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# Corticosteroid Treatment and Intensive Insulin Therapy for Septic Shock in Adults

## A Randomized Controlled Trial

The COITSS Study Investigators\*

**S**EP TIC SHOCK IS A MAJOR COMPLICATION of infectious diseases with a mortality rate of 60% within a short period.<sup>1</sup> 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.<sup>1</sup>

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.<sup>2</sup> However, the 2 largest trials included in this meta-analysis yielded different treatment effects on mortality in short periods.<sup>3,4</sup> 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,<sup>3</sup> whereas the second trial found no evidence of a beneficial treatment effect.<sup>4</sup> 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.<sup>5</sup>

Corticosteroids are associated with hyperglycemia,<sup>2</sup> a complication that

**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 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.

**Trial Registration** clinicaltrials.gov Identifier: NCT00320099

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may per se affect patient outcomes while they are in the intensive care unit [ICU].<sup>6,7</sup> The first large randomized trial assessing intensive insulin therapy<sup>8</sup> 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 sepsis<sup>9</sup> or in a general ICU population.<sup>10</sup> Nevertheless,

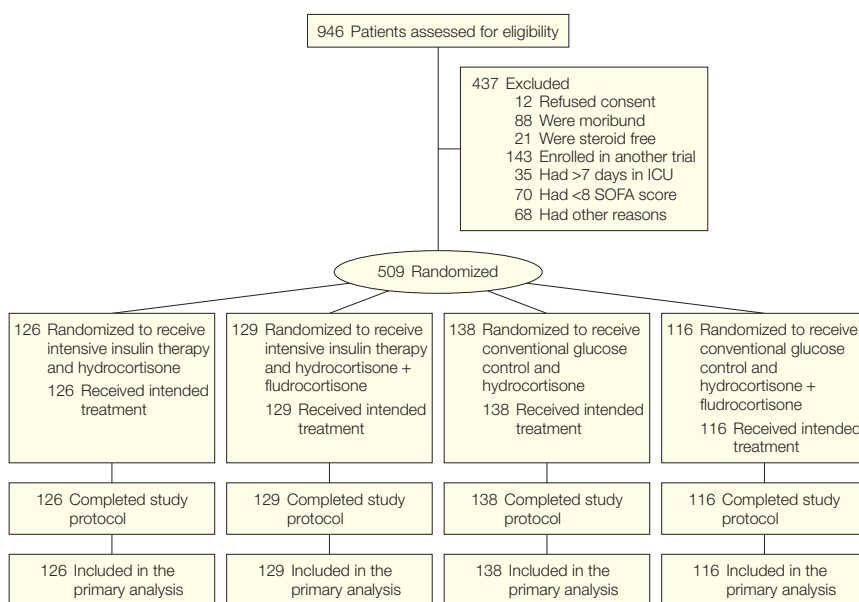
patients whose septic shock is treated with hydrocortisone commonly have blood glucose levels higher than 180

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For editorial comment see p 365.

**Figure 1.** Flowchart of the Trial

ICU indicates intensive care unit; SOFA, Sequential Organ Failure Assessment.

mg/dL (to convert to millimoles per liter, multiply by 0.0555).<sup>11</sup> These levels have clearly been associated with marked increase in the risk of dying.<sup>7</sup>

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 (COITSS) 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 Co-

mité 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,<sup>12</sup> (2) multiple organ dysfunction as defined by a Sequential Organ Failure Assessment (SOFA) score of 8 or more,<sup>13</sup> (3) need for vasopressor therapy (any dose of dopamine, adrenaline, noradrenalin, 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.<sup>8</sup> The protocol is detailed in the eSupplement (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.<sup>14</sup>

9- $\alpha$ -Fludrocortisone was prepared as 50- $\mu$ g tablets. Those in the experimental group received 1 tablet via nasoga-

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.<sup>14</sup>

### 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).<sup>13</sup> **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 de-

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<sup>15</sup> (to convert to nanomoles per liter, multiply by 27.588).

