Steroids in septic shock: Magic bullet or hype?

The ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group; Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, Billot L, Correa M, Glass P, Harward M, Joyce C, Li Q, McArthur C, Perner A, Rhodes A, Thompson K, Webb S, Myburgh J. (The George Institute for Global Health, University of New South Wales; St George Clinical School, St George Hospital; Sydney Medical School, University of Sydney; Royal North Shore Hospital, Sydney; the Princess Alexandra Hospital and Royal Brisbane and Women's Hospital, University of Queensland, and the Wesley Hospital, Brisbane; Austin Hospital, the School of Medicine, University of Melbourne, and the Australian and New Zealand Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria; Royal Perth Hospital and the School of Medicine and Pharmacology, University of Western Australia, Perth—all in Australia; King Saud Bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, Riyadh, Saudi Arabia; Department of Critical Care Medicine, Auckland City Hospital, Auckland, New Zealand; Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; and St George's University Hospitals NHS Foundation Trust, St George's University of London, London, UK.) Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med* 2018;**378:**797–808.

APROCCHSS Trial and CRICS-TRIGGERSEP Network; Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot J-P, Siami S, Cariou A, Forceville X, Schwebel C, Martin C, Timsit J-F, Misset B, Benali MA, Colin G, Souweine B, Asehnoune K, Mercier E, Chimot L, Charpentier C, François B, Boulain T, Petitpas F, Constantin J-M, Dhonneur G, Baudin F, Combes A, Bohé J, Loriferne J-F, Amathieu R, Cook F, Slama M, Leroy O, Capellier G, Dargent A, Hissem T, Maxime V, Bellissant E. (Service de Médecine Intensive et Réanimation, Hôpital Raymond Poincaré, Garches, Laboratory of Infection and Inflammation Unité 1173, University of Versailles Saint-Quentin-en-Yvelines, INSERM, Montignyle-Bretonneux, Service de Pharmacologie Clinique–Centre d'Investigation Clinique [CIC] INSERM 1414, Centre Hospitalier Universitaire [CHU] de Rennes–Université de Rennes 1, Hôpital Pontchaillou, Rennes, Service de Réanimation Médicale and Service d'Anesthésie et des Réanimations Chirurgicales, Hôpital Henri-Mondor [Assistance Publique–Hôpitaux de Paris—AP-HP], Créteil, Réanimation Médicale et Toxicologique, Hôpital Lariboisière [AP-HP], Université Paris-Diderot, INSERM Unité Mixte de Recherche Scientifique [UMRS] 1144, Réanimation Médicale–Hôpitaux Universitaires Paris Centre–Site Cochin [AP-HP] and Université Paris Descartes, Médecine Intensive et Réanimation, Pôle 2i, Infection et Immunité, Hôpital Bichat–Claude Bernard, AP-HP, Infection, Antimicrobiens, Modélisation, Evolution [IAME] Unité 1137, Université Paris Diderot, INSERM, Service d'Anesthésie et Réanimations Chirurgicales, Hôpitaux Universitaires Paris Centre–Site Cochin [AP-HP], and Service de Réanimation Médicale, Hôpital Pitié-Salpêtrière [AP-HP], and Université Paris Sorbonne INSERM, UMRS 1166–Institute of Cardiometabolism and Nutrition, Paris, Service de Réanimation Médicale, Hôpital Universitaire François Mitterrand, Lipness Team, INSERM Research Center Lipids, Nutrition, Cancer–Unité Mixte de Recherche [UMR] 1231 and Laboratoire d'Excellence LipSTIC, and CIC 1432, Epidémiologie Clinique, Université de Burgundy, Dijon, Service d'Anesthésie–Réanimation, Centre Hospitalier d'Etampes, Etampes, Réanimation Médico-Chirurgicale, CIC INSERM 1414, Grand Hôpital de l'Est Francilien Site de Meaux, Hôpital Saint Faron, Meaux, Service de Réanimation Médicale, CHU de Grenoble, Grenoble, Service d'Anesthésie et de Réanimation, Assistance Publique–Hôpitaux de Marseille, Hôpital Nord, Aix Marseille Université, CIC 1409, and CIC 9502, Marseille, Service de Réanimation Polyvalente, Groupe Hospitalier Paris Saint Joseph, and Service de Réanimation Médicale, CHU de Rouen–Hôpital Charles Nicolle, Rouen, Service de Réanimation Polyvalente, Centre Hospitalier de Valenciennes, Valenciennes,

