Development of a definitive RCT of steroids in critically ill patients

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THE INFLUENCE OF THE ADRENAL GLANDS ON RESISTANCE.

II. THE TOXIC EFFECT OF KILLED BACTERIA IN ADRENALECTOMIZED RATS.

CONCLUSION.

1. The resistance of rats to bacterial intoxication is greatly decreased after double adrenalectomy.

2. This decreased resistance is dependent upon a functional insufficiency of the adrenal cortex.

3. A dose of killed streptococci or staphylococci can be obtained that is invariably fatal to adrenalectomized rats, before hypertrophy of cortical accessories, but never kills control rats.
CORTISOL SECRETION DURING ACUTE BACTERIAL INFECTIONS IN MAN

Summary of results in ten subjects during the acute period of illness and after recovery.

<table>
<thead>
<tr>
<th></th>
<th>Acute stage mean ± S. D.</th>
<th>Recovery mean ± S. D.</th>
<th>Significance $P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol secretion rate (CSR) (mg/d)</td>
<td>37.8 ± 8.3</td>
<td>21.0 ± 7.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Urinary 11-deoxysteroids (mg/d)</td>
<td>1.9 ± 1.3</td>
<td>0.9 ± 0.4</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Urinary 11-oxysteroids (mg/d)</td>
<td>11.0 ± 4.7</td>
<td>7.4 ± 2.2</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Total 17-ketogenic steroids (mg/d)</td>
<td>12.9 ± 5.4</td>
<td>8.2 ± 2.4</td>
<td>&lt; 0.025</td>
</tr>
<tr>
<td>CSR / 11-oxysteroids</td>
<td>3.54 ± 0.77</td>
<td>2.83 ± 0.61</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>11-deoxy- / 11-oxysteroids</td>
<td>0.18 ± 0.14</td>
<td>0.12 ± 0.04</td>
<td>&gt; 0.20</td>
</tr>
<tr>
<td>Urinary radioactivity 0–24 h (%) of administered radioactivity</td>
<td>81.0 ± 5.8</td>
<td>82.5 ± 5.7</td>
<td>&gt; 0.30</td>
</tr>
<tr>
<td>Urinary radioactivity 0–48 h (%) of administered radioactivity</td>
<td>88.2 ± 6.7</td>
<td>88.8 ± 7.0</td>
<td>&gt; 0.80</td>
</tr>
</tbody>
</table>
Hormonal Responses to Graded Surgical Stress

*P<.05 Compared With Baseline
†P<.05 Compared With Grade 1
Steroid therapy in sepsis

1950

Steroid success era

Mid 80s

REDUCTION OF MORTALITY IN CHLORAMPHENICOL-TREATED SEVERE TYPHOID FEVER BY HIGH-DOSE DEXAMETHASONE


THE NEW ENGLAND JOURNAL OF MEDICINE

Jan. 12, 1984
Steroid therapy in sepsis

1950 - Steroid success era

1980 - Steroid excess
The New England Journal of Medicine

Volume 311, November 1, 1984, Number 18

THE EFFECTS OF HIGH-DOSE CORTICOSTEROIDS IN PATIENTS WITH SEPTIC SHOCK
A Prospective, Controlled Study
CHARLES L. SPRUNG, M.D., PANAGIOTA V. CARALIS, M.D., EILEEN H. MARCIAL, R.R.T.,
MARGARET PIERCE, R.N., MARK A. GELBARD, M.D., WILLIAM M. LONG, PH.D., ROBERT C. DUNCAN, PH.D.,
MOSES D. TENDLER, PH.D., AND MICHAEL KARPF, M.D.

