Steroids and Sepsis

Not Cool

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Disclosures

• The Cincinnati Children’s Hospital Research Foundation and the Speaker have patent applications pending for the biomarker work described in this lecture.

• New Co. launch underway based on the stratification biomarkers described in this lecture—Persepsys Biomedical.
Disclosures

• The speaker has a strong historical bias in favor of using corticosteroids for patients with refractory septic shock.
Hydrocortisone Therapy for Patients with Septic Shock

Charles L. Sprung, M.D., Djillali Annane, M.D., Ph.D., Didier Keh, M.D., Rui Moreno, M.D., Ph.D., Maria Silva, M.D., J.R.C.P., Klaus Fehroggel, Ph.D., Yuriy G. Weiss, M.D., Julie Benenhoul, R.N., Armin Kaltenka, M.D., Helmut Forst, M.D., Ph.D., Pierre-Francois Laterre, M.D., Konrad Reinhard, M.D., Brian H. Cuthbertson, M.D., Didier Payen, M.D., Ph.D., and Josef Briel, M.D., Ph.D., for the CORTICUS Study Group

ABSTRACT

Hydrocortisone is widely used in patients with septic shock even though a survival benefit has been reported only in patients who remained hypotensive after fluid and vasopressor resuscitation and whose plasma cortisol levels did not rise appropriately after the administration of corticotropin.

METHODS

In this multicenter, randomized, double-blind, placebo-controlled trial, we assigned 251 patients to receive 50 mg of intravenous hydrocortisone and 248 patients to receive placebo every 6 hours for 5 days; the dose was then tapered during a 6-day period. At 28 days, the primary outcome was death among patients who did not have a response to corticotropin test.

RESULTS

Of the 499 patients in the study, 233 (46.7%) did not have a response to corticotropin (125 in the hydrocortisone group and 108 in the placebo group). At 28 days, there was no significant difference in mortality between patients in the two study groups who did not have a response to corticotropin (59.6% in the hydrocortisone group and 63.1% in the placebo group; P=0.69) or between those who had a response to corticotropin (78.5% in the hydrocortisone group and 78.7% in the placebo group; P=1.00). At 28 days, 86 of 251 patients in the hydrocortisone group (34.3%) and 78 of 248 patients in the placebo group (31.5%) had died (P=0.51). In the hydrocortisone group, shock was reversed more quickly than in the placebo group. However, there were more episodes of superinfection, including new sepsis and septic shock.

CONCLUSIONS

Hydrocortisone did not improve survival or reversal of shock in patients with septic shock, either overall or in patients who did not have a response to corticotropin, although hydrocortisone hastened reversal of shock in patients in whom shock was reversed.

Caring for the Critically Ill Patient

Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock

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*Members of the CORTICUS Therapy of Sepsis Shock (CORTICUS) study group are listed in the Appendix.


Sepsis remains an important cause of death, accounting for 3.3% of all deaths in the United States in 1999.1 If our understanding of the pathophysiology of sepsis allows us to predict who will respond to stress and has strongly progressed during the last decades,2 the various drugs developed for specific targets of the cytokine cascade have failed to improve patient survival.3,4 Corticosteroids were the first anti-inflammatory drugs tested in randomized trials. At high doses during short courses, they did not induce favorable effects.5 However, the observation that severe sepsis may be associated with relative adrenal insufficiency6 or systemic inflammation-induced glucocorticoid receptor resistance7 prompted renewed interest in a replacement therapy.

Corticosteroids have been used with the aim of improving survival in patients with septic shock and have been part of the standard treatment of patients with septic shock.8 The high incidence of superinfection associated with corticosteroid use is well established, including infection from the gastrointestinal tract and fungal infections.9-11 The use of corticosteroids is associated with a reduced mortality only in patients receiving high doses of corticosteroids.12-14 Corticosteroids are widely used in the treatment of severe sepsis,15 but their use has not been associated with a survival benefit in the treatment of septic shock.16-18 The effects of low-dose corticosteroid therapy on mortality in patients with septic shock have not been evaluated.