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SUMMARY

The role of hydrocortisone administration in patients with septic shock is unclear. The first trial, among the two summarized here, which tried to answer this question was conducted in intensive care units (ICUs) in Australia, New Zealand, Denmark and the UK. It enrolled 3800 patients with septic shock who were on mechanical ventilation. The investigators randomly assigned these patients to receive a continuous infusion either of hydrocortisone (in a dose of 200 mg/day) or of a matched placebo. Hydrocortisone was given for a maximum of 7 days (with no tapering off of dose) or until death or discharge, whichever was earlier. The primary outcome, i.e. mortality at 90 days, data on which were available for 3658 patients, was equally frequent in the hydrocortisone (511/1832 [27.9%]) and placebo (526/1826 [28.8%]) groups (odds ratio [OR] 0.95; 95% confidence interval [CI] 0.82–1.10; p=0.5). Among the secondary outcomes, time to reversal of shock (median [interquartile range]=3 [2–5] days *v*. 4 [2–9] days) and to initial weaning off mechanical ventilation (6 [3–18] *v*. 7 [3–24] days) was shorter in the hydrocortisone group; this group also needed blood transfusions less often (37% *v*. 41.7%; OR 0.92; 95% CI 0.72–0.94; p=0.004). However, there was no difference in 28-day mortality, rate of recurrence of shock, the number of days the patients were alive and out of ICU, the number of days patients were alive and out of hospital, rate of need for renal replacement therapy, or rates of new onset bacteraemia or fungaemia in ICU. The effect of hydrocortisone was similar in subgroups based on six pre-specified factors—dose of catecholamine infusion; primary site of sepsis; sex; APACHE II score and duration of shock. These data indicate that a continuous infusion of hydrocortisone does not reduce 90-day mortality in patients with septic shock receiving mechanical ventilation.

The second study is a multicentre double-blind trial that included 1241 patients with septic shock (of <24-hour duration) and evaluated the effect of hydrocortisone plus fludrocortisone, activated protein C, the combination of 3 drugs or their respective placebos. Due to withdrawal of activated protein C from the market in 2011, the trial continued with a parallel 2-group design, with 1 group receiving hydrocortisone plus fludrocortisone versus the other group receiving placebos. Hydrocortisone was given as an intravenous bolus of 50 mg 6 hourly, while fludrocortisone was given enterally (through a nasogastric tube) as a 50 µg tablet once daily. The primary outcome, i.e. 90-day mortality, occurred in 49.1% of subjects in the placebo group versus 43% in the hydrocortisone and fludrocortisone groups, which was statistically significant (p=0.03). The relative risk of death in hydrocortisone plus fludrocortisone group was 0.88 (95% CI 0.78–0.89). There was significant decrease in mortality in the intervention group at ICU discharge (35.4% *v*. 41.0%; p=0.04), hospital discharge (39% *v*. 45.3%; p=0.02) and day 180 (46.6% *v*. 52.5%; p=0.04). The number of days the patients were off vasopressors (17 *v*. 15 days; p<0.001) and were free of organ failure (14 *v*. 12 days; p=0.003) till day 28 was significantly higher in the intervention group than the placebo group. The number of ventilator-free days, as well as the rates of serious adverse events, was similar in both the groups.

COMMENT

Septic shock is defined as a condition with a documented or suspected infection, leading to tissue hypoperfusion in the form of hypotension not responding to fluid administration and requiring vasopressors. Treatment of septic shock includes use of broad-spectrum antibiotics, fluids and vasopressors along with control of the source of infection. The use of corticosteroids in septic shock remains controversial. Until the publication of the above 2 studies, there existed a recommendation, albeit weak, for their use in patients with shock who did not respond to vasopressors.[1] In the wake of this controversy, these 2 trials were undertaken.

Let us first review the effects of corticosteroids in sepsis and specifically, septic shock. These agents have an anti-inflammatory activity, with inhibition of cytokine production and migration of inflammatory cells into the tissues. Besides the anti-inflammatory effect, these drugs increase the vasoactive tone and hence augment the effect of vasopressors. Corticosteroids also improve blood volume through their mineralocorticoid activity and increase systemic vascular resistance, a response mediated through the endothelial glucocorticoid receptors. In septic shock, long-term use of vasopressors can lead to downregulation of adrenergic receptors; the use of steroids prevents this downregulation and hence desensitization; thus helping to maintain blood pressure.