N=59
MPS / DXM
Decreased early mortality

The New England Journal of Medicine

Volume 317, September 10, 1987, Number 11

A CONTROLLED CLINICAL TRIAL OF HIGH-DOSE METHYLPREDNISOLONE IN THE
TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK
ROGER C. BONE, M.D., CHARLES J. FISHER, JR., M.D., TERRY P. CLEMMER, M.D.,
GUS J. SLOTMAN, M.D., CRAIG A. METZ, M.S., ROBERT A. BALK, M.D.,
AND THE METHYLPREDNISOLONE SEVERE SEPSIS STUDY GROUP

N=382
Methyldpred 30mg/kg
Increased mortality
Steroid therapy in sepsis

1950: Steroid success era
1990: Steroid excess | Uncertainty
2000+: Resurgence in interest
Prospective
Double-blind
Multicentred (19 centres France 1995-1999)
Placebo controlled trial

Comparison of hydrocortisone (50mg 6h x 7days) + fludrocortisone vs placebo in patients with septic shock

**Primary outcome:**
28-day mortality in “non-responders”

**Secondary outcomes:**
28-day and 90-day mortality (all patients, “responders”)
Reversal of shock

n=300

Annane: JAMA 2002
Prospective
Double-blind
Multicentred (19 centres France 1995-1999)
Placebo controlled trial

Comparison of hydrocortisone (50mg 6h x 7days) + fludrocortisone vs placebo in patients with septic shock

No difference in landmark mortality

After adjustment: Improved mortality in “non responders:
60/114 vs 72/115 :p-0.02

Annane: JAMA 2002
Prospective
Double-blind
Multicentred (52 centres Europe)
Placebo controlled trial

Comparison of infusions of hydrocortisone (50mg 6h x 5days, tapered to day 11) vs placebo in patients with septic shock

Primary outcome:
28-day mortality in “non-responders”

Secondary outcomes:
28-day and 90-day mortality (all patients, “responders”)
Reversal of shock

n=800

Sprung: NEJM 2008
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., Mervyn Singer, M.D., F.R.C.P., Klaus Freivogel, Ph.D., Yoram G. Weiss, M.D., Julie Benbenishty, R.N., Armin Kalenka, M.D., Helmuth Forst, M.D., Ph.D., Pierre-Francois Laterre, M.D., Konrad Reinhart, M.D., Brian H. Cuthbertson, M.D., Didier Payen, M.D., Ph.D., and Josef Briegel, M.D., Ph.D., for the CORTICUS Study Group*

Primary outcome

A No Response to Corticotropin

B All Patients

125/252 (49.6%) v 108/248 (43.5%)

N=500/800

28-day mortality

28-day mortality

Sprung: NEJM 2008
### Steroids and shock reversal

#### Shock reversal at day 7

<table>
<thead>
<tr>
<th>Source</th>
<th>Treatment, No.</th>
<th>Control, No.</th>
<th>Risk Ratio (95% CI)</th>
<th>Favors Control</th>
<th>Favors Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total Patients</td>
<td>Events</td>
<td>Total Patients</td>
<td></td>
</tr>
<tr>
<td>Sprung et al., 1984</td>
<td>25</td>
<td>43</td>
<td>6</td>
<td>16</td>
<td>1.55 (0.78-3.06)</td>
</tr>
<tr>
<td>Bone et al., 1987</td>
<td>85</td>
<td>130</td>
<td>83</td>
<td>114</td>
<td>0.90 (0.76-1.06)</td>
</tr>
<tr>
<td>Bollaert et al., 1998</td>
<td>15</td>
<td>22</td>
<td>4</td>
<td>19</td>
<td>3.24 (1.30-8.10)</td>
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<tr>
<td>Chawla et al., 1999</td>
<td>16</td>
<td>23</td>
<td>9</td>
<td>21</td>
<td>1.62 (0.92-2.85)</td>
</tr>
<tr>
<td>Briegel et al., 1999</td>
<td>17</td>
<td>20</td>
<td>12</td>
<td>20</td>
<td>1.42 (0.95-2.12)</td>
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<tr>
<td>Annane et al., 2002</td>
<td>60</td>
<td>151</td>
<td>40</td>
<td>149</td>
<td>1.48 (1.06-2.06)</td>
</tr>
<tr>
<td>Oppert et al., 2005</td>
<td>14</td>
<td>18</td>
<td>16</td>
<td>23</td>
<td>1.12 (0.78-1.61)</td>
</tr>
<tr>
<td>Sprung et al., 2008</td>
<td>186</td>
<td>251</td>
<td>145</td>
<td>248</td>
<td>1.27 (1.12-1.44)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td><strong>418</strong></td>
<td><strong>658</strong></td>
<td><strong>315</strong></td>
<td><strong>610</strong></td>
<td><strong>1.29 (1.06-1.58)</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\tau = 0.04; \chi^2 = 21.48, \text{df} = 7 (P = .003); I^2 = 67\%$