### 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 Physi-

ology and Chronic Health Evaluation (APACHE)<sup>16</sup> disability scale and McCabe class<sup>17</sup>; severity of illness as assessed by vital signs, the Simplified Acute Physiology Score (SAPS) II,<sup>18</sup> 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<sup>a</sup>

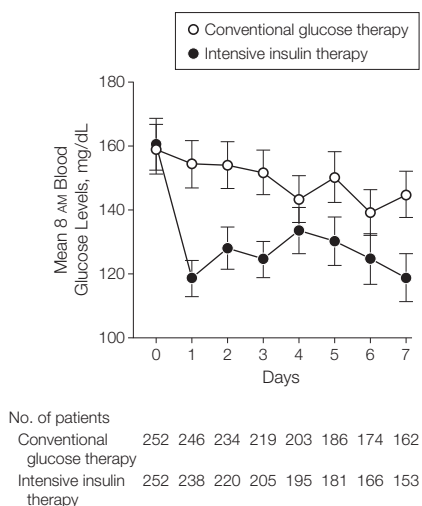
|  | Intensive Insulin Therapy (n = 255) | Conventional Glucose Control (n = 254) | Hydrocortisone + Fludrocortisone (n = 245) | Hydrocortisone Alone (n = 264) |
|--|-------------------------------------|--|--|--------------------------------|
| Age, mean (95% CI), y  | 63.7 (61.9-65.4)                    | 64.3 (62.4-66.1)                       | 64.0 (62.2-65.8)                           | 63.9 (62.1-65.7)               |
| Male sex, No. (%)  | 170 (66.7)                          | 160 (63.0)                             | 167 (68.2)                                 | 163 (61.7)                     |
| Admission days, median (IQR)                                 |                                     |  |  |                                |
| In hospital before ICU admission                             | 0 (0-1)                             | 0 (0-2)                                | 0 (0-1)                                    | 0 (0-2)                        |
| In ICU before randomization                                  | 1 (0-1)                             | 1 (0-1)                                | 1 (0-1)                                    | 1 (0-1)                        |
| Physiology scores, mean (95% CI)                             |                                     |  |  |                                |
| SAPS II  | 58.9 (56.9-60.9)                    | 60.4 (58.2-62.6)                       | 58.9 (56.7-61.0)                           | 60.4 (58.3-62.5)               |
| SOFA   | 10.4 (10.0-10.8)                    | 10.8 (10.3-11.2)                       | 10.6 (10.2-11.1)                           | 10.1 (10.1-11.0)               |
| Type of patients, No. %                                      | 218                                 | 220                                    | 207  | 231                            |
| Medical  | 193 (88.5)                          | 189 (85.9)                             | 186 (89.9)                                 | 196 (84.9)                     |
| Unscheduled surgery  | 22 (10.1)                           | 26 (11.8)                              | 17 (8.2)                                   | 31 (13.4)                      |
| Scheduled surgery  | 3 (1.4)                             | 5 (2.3)                                | 4 (1.9)                                    | 4 (1.7)                        |
| Type of infection, No./total (%)                             |                                     |  |  |                                |
| Community acquired   | 134/246 (54.5)                      | 115/247 (46.6)                         | 120/234 (51.3)                             | 129/259 (49.8)                 |
| Hospital acquired  | 112/246 (45.5)                      | 132/247 (53.4)                         | 114/234 (48.7)                             | 130/259 (50.2)                 |
| Infected patient, No.  | 245                                 | 246                                    | 233  | 258                            |
| Infection per patient, mean (95% CI)                         | 1.5 (1.4-1.6)                       | 1.6 (1.5-1.8)                          | 1.6 (1.4-1.7)                              | 1.5 (1.4-1.7)                  |
| Sites of infection, No.                                      |                                     |  |  |                                |
| Chest  | 173                                 | 180                                    | 168  | 185                            |
| Urogenital   | 41                                  | 35                                     | 36   | 40                             |
| Septicemia   | 32                                  | 36                                     | 37   | 31                             |
| Pathogens  |                                     |  |  |                                |
| Gram negative  | 107                                 | 97                                     | 98   | 106                            |
| Blood glucose levels, mean (95% CI), mg/dL [No. of patients] | 12.0 (11.0-13.0)                    | 11.3 (10.7-11.9) [253]                 | 11.8 (11.0-12.6)                           | 11.5 (10.7-12.4)               |
| Lactate levels, mean (95% CI), mg/dL                         | 44.2 (33.3-55.0) [248]              | 35.1 (30.6-38.7) [244]                 | 36.7 (27.0-45.1) [236]                     | 42.1 (36.0-54.1) [256]         |
| Cortisol levels, mean (SD), µg/dL [No. of patients]          |                                     |  |  |                                |
| Basal  | 39.8 (34.0-45.7) [227]              | 36.7 (35.6-43.8) [230]                 | 41.1 (34.9-47.4) [215]                     | 38.5 (34.7-42.4) [242]         |
| Peak   | 50.7 (45.0-56.3) [223]              | 50.1 (45.1-55.1) [225]                 | 50.1 (44.8-55.4) [211]                     | 50.7 (45.3-56.0) [237]         |
| Change   | 10.7 (5.5-16.0) [223]               | 10.5 (7.5-13.5) [225]                  | 9.2 (3.9-14.3) [211]                       | 11.9 (8.6-15.3) [237]          |
| Nonresponders, No. (%)                                       | 173 (67.8)                          | 169 (66.5)                             | 167 (68.2)                                 | 175 (66.3)                     |
| Mechanical ventilation, No. (%)                              | 218 (85.5)                          | 220 (86.6)                             | 213 (86.9)                                 | 225 (85.2)                     |
| Renal replacement therapy, No. (%)                           | 46 (18.7) [246]                     | 53 (21.5) [246]                        | 41 (17.2)                                  | 58 (22.9)                      |

