Low-Dose Steroids Cut Septic Shock Mortality

BY BRUCE JANCIN
Denver Bureau

LISBON — After decades of controversy, a consensus has emerged that corticosteroids provide major benefits in patients with severe sepsis or septic shock, Dr. Djillali Annane said at the 12th International Congress on Infectious Diseases.

The benefits, as shown in multiple randomized placebo-controlled trials, are improved 28-day mortality, shorter shock duration, improved hemodynamics, reduced organ dysfunction, and less systemic inflammation.

Studies involving low-dose therapy for at least 5 days show a robust 23% reduction in relative risk of mortality.

DR. ANNANE

These benefits accrue only with low-dose corticosteroids administered for at least 5 days, and only in the sizable patient subsets having adrenal insufficiency or refractory septic shock, said Dr. Annane of the University of Versailles, France.

Much of the lengthy controversy in this field was the result of great heterogeneity in clinical trials, particularly those done before 1992. For example, steroids for septic shock fell into disfavor all through the 1980s and 1990s because multiple trials before 1992 showed no benefit. That's because these negative studies used short-course, high-dose corticosteroids, Dr. Annane explained. Today, with the benefit of hindsight, it can be emphatically stated that no evidence supports the use of such therapy, he said at the congress, which was sponsored by the International Society for Infectious Diseases.

Dr. Annane was first author of a 2006 Cochrane Collaboration systematic review of corticosteroids for treatment of severe sepsis and septic shock (Cochrane Library ISSN 1464-780X).

In 15 randomized trials totaling more than 2,000 children and adults included in the analysis, steroid therapy didn't change 28-day all-cause mortality. But the results varied with dosing strategy. In nine trials of replacement-dose corticosteroids—the equivalent of hydrocortisone at 200-300 mg/day intravenously for 5 days or longer—there was a highly significant 20% reduction in the relative risk of 28-day mortality compared with placebo, along with a greater proportion of patients experiencing shock reversal by day 7. In contrast, patients on high-dose, short-course corticosteroids didn't benefit.

Several new trials have been published since completion of the Cochrane review. An updated analysis that incorporates these studies shows a significant 12% reduction in all-cause mortality with steroid therapy when all trials are considered. Looking only at those involving low-dose therapy for at least 5 days, the relative risk reduction in mortality is now an even more robust 23%, he said.

The Cochrane review found no significant increase in rates of superinfection, GI bleeding, or hyperglycemia linked to steroid therapy, but Dr. Annane found those trial results inconsistent with real-world practice. These adverse events are common with steroids, he cautioned, adding that only patients likely to obtain therapeutic benefit should be exposed to such risks.

That's why American College of Critical Care Medicine guidelines, which were coauthored by Dr. Annane, recommend low-dose steroids only in septic shock that is refractory or accompanied by adrenal insufficiency, as defined by an increase in cortisol of 9 mcg/dL or less in response to a corticotropin test (Crit. Care Med. 2004;32:1928-48). ■

Is Addition of Fludrocortisone to Steroids Effective in Severe Sepsis?

BY BRUCE JANCIN
Denver Bureau

LISBON — A key unresolved clinical issue regarding the use of corticosteroids in septic shock patients is whether the addition of fludrocortisone to low-dose hydrocortisone provides incremental benefit over hydrocortisone alone, Dr. Djillali Annane said at the 12th International Congress on Infectious Diseases.

"There is evidence of need for mineral corticoid supplementation in severe sepsis, and maybe what hydrocortisone provides is not enough," observed Dr. Annane of the Versailles Saint-Quentin-en-Yvelines University, Garches, France.