Test for overall effect: $z = 2.51 (P = .01)$
### Steroids and mortality

**Figure 3. Twenty-Eight-Day Mortality by Subgroup Based on Dose/Duration of Corticosteroid Therapy**

<table>
<thead>
<tr>
<th>Source</th>
<th>Treatment, No.</th>
<th>Control, No.</th>
<th>Risk Ratio (95% CI)</th>
<th>Favors Treatment</th>
<th>Favors Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total Patients</td>
<td>Events</td>
<td>Total Patients</td>
<td></td>
</tr>
<tr>
<td>Long course of low-dose corticosteroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bollaert et al,15 1998</td>
<td>7</td>
<td>22</td>
<td>12</td>
<td>19</td>
<td>0.50 (0.25-1.02)</td>
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<tr>
<td>Chawla et al,17 1999</td>
<td>6</td>
<td>23</td>
<td>10</td>
<td>21</td>
<td>0.55 (0.24-1.25)</td>
</tr>
<tr>
<td>Briegel et al,16 1999</td>
<td>3</td>
<td>20</td>
<td>4</td>
<td>20</td>
<td>0.75 (0.19-2.93)</td>
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<tr>
<td>Yildiz et al,19 2002</td>
<td>8</td>
<td>20</td>
<td>12</td>
<td>20</td>
<td>0.67 (0.35-1.27)</td>
</tr>
<tr>
<td>Annane et al,18 2002</td>
<td>82</td>
<td>151</td>
<td>91</td>
<td>149</td>
<td>0.89 (0.73-1.08)</td>
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<tr>
<td>Confalonieri et al,50 2005</td>
<td>0</td>
<td>23</td>
<td>6</td>
<td>23</td>
<td>0.08 (0.00-1.29)</td>
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<tr>
<td>Tandan et al,52 2005</td>
<td>11</td>
<td>14</td>
<td>13</td>
<td>14</td>
<td>0.85 (0.62-1.15)</td>
</tr>
<tr>
<td>Oppert et al,51 2005</td>
<td>10</td>
<td>23</td>
<td>11</td>
<td>25</td>
<td>0.99 (0.52-1.88)</td>
</tr>
<tr>
<td>Rinaldi et al,53 2006</td>
<td>6</td>
<td>26</td>
<td>7</td>
<td>26</td>
<td>0.86 (0.33-2.21)</td>
</tr>
<tr>
<td>Meciuri et al,56 2007</td>
<td>10</td>
<td>42</td>
<td>8</td>
<td>19</td>
<td>0.57 (0.27-1.20)</td>
</tr>
<tr>
<td>Cicarelli et al,55 2007</td>
<td>7</td>
<td>14</td>
<td>12</td>
<td>15</td>
<td>0.63 (0.35-1.12)</td>
</tr>
<tr>
<td>Sprung et al,22 2008</td>
<td>86</td>
<td>251</td>
<td>78</td>
<td>248</td>
<td>1.09 (0.85-1.40)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>236</td>
<td>629</td>
<td>264</td>
<td>599</td>
<td>0.84 (0.72-0.97)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: τ = 0.01; χ² = 12.89, df = 11 (P = .30); I² = 15%
Test for overall effect: z = 2.31 (P = .02)
Rationale for a definitive trial

“After more than 50 years of research, we are still dogged by uncertainty and confusion”

- Steroids of benefit in discrete focal septic states
- Steroids improve pressor responsiveness in SS
- High dose steroids increase mortality in SS
- Low dose steroids effect on mortality in SS
Global utilization of low-dose corticosteroids in severe sepsis and septic shock: a report from the PROGRESS registry

2002 - 2005
276 centres
8986 patients
With respect to the treatment of sepsis or septic shock with steroids, which of the following best describes your usual practice? I will consider prescribing steroids.

