

## CAGS AND ACS EVIDENCE BASED REVIEWS IN SURGERY. 35

## Efficacy and safety of low-dose hydrocortisone therapy in the treatment of septic shock

Prosanto Chaudhury, MD  
John C. Marshall, MD  
Joseph S. Solomkin, MD  
for the Members of the  
Evidence Based Reviews  
in Surgery Group\*

\*The CAGS/ACS Evidence Based Reviews in Surgery Group comprises Drs. N.N. Baxter, K.J. Brasel, C.J. Brown, P. Chaudhury, C.S. Cutter, C.M. Divino, E. Dixon, L. Dubois, G.W.N. Fitzgerald, H.J.A. Henteleff, A.W. Kirkpatrick, S. Latosinsky, A.R. MacLean, T.M. Mastracci, R.S. McLeod, A.M. Morris, L.A. Neumayer, L.K. Temple and Ms. M.E. McKenzie.

**Correspondence to:**  
Ms. Marg McKenzie, RN  
Administrative Coordinator, EBRS  
Mount Sinai Hospital, L3-010  
60 Murray St., PO Box 23  
Toronto ON M5T 3L9  
fax 416 586-5932  
mmckenzie@mtsinai.on.ca

The term “evidence-based medicine” was first coined by Sackett and colleagues as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.”<sup>1</sup> The key to practising evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding. For clinicians to practise evidence-based medicine, they must have the skills to read and interpret the medical literature so that they can determine the validity, reliability, credibility and utility of individual articles. These skills are known as critical appraisal skills, and they require some knowledge of biostatistics, clinical epidemiology, decision analysis and economics, and clinical knowledge.

Evidence Based Reviews in Surgery (EBRS) is a program jointly sponsored by the Canadian Association of General Surgeons (CAGS) and the American College of Surgeons (ACS) and is supported by an educational grant from ETHICON and ETHICON ENDO-SURGERY, both units of Johnson & Johnson Medical Products, a division of Johnson & Johnson and ETHICON Inc. and ETHICON ENDO-SURGERY Inc., divisions of Johnson & Johnson Inc. The primary objective of EBRS is to help practising surgeons improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. They are selected for their clinical relevance to general surgeons and because they cover a spectrum of issues important to surgeons, including causation or risk factors for disease, natural history or prognosis of disease, how to quantify disease, diagnostic tests, early diagnosis and the effectiveness of treatment. A methodological article guides the reader in critical appraisal of the clinical article. Methodological and clinical reviews of the article are performed by experts in the relevant areas and posted on the EBRS website, where they are archived indefinitely. In addition, a listserv allows participants to discuss the monthly article. Surgeons who participate in the monthly packages can obtain Royal College of Physicians and Surgeons of Canada Maintenance of Certification credits and/or continuing medical education credits for the current article only by reading the monthly articles, participating in the listserv discussion, reading the methodological and clinical reviews and completing the monthly online evaluation and multiple choice questions.

We hope readers will find EBRS useful in improving their critical appraisal skills and in keeping abreast of new developments in general surgery. Four reviews are published in condensed versions in the *Canadian Journal of Surgery* and 4 are published in the *Journal of the American College of Surgeons*. For further information about EBRS, please refer to the CAGS or ACS websites. Questions and comments can be directed to the program administrator, Marg McKenzie, at mmckenzie@mtsinai.on.ca.

### Reference

1. Evidence-Based Medicine Working Group. Evidence-based medicine. *JAMA* 1992;268:2420-5.

## SELECTED ARTICLE

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

## ABSTRACT

**Objective:** To evaluate the efficacy and safety of low-dose hydrocortisone therapy in patients with septic shock. **Design:** Multicentre, randomized, double-blind, placebo-controlled trial. **Setting:** Nine centres (including 52 intensive care units) in Europe and the Middle East. **Patients:** Patients with clinical evidence of infection, evidence of systemic response to infection and onset of shock within the previous 72 hours (defined by systolic blood pressure < 90 mm Hg despite adequate fluid replacement or a need for vasopressors for at least 1 hour) and hypoperfusion or organ dysfunction attributable to sepsis. **Intervention:** Intervention group ( $n = 251$ ) was randomly assigned to receive 50 mg of hydrocortisone intravenously, and the control group ( $n = 248$ ) was randomly assigned to receive placebo every 6 hours for 5 days; the dose was tapered during a 6-day period. **Main outcome measure:** Death at 28 days in patients who did not have a response to corticotrophin. **Results:** In all, 233 (46.7%) patients did not have a response to corticotrophin (125 in the treatment group and 108 in the placebo group). At 28 days, there was no significant difference in mortality between patients in the 2 groups who did not have a response to corticotrophin (39.2% in the treatment group and 36.1% in the placebo group,  $p = 0.69$ ) or between those who had a response to corticotrophin (28.8% in the treatment group and 28.7% in the placebo group,  $p = 1.00$ ). At 28 days, 86 of 251 (34.3%) patients in the treatment group and 78 of 248 (31.5%) in the placebo group had died ( $p = 0.51$ ). In the treatment group, shock was reversed more quickly than in the placebo group. However, there were more episodes of superinfection, including new sepsis and septic shock. **Conclusion:** Hydrocortisone cannot be recommended as general adjuvant therapy for septic shock (vasopressor responsive), nor can corticotrophin testing be recommended to determine which patients should receive hydrocortisone therapy.