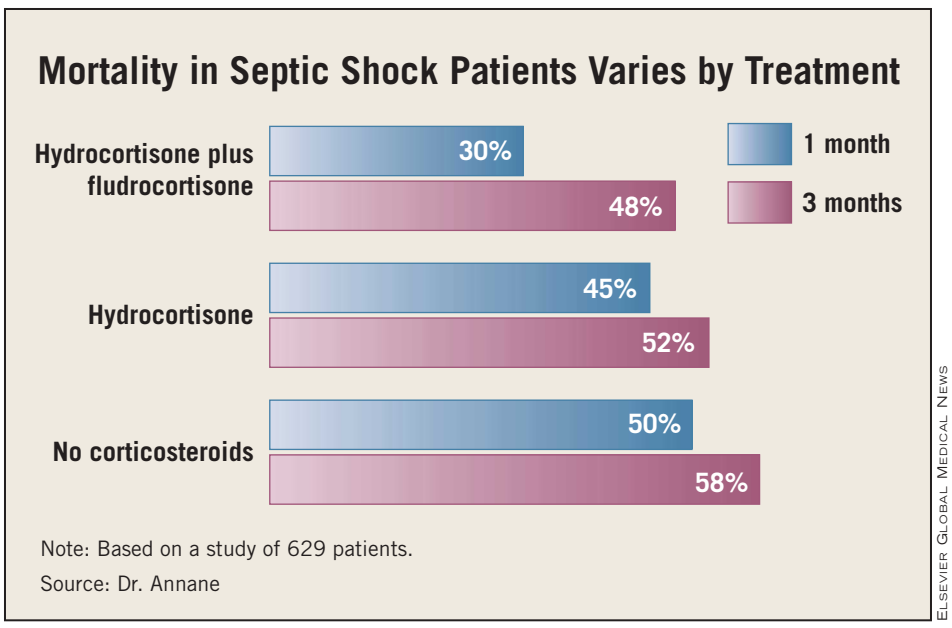
Among the suggestive evidence is a recent 19-site prospective study involving 629 patients with septic shock. The prescription of corticosteroids in this observational study was at the discretion of the treating physicians. Of the total, 163 patients received low-dose hydrocortisone, 249 got hydrocortisone and fludrocortisone, and 217 received no corticosteroids.

The patients in the three study groups were of similar age and disease severity. Yet their death rates were strikingly different, with the best outcomes seen in those who were treated with hydrocortisone plus fludrocortisone. (See chart.)

The findings of this observational study led to the launch earlier this year of an ongoing, multicenter, European randomized trial with a factorial design that is looking at the benefits and risks of combination steroid therapy, compared with hydrocortisone alone, Dr. Annane said at the congress, which was sponsored by the International Society for Infectious Diseases.

Much of the interest in combination steroid therapy in septic shock stems from a French multicenter double-blind trial that Dr. Annane and colleagues reported 4 years ago. In that trial, the researchers randomized 300 adults with septic shock either to hydrocortisone IV at 200 mg/day plus a daily 50-mcg tablet of fludrocortisone, or to matching placebos. The 28-day mortality was significantly lower in the combination steroid arm (JAMA 2002;288:862-71).

Ironically, the only reason fludrocortisone was included in the corticosteroid arm was that the study ethics committee insisted upon it, even though there was little evidence at the time to support that position, he recalled. ■



Early Administration of Antibiotics, Fluids Save Lives in Septic Shock

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

HALIFAX, N.S. — A protocol of early antibiotics and hemodynamic stabilization decreases mortality in patients with severe sepsis or septic shock, Dr. Robert Stenstrom said at the 11th International Conference on Emergency Medicine.

Initiating the program in the emergency department requires an increase in nursing and physician bedside time, but the 23% decrease in mortality makes the investment worthwhile, said Dr. Stenstrom, director of research at St. Paul's Hospital, Vancouver.

His review examined mortality and time-dependent treatment before and after emergency department implementation of a sepsis protocol. The protocol, based on that described by Dr. Emanuel Rivers in 2001 (N. Engl. J. Med. 2001;345:1368-77), calls for early IV fluids and antibiotics, followed by initiation of early goal-directed therapy aimed at hemodynamic stabilization, said Dr. Stenstrom, who is also an emergency physician at the hospital.

Included in the study were 50 patients admitted to the ICU directly from the emergency department with severe sepsis (one or more organs failing or a lactate level of 4.0 mmol/L or greater) or septic shock (systolic blood pressure less than 90 mm Hg despite fluid bolus of 25 mL/kg). There were 20 patients in the preprotocol group and 30 in the protocol group. Their mean age was 50 years; the mean Acute Physiology and Chronic Health Evaluation score was 24.

In the preprotocol group, 7 of the 20 patients received first antibiotics in less than 1 hour, and the rest received the drugs in 1-10 hours. In the protocol group, 20 of 30 patients got antibiotics in less than 1 hour and 6 got them in 1-2 hours. Three more got the drugs by 4 hours, but one patient didn't receive them until almost 8 hours had passed. Time to completion of initial fluid bolus (usually 2 L of normal saline) decreased significantly, from about 2.5 hours in the preprotocol group to just over 1 hour in the protocol group.

In the preprotocol group, 14 patients were on early goal-directed therapy by 10 hours, but it took 12-60 hours in the other 6. In the protocol group, all were on early goal-directed therapy before 10 hours.

There was no significant difference in time to ICU transfer, Dr. Stenstrom said.

At 28 days, mortality was 46% in the preprotocol group and 23% in the protocol group—a decrease of 23%. ■