
<td>18/15</td>
<td>.28</td>
<td>15/25</td>
<td>7/9</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>27/53 (50.9)</td>
<td>20/37</td>
</tr>
<tr>
<td>Hypoglycemia, glucose &lt;40 mg/dL</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>
</tr>
<tr>
<td>No. of measures per patient, median (IQR)</td>
<td>42/72</td>
<td>20/44</td>
<td>.003</td>
<td>32/51</td>
<td>30/53</td>
</tr>
<tr>
<td>No. of episodes</td>
<td>0</td>
<td>211</td>
<td>234</td>
<td>121</td>
<td>192</td>
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<td></td>
<td>1</td>
<td>26</td>
<td>13</td>
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<td></td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>3</td>
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<td>4</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<tr>
<td></td>
<td>&gt;4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<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>
</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>
</tr>
<tr>
<td>MDRS day 28</td>
<td>3</td>
<td>11</td>
<td>.06</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>2</td>
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<td></td>
<td>4</td>
<td>9</td>
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<td>1</td>
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<tr>
<td></td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>6</td>
<td>6</td>
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</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.

**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.14 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 trial3 and greater than patients in the Corticosteroid Therapy of Septic Shock (CORTICUS) study.4 These findings suggest that in participating hospitals, physicians treated the sickest patients with corticosteroids in anticipa-
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 23% RR reduction. This estimate was based on the best evidence available at the time the study was designed. Indeed, the trial by Van den Berghe 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 Berghe 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 Berghe 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 difference 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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Obtained funding: Annane.

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Study supervision: Annane, Maxime, Azoulay, Wolf, Borlaert.

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INTENSIVE INSULIN VS CONVENTIONAL THERAPY FOR SEPTIC SHOCK

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

Financial Disclosures: None reported.

Funding/Support: Assistance Publique-Hôpitaux de Paris was the study sponsor.

Role of the Sponsor: The study sponsor took full administrative responsibility but had no role in the recruitment of patients, in the management, analysis or interpretation of the data or in the preparation, review, or approval of the article.

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

REFERENCES