- if noradrenaline or adrenaline dose exceeds 0.1 mcg/kg/min or dopamine... 28%
- if noradrenaline or adrenaline dose exceeds 0.15 mcg/kg/min or dopamine... 53%
- if noradrenaline or adrenaline dose exceeds 0.2 mcg/kg/min or dopamine...
- never or rarely prescribe steroids
The quest for meaningful outcomes

NICE-SUGAR: NEJM 2009

DECRA: NEJM 2011
Adjunctive corticosteroid treatment in critically ill patients with septic shock
Funding

Project Grant: Large Scale Clinical Trials
October 2011
To determine whether hydrocortisone therapy reduces all-cause day 90 mortality in patients admitted to an Intensive Care Unit with septic shock.
Design and oversight

Investigator-initiated, multicenter, prospective, blinded, parallel-group, randomised-controlled trial

55 adult medical-surgical ICUs in Australia and New Zealand

Lead ethics committee and institutional ethics committee approval:
- Written, informed consent pre-randomization OR
- Delayed consent from each patient, surrogate or IEC
ADJUNCTIVE CORTICOSTEROID TREATMENT IN CRITICALLY ILL PATIENTS WITH SEPTIC SHOCK (ADRENAL)

This study is not yet open for participant recruitment.
Verified February 2012 by The George Institute

First received on October 5, 2011. Last updated on February 22, 2012

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>The George Institute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collaborators</td>
<td>National Health and Medical Research Council, Australia, Australian and New Zealand Intensive Care Society Clinical Trials Group</td>
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<tr>
<td>Information provided by (Responsible Party)</td>
<td>The George Institute</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT01448109</td>
</tr>
</tbody>
</table>

**Trial Registration**

- **ACTR Number**: ACTRN12611001042932
- **ANZCTR Registration Title**: A multi-centre, blinded, randomised, placebo controlled trial to determine whether hydrocortisone therapy reduces 90-day mortality in patients admitted to intensive Care with septic shock.
- **Recruitment Status**: Not yet recruiting
- **Date Registered**: 5/10/2011
- **Start Date**: 1/02/2012
- **Prospective registration**: Yes
- **Ethics Approval**: Yes
Inclusion criteria

Adult patients.

Documented site / strong suspicion of infection
  At least 2 SIRS criteria
  Shock attributable to sepsis

Need for catecholamines
  MAP > 60
  Duration > 4 hours and present at randomisation

Requirement for positive pressure ventilation

No requirement for corticotropin response
Exclusion criteria

Clinical indication for systemic corticosteroids

Met all inclusion criteria > 24 hours ago

Death is deemed imminent and inevitable. An underlying disease process with a life expectancy of < 90 days
Design

Power

Assuming 5% loss to follow-up

To detection ARR 5% (15% RRR) from baseline mortality of 33% ($\alpha=0.05; \beta 0.9$)

$n=3800$
Outcomes

All-cause mortality at 90 days

- Interval mortality rates
- Resolution of shock
- Length of ventilation
- Re-intubation rate/tracheostomy
- RRT
- Recurrence of shock
- Bacteraemia (positive blood culture between 2-12 days post randomisation)
- Bleeding rates (>3U blood >2 consecutive days)

- Quality of life assessment (12 months)
- Health economics assessment
Study treatment

200 mg hydrocortisone/day given as an intravenous infusion over 24 hours for 7 days or till discharge from ICU

OR

placebo given as an intravenous infusion over 24 hours for 7 days or till discharge from ICU

Study treatments supplied in identical vials
Progress

NHMRC project grant received 2010

Management Committee
Operation committee
Ethics clearance

Sourcing placebo and study drug

FPI
  October 2011
  Inception period 5 years = 500 patients /year.

Site selection:
  At least 50 in ANZ
  International collaboration 20-30 sites