METHODS

Participants were randomly assigned to receive either hydrocortisone (50 mg intravenous bolus every 6 hours) and fludrocortisone (50 μg tablet once daily) (n=151) or matching placebo (n=149) for 7 days.

Main Outcome Measure Twenty-eight-day survival distribution in patients with relative adrenal insufficiency (nonresponders to the corticotropin test).

RESULTS One patient from the corticosteroid group was excluded from analyses because of consent withdrawal. There were 229 nonresponders to the corticotropin test (placebo, 115 corticosteroids, 114) and 70 responders to the corticotropin test (placebo, 84 corticosteroids, 36). In nonresponders, there were 73 deaths (63%) in the placebo group and 60 deaths (51%) in the corticosteroid group (hazard ratio, 0.67; 95% confidence interval, 0.47-0.95; P=0.02). Vasopressor therapy was withdrawn within 28 days in 48 patients (40%) in the placebo group and in 65 patients (57%) in the corticosteroid group (hazard ratio, 1.91; 95% confidence interval, 1.29-2.84; P=0.003). There was no significant difference between groups in responders. Adverse events rates were similar in the 2 groups.

Conclusion In our trial, a 7-day treatment with low doses of hydrocortisone and fludrocortisone significantly reduced the risk of death in patients with septic shock and relative adrenal insufficiency without increasing adverse events.

Context Septic shock may be associated with relative adrenal insufficiency. Thus, a replacement therapy of low doses of corticosteroids has been proposed to treat septic shock.

Objective To assess whether low doses of corticosteroids improve 28-day survival in patients with septic shock and relative adrenal insufficiency.


Patients Three hundred adult patients who fulfilled usual criteria for septic shock were enrolled after undergoing a short corticotropin test.

Intervention Patients were randomly assigned to receive either hydrocortisone (50-mg intravenous bolus every 6 hours) and fludrocortisone (50-μg tablet once daily) (n=151) or matching placebo (n=149) for 7 days.

Author Affiliations Service de Réanimation Médicale, Hôpital Raymond Poincaré, Université de Versailles, Faculté de Médecine Paris Ouest, Garches, France (D.J.), Service de Réanimation Médicale, Hôpital Charles Universitaire, Campus St. Joseph, Berlin, Campus Vinzenz Klinikum, Berlin (E.H.K.); Université Libre de Bruxelles, Brussels (P.L.L.); Friedrich Schiller University, Jena, Germany (N.E.R.); Darmstadt University of Technology, Darmstadt (C.B.); Université de Paris, Paris (D.B.); and Klinikum der Universität, Ludwig Maximilians Universität, Munich, Germany (C.B.). Address for reprint requests to Dr. Sprung at the General Intensive Care Unit, Department of Anesthesiology and Critical Care Medicine, Hadassah Hebrew University Medical Center, P.O. Box 10000, Jerusalem, Israel (e-mail: S10523@hadassah.int).

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ADJunctive coRticosteroid trEatment iN criticaLly iLL Patients With Septic Shock (ADRENAL)

This study is currently recruiting participants. (see Contacts and Locations)

Verified April 2014 by The George Institute

Sponsor:
The George Institute

Collaborators:
National Health and Medical Research Council, Australia
Australian and New Zealand Intensive Care Society Clinical Trials Group

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History of Changes

Pediatric Septic Shock Data

- Current guidelines recommend (strongly) the use of adjunctive corticosteroids for refractory shock.
- No large randomized trials.
- Meta-analyses.
- Observational data.
- Anecdotes and experience.
- There is no strong evidence that adjunctive corticosteroids are beneficial in pediatric septic shock.
Meta Analysis

- 447 cases.
- 8 trials, 7 published prior to 1996.
- 6 of 8 trials single center.
- All trials conducted in the developing world.
- 6 of 8 trials involved children with Dengue fever.
- No mortality benefit associated with corticosteroids (RR 0.74; CI$_{95}$ 0.5 – 1.2; $p = 0.197$)
Observational Data


