In the Literature

The Circle Continues Unbroken: Now Corticosteroids Are Not Effective for Septic Shock

Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008; 358:111–24.

The administration of corticosteroids to patients with sepsis of varying severity has become common. The recently updated guidelines of the Surviving Sepsis Campaign state, however, that "stress-dose steroid therapy be given only in septic shock after blood pressure is identified to be poorly responsive to fluid and vasopressor therapy" [1, p. 296]. Sprung and colleagues have reexamined the issue by randomizing 499 adults with septic shock to receive adjunctive therapy with 50 mg of either hydrocortisone or placebo every 6 h for 5 days, followed by a tapering dose given for an additional 6 days. Patients were required to have evidence of a systemic inflammatory response to infection, an onset of shock (defined as systolic blood pressure <90 mm Hg, despite receipt of adequate fluid replacement, and a need for vasopressor support for at least 1 h) within the previous 72 h, together with evidence of hypoperfusion or organ dysfunction attributable to sepsis.

No significant difference between treatment with hydrocortisone and placebo was identified with regard to the primary end point of the study (28-day mortality) for the patients who did not respond to a cortisone stimulation test (who constituted 46.7% of the total population). Thus, the 28-day mortality rate for this group was 39.2% for hydrocortisone recipients and 36.1% for placebo recipients ($P = .69$); the 28-day mortality rates for patients who responded appropriately in the hydrocortisone stimulation tests were 28.8% and 28.7%, respectively. Shock reversed more rapidly in hydrocortisone recipients among patients for whom this result was achieved. Any benefit, however, was offset by a greater risk of superinfection, sepsis, and septic shock in persons who received this corticosteroid.

No microbiologic information was provided by the study investigators, and importantly, neither was any assessment of the adequacy of the prescribed antibiotic therapy. Although there are a number of differences between this study and others that have reported improved outcomes for patients experiencing septic shock who receive hydrocortisone, and although the power of this study was somewhat limited by the sample size (which was lower than planned), this study provides no significant inkling of benefit for widespread adjunctive hydrocortisone treatment for patients with septic shock. The investigators do, however, acknowledge that there is a possible benefit for some patients, such as those who are treated very early after the onset of shock or who lack responsiveness to vasopressor therapy.

Reference

1. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med **2001**; 345:1359–67.

Intensive Attempts to Maintain Euglycemia Are Harmful to Patients with Severe Sepsis

Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008; 358:125–39.

Van den Berghe and colleagues previously reported the results of a randomized clinical trial from 2001 that found that maintenance of the blood glucose level at 80–110 mg/dL in critically ill patients who underwent surgery reduced the rate of subsequent mortality—in particular, the rate of mortality due to multiple-organ system failure with a septic focus [1]. Much of the apparent benefit of tight control of the glucose level was observed in patients who underwent cardiac surgery and who had received a large postoperative glucose load. Despite these limitations—especially the fact that patients in the study were not known to be infected at the time of study entry—these data have been widely extrapolated for use in patients with sepsis.

Brunkhorst and colleagues randomized patients with severe sepsis to receive either intensive insulin therapy or conventional insulin therapy. A second randomization examined the relative benefits of fluid resuscitation with either 10% pentastarch or Ringer's lactate. The authors found that pentastarch resuscitation was associated with an increased risk of acute renal failure and need for renal replacement therapy.

Among evaluable patients, intensive insulin therapy was associated with lower mean blood glucose levels (112 mg/dL vs. 151 mg/dL). There was no difference in the mortality rate or organ failure score at 28 days. However, the trial was aborted early because of an increased risk of hypoglycemic events in the intensive insulin therapy group. The blood glucose level decreased to ≤40 mg/dL in 17% of participants in the intensive therapy group and in 4.1% of those who received conventional therapy. Serious adverse events in general were also more common in the intensive insulin therapy group. Thus, there was no evidence of a benefit for intensive insulin therapy in patients with severe sepsis; on the contrary, such therapy was associated with harm. The most recent guidelines of the Surviving Sepsis Campaign recommend targeting (after initial stabilization) a blood glucose level of <150 mg/dL [2], which was the mean level achieved in this study in the conventional therapy group.

References

1. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med **2001**; 345:1359–67.
2. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med **2008**; 36:296–327.