Abbreviations: CI, confidence interval; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; SAPS, Simplified Acute Physiology Score.

SI 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.

<sup>a</sup>Each statistic was computed on the nonmissing value, ie, the whole sample unless specifically indicated.

**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.

utes after administration of a 250- $\mu$ g 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, severe proximal deficit or atrophy<sup>19</sup>—was recorded at study entry and at days 7, 14, 21, 28, or up to ICU discharge (depending 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 sedation. Vital status and neurological status 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 Scale<sup>20,21</sup> with a score of 30 or

more indicating the presence of post-traumatic stress disorders,<sup>22-24</sup> the Short-Form General Health Survey,<sup>25-27</sup> and the Hospital Anxiety and Depression scale in that order. The latter tool includes 2 scales evaluating depression (7 items) and anxiety (7 items).<sup>28-30</sup> Patients scoring 10 or more for each of these scales is at risk of major psychological distress.<sup>28</sup>

### Study Outcomes

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

Secondary outcomes included 28-, 90-, and 180-day mortality rates; number of vasopressor and mechanical ventilation-free days; time to reach a SOFA score of less than 8; ICU and hospital length of stay; and serious adverse events, including any episode in which arterial blood glucose levels decreased to less than 40 mg/dL; superinfection; presence of muscle weakness at ICU discharge or at the 90- or 180-day follow-up; or the presence of posttraumatic stress disorders at the 180-day follow-up.

Outcomes were investigated in the subgroup of patients who did not respond to corticotrophin.

### Statistical Analysis

We estimated 50% in-hospital mortality among patients with septic shock who became dependent on vasopressor and were treated with hydrocortisone.<sup>3</sup> 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 ( $\alpha = .05$  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.<sup>8</sup> The comparison of hydrocortisone to hydrocortisone plus fludrocortisone was a secondary objective 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. Active 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 continuous 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,<sup>31</sup> and adjusted comparison using predictors identified among baseline characteristics was performed by the Fine and Gray regression model.<sup>32</sup> Overall 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 between both randomizations and between-treatments effect and response to corticotrophin tests were assessed using the Gail and Simon<sup>33</sup> heterogeneity test. Assumption of proportionality for the Cox model was checked.<sup>34</sup> Finally, to assess the difference in the control of blood glucose across randomized groups, we fitted a linear mixed-effects model.<sup>35</sup> This allowed modeling observational heterogeneity incurred by repeated measurements of glucose levels and insulin doses over time in the same patient and accounted for the fixed and random nature of the study factors.

All tests were 2-sided. A *P* value of .05 was considered statistically significant. The only comparisons that were performed are those reported in the article. All were prefixed and scheduled in the protocol, and none of them were performed post hoc. All statistical analyses were performed using the SAS 9.1 (SAS Institute Inc, Cary, North Carolina) 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 treatment groups were well balanced at baseline (TABLE 1). None of the patients received 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, 45-96) 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;  $P = .78$ ; eFigure, available at <http://www.jama.com>). In the a priori defined subgroup of nonresponders to corticotrophin, there was no evidence of a difference in mortality between the 2 groups. 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