- Review of a national administrative database.
- 6,693 cases.
- Corticosteroids independently associated with increased mortality (OR 1.6; CI$_{95}$ 1.1 – 1.4).
- Not adjusted for illness severity.
Observational Data


- Review of the pediatric APC trial (RESOLVE).
- 477 subjects (193 received corticosteroids).
- Similar severity of illness between groups.
- Mortality the same between groups.
This is about the best that we have!
Recent Data

Multi-center clinical and biological repository of pediatric septic shock

• How do corticosteroids impact the genome-wide response in children with septic shock?
• Are the beneficial effects of corticosteroids in pediatric septic shock dependent on initial mortality risk?
Recent Data

Multi-center clinical and biological repository of pediatric septic shock

• How do corticosteroids impact the genome-wide response in children with septic shock?

• Are the beneficial effects of corticosteroids in pediatric septic shock dependent on initial mortality risk?
How do corticosteroids impact gene expression in children with septic shock?

• Compared gene expression in children with septic shock who received corticosteroids and those who did not receive corticosteroids:
  – 70 treated with corticosteroids
  – 110 not treated with corticosteroids.

• No difference regarding illness severity, organ failure burden, or mortality.
319 genes different between the two groups.

A majority of these genes corresponded to the adaptive immune system.

These adaptive immunity genes were repressed in the group that received steroids, compared to those who did not.
Recent Data

Multi-center clinical and biological repository of pediatric septic shock

• How do corticosteroids impact the genome-wide response in children with septic shock?

• Are the beneficial effects of corticosteroids in pediatric septic shock dependent on initial mortality risk?
Low-Dose Corticosteroid Treatment in Septic Shock: A Propensity-Matching Study*

Duane Funk, MD1,2; Steven Doucette, MSc3; Amarnath Pisipati, MSc1; Peter Dodek, MD3; John C. Marshall, MD4; Anand Kumar, MD4; the Cooperative Antimicrobial Therapy of Septic Shock Database Research Group

Objective: Given conflicting data and current guidelines, low-dose corticosteroids are often used in the treatment of septic shock. To evaluate the therapeutic benefit of early low-dose corticosteroid in patients with septic shock.

Design: Retrospective, multicenter, propensity-matched cohort study.


Subjects: Six thousand six hundred sixty-three eligible patients with septic shock of whom 1,838 received IV low-dose corticosteroid treatment within 48 hours of the diagnosis of septic shock and were matched to a comparable group who did not receive low-dose corticosteroid.

Measurements and Main Results: The primary outcome was 30-day mortality. Mortality analyses were stratified by severity of illness (Acute Physiology and Chronic Health Evaluation II quartile). Using a Cox proportional hazards model, corticosteroid therapy was associated with similar 30-day mortality when compared with the matched control cohort (65/1,838 [35.6%] vs 641/1,838 [34.9%]; hazard ratio, 0.98; 95% CI, 0.88–1.10; p = 0.77). In the subgroup of patients with the acute physiology and chronic health evaluation II score quartile more than or equal to 30, low-dose corticosteroid was associated with lower mortality (292/481 [50.6%] vs 261/450 [55.8%]; hazard ratio, 0.81; 95% CI, 0.68–0.97; p = 0.02). In logistic regression models, corticosteroid therapy was not associated with reductions in ICU (65/1,838 [30.3%] vs 566/1,838 [30.4%]; odds ratio, 0.99; 95% CI, 0.86–1.15; p = 0.94) or hospital mortality (797/1,838 [43.4%] vs 773/1,838 [42.1%]; odds ratio, 1.05; 95% CI, 0.93–1.20; p = 0.42). Similarly, there were no significant differences in ventilation-free days (median and interquartile range, 13 [0–26] vs 15 [0–25]; p = 0.8) and pressor/infotrope-free days (median and interquartile range, 25 [3–27] vs 24 [2–28]; p = 0.63) up to 30 days between groups.