The first trial on the use of corticosteroids in critical care was done by Annane *et al*., a French group, in 2002. They found that the use of corticosteroids in patients with septic shock who did not respond to adrenocorticotropic hormone (ACTH) stimulation test (rise in serum cortisol <9 µg/dl), led to a mortality benefit.[2] They used hydrocortisone along with fludrocortisone, for 7 days, without any weaning from hydrocortisone. However, in a subsequent trial published in 2008 (the Corticus trial), this group found that the administration of corticosteroids did not provide any mortality benefit in either responders or non-responders to ACTH.[3] There were some differences between these 2 trials, i.e. in the Corticus trial, fludrocortisone was not used, weaning doses of hydrocortisone were used and the entry window for patients was much longer, i.e. up to 72 hours after the onset of hypotension (compared to 8 hours in the trial by Annane *et al*.). In 2016, the HYPRESS trial (Hydrocortisone for prevention of septic shock in patients with hospital-acquired sepsis) was published.[4] In this trial, patients

were given corticosteroids pre-emptively to see whether its use prevented development of septic shock in the next 14 days, but with no demonstrable benefit. However, this trial was underpowered to address the effect of hydrocortisone on mortality and did not include patients with septic shock.[4] Meta-analyses and systematic reviews have also not consistently shown any beneficial effects of corticosteroids in septic shock. In view of this conflicting evidence, the Surviving Sepsis Campaign 2016 Guidelines recommended: 'We suggest against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor are able to restore hemodynamic stability. If this is not achievable, we suggest the use of hydrocortisone at a dose of 200 mg/day (weak recommendation, low quality of evidence).'[1]

The 2 current trials were similar with a unique feature that the previous studies did not have, i.e. these included patients with septic shock on mechanical ventilation and who are the sickest even among patients with septic shock. The 2 previous French trials, i.e. Corticus[3] and by Annane *et al*.,[2] included patients with severe sepsis (not necessarily septic shock) and did not have mechanical ventilation as an inclusion criterion.[2,3]

Notably, the 2 current studies had conclusions that were at variance with each other. This makes it important to look at the differences in these 2 trials, and there were a few. First, the mortality rate was 28% in the ADRENAL trial and 43% in the APROCCHSS trial. One of the reasons could be inclusion of fewer medical patients in the ADRENAL trial (31% surgical patients) than in the APROCCHSS trial (18% surgical patients). In surgical patients, source control of infection, which plays an important role in treatment of sepsis, is more often feasible. This difference in case mix could thus explain the lower mortality in the ADRENAL trial. Although it is clear that both trials included seriously ill patients (with similar predicted mortality rates of 40%–50%), but one cannot easily compare the seriousness of disease between the 2 studies, since the ADRENAL trial used APACHE II score and the APROCCHSS trial used SOFA score. Third, renal replacement therapy was needed twice as often in the APROCCHSS trial than in the ADRENAL trial (27.6% *v*. 12.7%). Fourth, patients in the ADRENAL trial had abdominal infections more often whereas those in the APPROCHSS trial had other types of infections (blood stream infections, urinary tract infections, respiratory tract infections) at admission; the latter have higher mortality.

The results of these 2 trials suggest that corticosteroids have a role in weaning patients with septic shock who are on mechanical ventilation off vasopressors and mechanical ventilation and, perhaps, also provide a mortality benefit, as was seen in the APROCCHSS trial. All the previous studies of corticosteroids in septic shock have consistently shown that haemodynamics improved with hydrocortisone. Importantly, both the trials showed that there was no increase in infectious complications in the patients who received corticosteroids.

The difference between the results of the 2 studies could be related to the differing severities of illness in patients in the 2 studies. In septic shock, fluid resuscitation, early antibiotics and initial source control are the most important pillars of management, and it may be naive to think that corticosteroids would act as a magical bullet and cure the condition in everyone. Perhaps, where fluid resuscitation, early antibiotics and control of the source of infection are possible, the addition of corticosteroids does not show an additional benefit. It is in the sickest patients with mortality over 40% that corticosteroids show benefit as in the APROCCHHS trial.[2]

Overall, we believe that corticosteroids form an important part of the intensivists' armamentarium against septic shock, where its use is important in specific situations, such as patients already on long-term corticosteroids and septic shock not responding to administration of fluids and vasopressors. Their use in such selected situations should be beneficial provided emphasis is placed on simultaneous appropriate antibiotics and source control.

Conflicts of interest. None declared

REFERENCES

1 Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, *et al*. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 2017;**43:**304–77.
2 Annane D, Sébille V, Charpentier C, Bollaert PE, François B, Korach JM, *et al*. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002;**288:**862–71. Erratum in: *JAMA* 2008;**300:**1652.
3 Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, *et al*. Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008;**358:**111–24.
4 Keh D, Trips E, Marx G, Wirtz SP, Abduljawwad E, Bercker S, *et al*. Effect of hydrocortisone on development of shock among patients with severe sepsis: The HYPRESS randomized clinical trial. *JAMA* 2016;**316:**1775–85.

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