## COMMENTARY

The notion that exogenous corticosteroid administration might improve the outcome of patients with infection arose at the same time as the introduction of antibiotics in the early 20th century. As early as 1972, Lillehei and colleagues<sup>1</sup> published on the role of steroids in sepsis. This was followed by a small randomized controlled trial (RCT) published in the 1970s<sup>2</sup> in which there was a dramatic reduction in mortality from close to 40% to just

over 10% with the administration of steroids; this study laid the ground work for current investigations into the therapeutic role of exogenous corticosteroids in sepsis. Subsequent work has yielded complicated and often conflicting conclusions, and despite the publication of the Corticosteroid Therapy of Septic Shock (CORTICUS) study<sup>3</sup> last year, multiple questions remain.

Two RCTs published in the late 1980s<sup>4,5</sup> concluded that for patients with sepsis defined by nonspecific physiologic criteria, the use of high doses of methylprednisolone was not effective and possibly harmful. Subsequent studies, however, suggested that critical illness is associated with a state of relative adrenal insufficiency that can be identified by an abnormal response to an adrenocorticotrophic hormone (ACTH) stimulation test<sup>6</sup> and treated with pharmacologic doses of glucocorticoids and mineralocorticoids.<sup>7</sup> Pooled data from the published literature show a statistically significant survival benefit for the use of pharmacologic doses of corticosteroids.<sup>6</sup>

The primary end point of the CORTICUS study was 28-day mortality.<sup>3</sup> There were 49 deaths in 125 patients in the hydrocortisone group (39.2%, 95% confidence interval [CI] 30.5%–47.9%) and 39 deaths in 108 patients in the placebo group (36.1%, 95% CI 26.9%–45.3%). Thus, the difference in 28-day mortality was 3.1%, (95% CI –9.5 to 15.7,  $p = 0.69$ ). In addition, there was no statistically significant difference for the subgroup of patients who did respond to corticotrophin, and no difference overall. An additional 21 post-hoc subgroup analyses were performed and failed to find any statistically significant differences in outcome.

An important concern in this trial is the rather large window (72 h) for initiation of steroid treatment after the hypotensive episode. This meant that many patients had already recovered from their hypotension when therapy was begun. Therefore, the study tested whether this dosage of hydrocortisone would improve mortality by impacting events occurring after the hypotensive event.

In retrospect, the trial did not meet its enrolment targets. The CORTICUS study investigators initially planned to enrol 800 patients, but, largely for reasons of lack of funding, curtailed enrolment at 500 patients. Whereas this is a moderately large sample, given the intrinsic heterogeneity of patients with sepsis, it is entirely possible that the study signal might have changed over time and that with larger numbers a more robust signal for benefit or harm might have been observed. The actual death rate for patients who did not respond to corticotrophin was 36.1% (13.9% lower than that estimated in the sample size calculation). The nonresponders to corticotrophin actually form 46% of the study population, slightly more than the assumption of 40%. The fact that the study did not meet its planned enrolment and that the estimated mortality used to calculate sample size differed largely from the observed mortality greatly undermines the power of this

study. Caution must therefore be exercised when making conclusions.

Shock was reversed more rapidly in the hydrocortisone group than the placebo group, but this did not translate into clinically important patient benefit, and there was a significantly higher risk of subsequent infection in treated patients.

Subtle differences in the nature of the study population can have a substantial impact on the magnitude and even the direction of a treatment effect. In contrast to the earlier study of Annane and colleagues,<sup>8</sup> Sprung and colleagues<sup>3</sup> recruited a less seriously ill population of patients with a lower mortality risk and with lesser degrees of shock. Moreover, patients in the study by Annane and colleagues<sup>8</sup> received both hydrocortisone and fludrocortisone.

Even more importantly, but difficult to quantify, the CORTICUS study was undertaken in a group of intensive care units (ICUs) where the use of corticosteroids in the treatment of septic shock was quite common.<sup>3</sup> Patients were excluded if the clinician felt that a patient should receive open-label corticosteroids, and so the population ultimately recruited may well represent a systematically different group of patients for whom clinicians were less convinced of the need for steroids. The impact of the systematic exclusion of potentially eligible patients is difficult to assess.

A consistent finding in the CORTICUS study as well as in other studies of corticosteroids in septic shock has been that corticosteroids can reverse the hypotensive effects of the sedative agent etomidate. Etomidate is quite widely used in European ICUs and is known to cause relative adrenal suppression. Rates of etomidate treatment across trials are not well documented.

It is recognized that there is a learning curve with ICU-based clinical trials and that it is difficult to standardize care across a large number of sites. The authors state that “evidence-based guidelines for the treatment of patients were encouraged,” but it does not appear that a treatment algorithm was part of the protocol. The CORTICUS study involved patients from 52 different sites, therefore

the number of patients per site was small, increasing the likelihood of noise from both a learning curve and site-to-site variations in care.

Whether the ACTH stimulation test is a reliable diagnostic marker of a patient with relative adrenal insufficiency is an equally murky question. Variability in the dose of ACTH used and in the platforms used to perform the analyses may well be responsible for some of the divergent conclusions reached. At any rate, until there is greater standardization of this test, reliance on its results should be discouraged.

How then should the results of the CORTICUS study be interpreted? Clearly, the corticosteroid controversy has not been settled, and further large and adequately powered clinical trials are warranted.

**Competing interests:** None declared.

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