Conclusion: Early administration of low-dose corticosteroid is not associated with decreased mortality when it is administered to unselected patients with septic shock. A beneficial effect of low-dose corticosteroid on mortality may exist in patients with the highest severity of illness. Future trials of low-dose corticosteroid.

- Retrospective, propensity-matched cohort.
- 6,663 subjects, 28 hospitals, 3 countries.
- 31% received steroids.
- Subjects stratified into quartiles of illness severity (APACHE II).
- Steroids associated with a mortality reduction in subjects within the highest quartile (APACHE ≥ 30).
- H.R. 0.8; CI95 0.7 – 1.1 p = 0.02
Corticosteroids and Pediatric Septic Shock Outcomes

A Risk Stratified Analysis

• 496 children with septic shock
• 18 pediatric centers in the U.S.
• Approximately half received corticosteroids.
• Stratified according to “PERSEVERE”.
  – A multi-biomarker-based risk model to assign a mortality probability.
• 3 mortality risk strata:
  – Low: \( \leq 2.5\% \)
  – Intermediate: >2.5 \%, up to 27%.
  – High: >27\%
Corticosteroids and Pediatric Septic Shock Outcomes

*A Risk Stratified Analysis*

• Primary outcome variable: all cause 28 day mortality.

• Secondary outcome variable: “complicated course”:
  – Death within 28 days or persistence of ≥2 organ failures on day 7 of septic shock.

• Logistic regression **within risk strata** to test the association between corticosteroids and outcome.
### Association between corticosteroids and mortality

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Secondary Analyses

• Stratification based on PRISM.
• Risk stratification limited to children without comorbidities (n = 321).
• Same results: could not detect a beneficial effect of corticosteroids in any risk group.
Where does this leave us?

• We (the pediatric critical care community) should be willing to randomize our “sickest” patients in a trial testing the efficacy of adjunctive corticosteroids for septic shock.

• Which of your patients is most likely to benefit from adjunctive corticosteroids?
  – *The ACTH test does not seem to be enough*...
Reduced Cortisol Metabolism during Critical Illness

Eva Boonen, M.D., Hilde Vervenne, Ph.D., Philippe Meersseman, M.D., Ruth Andrei, Ph.D., Leen Mortier, Ph.D., Peter E. Declercq, Pharm.D., Ph.D., Tsoo-Meei Vanwijngaarden, M.D., Isabel Spriet, Pharm.D., Ph.D., Pieter J. Wouters, M.Sc., Sarah Vander Perre, B.Sc., Lies Langouche, Ph.D., Ilse Vanhoebeek, Ph.D., Brian R. Walker, M.D., and Greet Van den Berghe, M.D., Ph.D.

ABSTRACT

BACKGROUND
Critical illness is often accompanied by hypercortisolemia, which has been attributed to stress-induced activation of the hypothalamic–pituitary–adrenal axis. However, low corticotropin levels have also been reported in critically ill patients, which may be due to reduced cortisol metabolism.

METHODS
In a total of 158 patients in the intensive care unit and 64 matched controls, we tested five aspects of cortisol metabolism: daily levels of corticotropin and cortisol; plasma cortisol clearance, metabolism, and production after infusion of deuterium-labeled steroid hormones as tracers; plasma clearance of 100 mg of hydrocortisone; levels of urinary cortisol metabolites; and levels of messenger RNA and protein in liver and adipose tissue, to assess major cortisol-metabolizing enzymes.

RESULTS
Total and free circulating cortisol levels were consistently higher in the patients than in controls, whereas corticotropin levels were lower (P<0.001 for both comparisons). Cortisol production was 89% higher in the patients (P<0.02). There was a reduction of more than 50% in cortisol clearance during tracer infusion and after the administration of 100 mg of hydrocortisone in the patients (P<0.05 for both comparisons). All these factors accounted for an increase by a factor of 3.5 in plasma cortisol levels in the patients, as compared with controls (P<0.001). Impaired cortisol clearance also correlated with a lower cortisol response to corticotropin stimulation. Reduced cortisol metabolism was associated with reduced inactivation of cortisol in the liver and kidney, as suggested by urinary steroid ratios, tracer kinetics, and assessment of liver-biopsy samples (P<0.004 for all comparisons).

