Steroids in Septic Shock: An Update

Charles L. Sprung, M.D.
Surviving Sepsis Campaign (SSC) Guidelines - Steroids

- Treat patients who still require vasopressors despite fluid replacement with hydrocortisone 200-300 mg/day, for 7 days in three or four divided doses or by continuous infusion.

  Grade C

- Optional:
  - Adrenocorticotropic hormone (ACTH) stimulation test (250-µg)
  - Continue treatment only in nonresponders (delta cortisol $\leq$ 9 µg/dl)

  Grade E

Dellinger P. Crit Care Med 2004;32:858-873
STEROID THERAPY OF SEPTIC SHOCK

• 18 YEARS OR OLDER
• DOCUMENTED INFECTION OR SUSPICION
• TEMPERATURE > 38.3°C OR < 35.6°C
• HEART RATE > 90 BEATS/MIN
• SBP < 90 mmHg > 1 HR DESPITE FLUID & VP
• UO < 0.5 ml/kg/hr OR PaO2/FIO2 < 280
• NEED FOR MECHANICAL VENTILATION
• ACTH STIMULATION TEST

Annane D. JAMA 2002:288:862-871
Hazard Ratio: 0.71 (95% CI, 0.53-0.97)

\( p = 0.03 \)

Annane JAMA 2002;288:862-871
28-Day Survival

Hazard Ratio: 0.67 (95% CI, 0.47-0.95)

p = 0.02

Annane JAMA 2002;288:862-871
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., Helmut 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*

Sprung CL. 2008;358:111-124
RESULTS: 28-day mortality - all patients

Sprung CL. NEJM 2008;358:111-124

% mortality

P = 0.51
RESULTS: 28-day mortality - by response to ACTH stimulation

Sprung CL. NEJM 2008;358:111-124

% mortality

Responders

<table>
<thead>
<tr>
<th></th>
<th>Steroids (n=118)</th>
<th>Placebo (n=136)</th>
<th>P = 1.000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>34 (28.8%)</td>
<td>39 (28.7%)</td>
<td></td>
</tr>
</tbody>
</table>

Non-responders

<table>
<thead>
<tr>
<th></th>
<th>Steroids (n=125)</th>
<th>Placebo (n=108)</th>
<th>P = 0.69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>49 (39.2%)</td>
<td>39 (36.1%)</td>
<td></td>
</tr>
</tbody>
</table>

P = 1.000

P = 0.69
## RESULTS
Reversal of shock

<table>
<thead>
<tr>
<th></th>
<th>Steroids (n=251)</th>
<th>Placebo (n=248)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>200 (79.7%)</td>
<td>184 (74.2%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Non-responders</td>
<td>95 (76.0%)</td>
<td>76 (70.4%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Responders</td>
<td>100 (84.7%)</td>
<td>104 (76.5%)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Sprung CL. NEJM 2008;358:111-124
RESULTS: Time to reversal of shock
Median time in days (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Steroids (n=251)</th>
<th>Placebo (n=248)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>3.3 (2.9-3.9)</td>
<td>5.8 (5.2-6.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Non-responders</td>
<td>3.9 (3.0-5.2)</td>
<td>6.0 (4.9-9.0)</td>
<td>0.056</td>
</tr>
<tr>
<td>Responders</td>
<td>2.8 (2.1-3.3)</td>
<td>5.8 (5.2-6.9)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Sprung CL. NEJM 2008;358:111-124
## Frequency of superinfections

<table>
<thead>
<tr>
<th></th>
<th>Steroids (n=234)</th>
<th>Placebo (n=232)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superinfection</td>
<td>78 (33%)</td>
<td>61 (26%)</td>
</tr>
<tr>
<td>No superinfection</td>
<td>156 (67%)</td>
<td>171 (74%)</td>
</tr>
</tbody>
</table>

**SI- Relative risk (95% CI) = 1.27 (0.96-1.68)**

**SI+ new S + SS- Relative risk (95% CI) = 1.37 (1.05-1.79)**

Sprung CL. NEJM 2008;358:111-124
## 28-day Mortality

<table>
<thead>
<tr>
<th></th>
<th>Annane</th>
<th>Corticus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>82/150 (55%)</td>
<td>86/251 (34.3%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>91/149 (61%)</td>
<td>78/248 (31.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>173/299 (58%)</td>
<td>164/499 (32.9%)</td>
</tr>
<tr>
<td>Study Differences</td>
<td>Annane</td>
<td>Corticus</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Entry window</td>
<td>8 hours</td>
<td>72 hours</td>
</tr>
<tr>
<td>SBP &lt; 90 mmHg</td>
<td>&gt; 1 hour</td>
<td>&lt; 1 hour</td>
</tr>
<tr>
<td>Treatment</td>
<td>Fludrocortisone</td>
<td>None</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>7 days</td>
<td>11 days</td>
</tr>
<tr>
<td>Weaning</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Practice/Guidelines</td>
<td>None</td>
<td>Steroids used</td>
</tr>
<tr>
<td>SAPS II</td>
<td>59 ± 21</td>
<td>49 ± 17</td>
</tr>
<tr>
<td>Non-responders</td>
<td>229 (77%)</td>
<td>233 (47%)</td>
</tr>
</tbody>
</table>
Steroid Meta-analyses