| Variables   | Intensive Insulin Therapy<br>(n = 255) | Conventional Glucose Control<br>(n = 254) | P Value           |                       | Hydrocortisone + Fludrocortisone<br>(n = 245) | Hydrocortisone Alone<br>(n = 264) | P Value          |                       |
|---|--|---|-------------------|-----------------------|---|-----------------------------------|------------------|-----------------------|
|   |  |   | Unadjusted        | Adjusted <sup>a</sup> |   |                                   | Unadjusted       | Adjusted <sup>a</sup> |
| In-hospital death, No./total (%)                        | 117/255 (45.9)                         | 109/254 (42.9)                            | .50               | .37                   | 105 (42.9)                                    | 121 (45.8)                        | .50              | .91                   |
| Overall survival  |  |   |                   |                       |   |                                   |                  |                       |
| Deaths, No. (%)   | 122 (47.9)                             | 118 (46.5)                                |                   |                       | 112 (45.7)                                    | 128 (48.5)                        |                  |                       |
| Kaplan-Meier estimate of survival rates, HR (95% CI), d | 1.04 (0.80-1.34)                       | 1 [Reference]                             | .78               | .39                   | 0.94 (0.73-1.21)                              | 1 [Reference]                     | .61              | .67                   |
| 28  | 62.2 (56.4-68.5)                       | 61.1 (55.3-67.5)                          |                   |                       | 62.5 (56.6-68.9)                              | 60.9 (55.2-67.1)                  |                  |                       |
| 90  | 51.8 (45.9-58.4)                       | 54.8 (48.9-61.4)                          |                   |                       | 54.2 (48.2-61.0)                              | 52.4 (46.6-58.9)                  |                  |                       |
| 180   | 50.9 (45.0-57.6)                       | 52.1 (46.2-58.8)                          |                   |                       | 52.9 (46.9-59.7)                              | 50.2 (44.4-56.8)                  |                  |                       |
| No. of patients who died                                | 103                                    | 82  |                   |                       | 105   | 121                               |                  |                       |
| Causes of death, No. (%)                                |  |   |                   |                       |   |                                   |                  |                       |
| Multiple organ failure                                  | 92 (78.6)                              | 66 (60.6)                                 | .004 <sup>b</sup> | .005 <sup>b</sup>     | 75 (71.4)                                     | 83 (68.6)                         | .67 <sup>b</sup> | .74 <sup>b</sup>      |
| Cardiovascular  | 9 (8.7)                                | 7 (8.5)                                   |                   |                       | 7 (6.7)                                       | 9 (7.4)                           |                  |                       |
| Stroke  | 1 (1.0)                                | 2 (2.4)                                   |                   |                       | 3 (2.9)                                       | 0                                 |                  |                       |
| Brain hemorrhage  | 0                                      | 2 (2.4)                                   |                   |                       | 0   | 2 (1.7)                           |                  |                       |
| Refractory hypoxia                                      | 1 (1.0)                                | 2 (2.4)                                   |                   |                       | 2 (1.9)                                       | 1 (0.8)                           |                  |                       |
| Unknown   | 0                                      | 3 (3.7)                                   |                   |                       | 3 (2.9)                                       | 0                                 |                  |                       |
| No. of days, median (IQR)                               |  |   |                   |                       |   |                                   |                  |                       |
| Vasopressor-free within the first 7 days                | 4 (1-6)                                | 4 (2-5)                                   | .58               | .60                   | 4 (2-5)                                       | 4 (1-5)                           | .62              | .61                   |
| Mechanical ventilation-free within 28 days              | 10 (2-22)                              | 13 (2-23)                                 | .51               | .29                   | 12 (2-23)                                     | 12 (2-22.5)                       | .50              | .81                   |
| Cumulative incidence of SOFA <8 at day 7 (95% CI)       | 64.3 (58.6-70.1)                       | 60.6 (54.7-66.6)                          | .38               | .75                   | 63.3 (57.3-69.2)                              | 61.7 (56.0-67.5)                  | .75              | .78                   |
| Length of stay, median (IQR), d                         |  |   |                   |                       |   |                                   |                  |                       |
| ICU   |  |   |                   |                       |   |                                   |                  |                       |
| All patients  | 9 (4-19)                               | 9 (4-15)                                  | .70               | .39                   | 9 (4-16)                                      | 9 (4-17.5)                        | .86              | .35                   |
| Survivors   | 10 (6-19)                              | 9 (5-15)                                  | .68               | .46                   | 10 (6-16)                                     | 9 (5-17)                          | .52              | .10                   |
| Hospital  |  |   |                   |                       |   |                                   |                  |                       |
| All patients  | 16 (6-34)                              | 15 (7-30)                                 | .87               | .94                   | 14 (6-25)                                     | 18 (7-34)                         | .15              | .07                   |
| Survivors   | 24 (12-43)                             | 22 (11-39)                                | .87               | .57                   | 19 (5-40)                                     | 25.5 (14-42)                      | .09              | .13                   |

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

<sup>a</sup>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.

<sup>b</sup>Comparison of multiple organ failure vs other causes.

