

## Selected Summary

### Does low dose hydrocortisone reduce mortality in septic shock?

Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, Laterre PF, Reinhart K, Cuthbertson BH, Payen D, Briegel J; CORTICUS Study Group. (Hadassah Hebrew University Medical Center, Jerusalem; Raymond Poincaré Hospital, University of Versailles, UniverSud Paris, Garches, France; Charité Universitätsmedizin Berlin, Campus Virchow-Klinikum, Berlin; Hospital de St. António dos Capuchos, Centro Hospitalar de Lisboa Central, Lisbon, Portugal; Bloomsbury Institute of Intensive Care Medicine, University College London, London; Analytica International, Loerrach, Germany; Klinikum Mannheim, Mannheim, Germany; Zentralklinikum Augsburg, Augsburg, Germany; St. Luc University Hospital, Université Catholique de Louvain, Brussels; Friedrich Schiller Universität, Jena, Germany; Health Services Research Unit, University of Aberdeen, Aberdeen, United Kingdom; Hôpital Lariboisière, Denis Diderot University of Paris, Paris, France; Klinikum der Universität, Ludwig Maximilians Universität, Munich, Germany). Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008;**358**:111–24.

#### SUMMARY

The use of corticosteroids has been advocated in severe sepsis. However, for several decades, there has been no consensus on this recommendation. The Corticosteroid Therapy of Septic Shock (CORTICUS) study evaluated the efficacy and safety of low dose hydrocortisone therapy in septic shock. This multicentre, randomized, double-blind, placebo-controlled study included 499 patients from 52 participating intensive care units (ICUs). The eligibility criteria were age  $\geq 18$  years with clinical evidence of infection and a systemic response, onset of shock within the previous 72 hours and organ dysfunction or hypoperfusion attributable to sepsis. Those excluded were patients on immunosuppressive agents (corticosteroids), a life expectancy  $< 24$  hours or a disease with a poor prognosis. Participants were randomized to receive either hydrocortisone 50 mg every 6 hours for five days which was then tapered over the next 7 days, or a placebo. Stratified block randomization was done. The Sequential Organ Failure Assessment (SOFA) score was used to measure organ system failure. The general characteristics, assessment of severity, progression and interventions were studied. A short corticotrophin stimulation test was done after administering an intravenous bolus of 0.25 mg of cosyntropin and obtaining a blood sample after 60 minutes. The primary end-point was the mortality rate at 28 days in those with no response to corticotrophin. The secondary end-points included rate of death in those who had a corticosteroid response to corticotrophin and the whole cohort, ICU and hospital death rate, duration of stay, reversal of organ system failure and rate of death 1 year after randomization. Participants were monitored for all possible adverse effects of corticosteroids. A sample size of 800 was arrived at, for 80% power to detect a 10% decrease in mortality from an existing mortality rate of 50%. Of the 499 patients, 233 (46.7%) had

a response to corticotrophin. The baseline characteristics of the patients were comparable. Though the time taken for reversal of shock was significantly shorter among those receiving hydrocortisone, the rate of death at 28 days was not significantly different between the intervention and placebo groups, either among those who had no response to corticotrophin or among those who responded. There was an increased incidence of superinfections, new episodes of sepsis and septic shock, increased incidence of hyperglycaemia and hypernatraemia in the hydrocortisone group.

#### COMMENT

Though there was much enthusiasm about the role of high dose corticosteroids in sepsis, in large controlled studies they were found to increase the mortality due to superinfections.<sup>1,2</sup> Hence, their popularity waned over time. However, lower doses for longer durations were shown to lead to an earlier reversal of shock and improved survival.<sup>3</sup> Also, a study from France showed encouraging results in patients who received physiological doses of hydrocortisone and fludrocortisone.<sup>4</sup> However, several concerns were raised including the reliability of the corticotrophin stimulation test, the statistical analysis and the criteria used for relative adrenal insufficiency.<sup>5</sup> A meta-analysis of the role of low dose corticosteroids had similar conclusions, favouring the role of physiological doses of corticosteroids in septic shock.<sup>6</sup> The benefit was noted to be more in those who did not respond to corticotrophin stimulation. Hence, the administration of physiological dose corticosteroids was incorporated in the guidelines for the management of sepsis.<sup>7</sup>

The CORTICUS trial was a well-designed, multicentric, placebo-controlled trial that aimed to study the effect of physiological doses of hydrocortisone on patients with septic shock. This trial failed to demonstrate any reduction in mortality over a 28-day period. One conclusion consistent with earlier findings was that the time to reversal of shock in the hydrocortisone group was earlier than that in the control group. This trial highlights the fact that in patients with septic shock resistant to vasopressin, though there is a transient response to steroids, it does not translate to a reduction in mortality. The primary reason for this is the increased incidence of superinfections and new episodes of sepsis. Hence, if superinfections could be prevented, steroids may be of use in patients with septic shock. While the authors had initiated this trial to study the effect of hydrocortisone in those who responded to corticotrophin stimulation, the relevance and reliability of corticotrophin stimulation in sepsis and the validity of subclassifying patients based on their response is an undefined area.<sup>8</sup> The study had to be stopped before the required sample size was achieved due to slow recruitment and expiry of the study drug. These factors, along with the lower mortality in the overall group compared to what was estimated for the sample size calculation, considerably reduces the power of the study, which may be  $< 35\%$  to detect a 20% reduction in death.<sup>9</sup> However, the findings of the CORTICUS trial have raised doubts on the role of low dose corticosteroids in septic shock, emphasizing the need for more robust evidence. Following the publication of the abstract of the CORTICUS, the recently published international guidelines for the management of severe sepsis and septic shock of the Surviving Sepsis Campaign has reserved the role of intravenous hydrocortisone for adult patients with septic shock after it has

been confirmed that their blood pressure is poorly responsive to fluid resuscitation and vasopressor therapy.<sup>10</sup> This trial has also highlighted that several critical care guidelines, algorithms and recommendations are based on inadequately powered, small scale trials and these are not only misleading in clinical decision-making, but jeopardize recruitment to well designed trials.

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