- Marik et al and Sligl et al meta-analyses evaluated only patients treated with low doses of corticosteroids who were in septic shock

- Steroids provided no benefit in decreasing mortality, a benefit in reversing septic shock and overall no difference in superinfections

  Sligl WI. Clinical Infectious Diseases 2009;49:93–101

- Similar to Corticus study findings
Steroid Meta-analyses

- If steroids do indeed improve shock reversal, why is this not translated into an improved survival?
- Although there is no greater statistically significant difference in adverse effects in the steroid-treated patients, there is some unidentified steroid effect which although improving shock reversal does not lead to an improved survival.
Steroid Meta-analyses

• What should the endpoint for steroid therapy be?
• As steroids work by enhancing vasomotor tone via their interaction with adrenergic receptors and are acting similar to vasopressors, then reversing shock might be an acceptable endpoint.
• Unfortunately, the actions of corticosteroids are not just like those of a vasopressor.
• Steroids are also anti-inflammatory agents with potent adverse effects.
Steroid Meta-analyses

• If there is no improved survival benefit by using steroids and shock reversal maybe merely a 'disguised' vasopressor effect of steroids because of its vasomotor properties, there is no advantage for using steroids than standard vasopressor agents which have far less side effects.

• A few additional days of norepinephrine therapy are probably a better therapeutic choice than steroids.
STEROID USE

- Doctors see the reversal of shock very quickly and associate the improvement to steroid use.

- Doctors do not associate the late complications with steroids as they are not temporally related.

- These include superinfections, new sepsis, new septic shock and CMV.
STEROID USE

- When should steroids be used?
- Without a strong signal for a decrease in mortality with steroid therapy, physicians should not be using steroids for all patients in septic shock.
- Only in patients with severe septic shock meeting the Annane et al entry criteria of a systolic blood pressure < 90 mmHg for more than one hour where steroids did improve survival.

Sprung CL. Intensive Care Med 2012;38:1911-1913
Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock

Slide Presentations


http://www.survivingsepsis.org/Resources/Pages/Media.aspx

Dellinger RP. Crit Care Med. 2013;41:580–637
Dellinger RP. Intensive Care Med. 2013;39:165-228
We suggest not using intravenous hydrocortisone in adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. In case this is not achievable, we suggest intravenous hydrocortisone at a maximum dose of 200 mg per day. Grade 2C

Annane JAMA 2002;288:862-871
Sprung CL. NEJM 2008;358:111-124
Dellinger P. Crit Care Med 2013; 41:580–637
Surviving Sepsis Campaign (SSC) 2012 Guidelines - Steroids

• We suggest not using the ACTH stimulation test to identify the subset of adults with septic shock who should receive hydrocortisone. Grade 2B
  Sprung CL. NEJM 2008;358:111-124

• We recommend that hydrocortisone alone be used instead of hydrocortisone plus fludrocortisone. Grade 1B
  Annane D. COllTSS Investigators. JAMA 2010;303:341-348
  Dellinger P. Crit Care Med 2013; 41:580–637
Surviving Sepsis Campaign (SSC) 2012 Guidelines- Steroids

- We suggest that clinicians taper the patient from steroid therapy when vasopressors are no longer required.  
  Grade 2D  
  Keh  AJRCCM 2003; 167:512-520

- We recommend use of 200 mg of hydrocortisone daily rather than higher doses in septic shock.  
  Grade 1A  
  Bone, et al.  NEJM 1987; 317:658  
  VA Sepsis Study Group.  NEJM 1987; 317:659-665  
  Dellinger P.  Crit Care Med 2013; 41:580–637
**Surviving Sepsis Campaign (SSC) 2012 Guidelines - Steroids**

- We recommend that corticosteroids not be administered for the treatment of sepsis in the absence of shock.  
  **Grade 1D**

- When low-dose hydrocortisone is given, we suggest using continuous infusion rather than repetitive bolus injections.  
  **Grade 2C**


  Dellinger P. *Crit Care Med* 2013; 41:580–637
ADRENAL TRIAL

- Prospective, randomized, double-blind, placebo-controlled trial of hydrocortisone 200 mg or placebo daily for 7 days as a continuous intravenous infusion

- 3800 ICU patients with septic shock will be evaluated for all cause mortality at 90 days.

- Entry criteria - Documented site of infection with 2 of 4 clinical signs of inflammation, mechanical ventilation, vasopressors or inotropes for 4 hours to maintain a SBP > 90mmHg or MAP > 60mmHg or a MAP target for maintaining perfusion.
Steroids For Treatment of Infections, Sepsis and Septic Shock - *Ups and Downs*

- Weizmann (review) 1974
- Schumer 1976
- Sprung 1984
- VA-Coop Bone 1987
- Cronin Lefering (meta-analyses) 1995
- Bollaert 1998
- Briegal 1999
- Annane 2002
- Surviving Sepsis Campaign 2004
- Corticus 2008

Used in Clinical Practice

YES

„high-dose“

„low-dose“