(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 died ( $P=.50$ ). 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 vasopressor-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.<sup>14</sup> 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<sup>3</sup> and greater than patients in the Corticosteroid Therapy of Septic Shock (CORTICUS) study.<sup>4</sup> These findings suggest that in participating hospitals, physicians treated the sickest patients with corticosteroids in anticipa-

**Table 3.** Serious Adverse Events

| Variables   | Intensive Insulin Therapy (n = 255) | Conventional Glucose Control (n = 254) | P Value | Hydrocortisone + Fludrocortisone (n = 245) | Hydrocortisone Alone (n = 264) | P Value |
|---|-------------------------------------|--|---------|--|--------------------------------|---------|
| Superinfection, No. of patients/episodes                            |                                     |  |         |  |                                |         |
| Total   | 47/106                              | 43/132                                 | .66     | 53/144                                     | 37/94                          | .02     |
| Lung  | 35/59                               | 29/94                                  | .43     | 36/82                                      | 28/71                          | .18     |
| Peritoneal  | 4/10                                | 1/1                                    | .37     | 4/10                                       | 1/1                            | .20     |
| Urinary tract   | 7/8                                 | 13/16                                  | .18     | 15/17                                      | 5/7                            | .02     |
| Central nervous system  | 0/0                                 | 1/1                                    | .50     | 1/1  | 0/0                            | .48     |
| Blood   | 9/10                                | 4/5                                    | .26     | 8/9  | 5/6                            | .40     |
| Others  | 14/19                               | 8/15                                   | .28     | 15/25                                      | 7/9                            | .08     |
| In-hospital death among patients with superinfection, No./total (%) | 26/47 (55.3)                        | 21/43 (48.8)                           | .67     | 27/53 (50.9)                               | 20/37 (54.1)                   | .83     |
| Hypoglycemia, glucose <40 mg/dL                                     |                                     |  |         |  |                                |         |
| No. of measures per patient, median (IQR)                           | 72 (43-110)                         | 44 (32-56)                             | <.001   | 51 (31-79)                                 | 53 (38-81)                     | .36     |
| No. of patients/episodes  | 42/72                               | 20/44                                  | .003    | 32/51                                      | 30/53                          | .59     |
| No. of episodes   |                                     |  |         |  |                                |         |
| 0   | 211                                 | 234                                    | .002    | 212  | 233                            | .54     |
| 1   | 26                                  | 13                                     |         | 19   | 20                             |         |
| 2   | 9                                   | 3                                      |         | 8  | 4                              |         |
| 3   | 5                                   | 1                                      |         | 3  | 3                              |         |
| 4   | 1                                   | 2                                      |         | 2  | 2                              |         |
| >4  | 1                                   | 1                                      |         | 1  | 1                              |         |
| Episodes, mean (SD)   | 0.289 (0.90)                        | 0.139 (0.58)                           | .003    | 0.238 (0.86)                               | 0.198 (0.68)                   | .63     |
| In-hospital death among patients with hypoglycemia, No./total (%)   | 19/42 (45.2)                        | 10/20 (50.0)                           | .79     | 14/32 (43.8)                               | 15/30 (50.0)                   | .80     |
| MDRS day 28   |                                     |  |         |  |                                |         |
| 1   | 3                                   | 11                                     | .06     | 5  | 9                              | .10     |
| 2   | 3                                   | 3                                      |         | 4  | 2                              |         |
| 3   | 3                                   | 1                                      |         | 2  | 2                              |         |
| 4   | 9                                   | 3                                      |         | 1  | 1                              |         |
| 5   | 5                                   | 3                                      |         | 6  | 6                              |         |

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.<sup>5</sup> The observed mortality was concordant with the benefit from corticosteroids reported in the Ger-Inf-05 trial.<sup>3</sup> Otherwise, the study population mimicked common characteristics of septic shock.<sup>1</sup> 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 Berghe et al<sup>8</sup> 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),<sup>36</sup> CORTICUS,<sup>4</sup> and Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP)<sup>9</sup> 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<sup>9</sup> or the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trials<sup>10</sup> and more in the range of levels reported in the trial by Van den Berghe and colleagues.<sup>8</sup> 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.<sup>14</sup> 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.<sup>14</sup> The median doses of insulin in both groups were very similar to those observed in the Van den Berghe trial,<sup>8</sup> 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.<sup>10</sup> 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.<sup>3,11</sup> 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,<sup>9,10</sup> 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.<sup>5</sup> On the other hand, the 11  $\beta$ -hydroxysteroid dehydrogenase type II enzyme that inactivates cortisol to prevent its binding to mineralocorticoid receptors may be up-regulated in sepsis.<sup>37</sup> The use of fludrocortisone was also suggested as a potential explanation for the difference in outcome benefits observed in the Ger-Inf-05 trial<sup>3</sup> and in the CORTICUS trial.<sup>4</sup> 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.<sup>14</sup> 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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