CONCLUSIONS
During critical illness, reduced cortisol breakdown, related to suppressed expression and activity of cortisol-metabolizing enzymes, contributed to hypercortisolemia and hence corticotropin suppression. The diagnostic and therapeutic implications for critically ill patients are unknown. (Funded by the Belgian Fund for Scientific Research and others; ClinicalTrials.gov numbers, NCT00512122 and NCT00115479; and Current Controlled Trials numbers, ISRCTN49433936, ISRCTN49300926, and ISRCTN08083905.)
A Single Nucleotide Polymorphism in the Corticotropin Receptor Gene Is Associated With a Blunted Cortisol Response During Pediatric Critical Illness*

David Jardine, MD; Mary Emond, PhD; Kathleen L. Meert, MD; Rick Harrison, MD; Joseph A. Caccilo, MD; Kanwaljeet J. S. Anand, MBBS, DPhil; John Berger, MD; Christopher J. L. Newth, MD, FRCPC; Douglas F. Wilson, MD; Carol Nicholson, MD; J. Michael Dean, MD; and Jerry J. Zimmerman, MD, PhD, for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network

Objectives: The cortisol response during critical illness varies widely among patients. Our objective was to examine single nucleotide polymorphisms in candidate genes regulating cortisol synthesis, metabolism, and activity to determine if genetic differences were associated with variability in the cortisol response among critically ill children.

Design: This was a prospective observational study employing tag single nucleotide polymorphism methodology to examine genetic

1. OneHDD49945-05S1

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- Studied SNPs in various genes for cortisol synthesis, metabolism, and activity.
- 92 critically ill children.
- SNP (rs1941088) in the gene encoding the ACTH receptor.
- AA genotype was associated with 7 times the risk of having a blunted cortisol response during critical illness.
- A genetic basis to account for cortisol response variability during critical illness.
Gene Expression-Based Subclasses of Pediatric Septic Shock

- A 100 gene expression signature that differentiates children with septic shock.
- Subclasses “A” and “B”.
- Logistic regression adjusting for illness severity, age, and comorbidity: allocation to subclass A is independently associated with mortality (O.R. = 2.8).
Have now evaluated 300 patients with this approach....

- The genes that enable sub classification correspond to adaptive immunity and the glucocorticoid receptor signaling pathway.
- These genes are repressed in the subclass A patients.
- “Theranostic” implications.
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- The genes that enable sub classification correspond to adaptive immunity and the glucocorticoid receptor signaling pathway.
- These genes are repressed in the subclass A patients.
- “Theranostic” implications.
- The use of corticosteroids is independently associated with 4 times the risk of dying in the subclass A patients.
• Digital mRNA measurements.
• Reactions in solution phase.
• No amplification step.
• Color-coded reporter probes allow for assays to be run within the time constraints of the ICU.
Measuring Glucocorticoid Receptor (GCR) Expression in Critically Ill Children

- Flow cytometry based protocol to quantify GCR expression peripheral WBCs.
- Estimate associations between GCR expression and clinical phenotypes.
Preliminary Data: *GCR expression is inversely related to illness severity*

Patients grouped based on presence or absence of cardiovascular (CV) failure.

Patients grouped based on ≤ 1 organ failing, or > 1 organs failing.
Preliminary Data: There is no correlation between GCR expression and serum cortisol concentrations.
Summary

- Adult intensivists have large randomized trials to inform their decision-making surrounding adjunctive corticosteroids for septic shock.
- Pediatric intensivists do not.
- The available pediatric evidence is not consistent with a beneficial effect.
- A randomized trial is warranted, and “we” should be willing to randomize.
- Phenotyping, beyond the ACTH stimulation test, may allow for better selection of patients more likely to respond favorably.
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