Corticosteroids in Sepsis

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Conflict of Interest

- I am a clinical practice guideline methodologist for SCCM, ATS, ERS, Canadian Blood Services, ASH
“Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.”

This is not a new therapy

The Effectiveness of Hydrocortisone in the Management of Severe Infections

A Double-Blind Study

Cooperative Study Group *
Table 1.—Effect of Hydrocortisone and Placebo on Mortality: All Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Sex</th>
<th>Patients, No.</th>
<th>Died, No.</th>
<th>Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Age &gt;16</td>
<td>Age &lt;16</td>
<td>Age &gt;16</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>M</td>
<td>68</td>
<td>34</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>28</td>
<td>40</td>
<td>16</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td></td>
<td>96</td>
<td>74</td>
<td>54</td>
</tr>
<tr>
<td>Placebo</td>
<td>M</td>
<td>63</td>
<td>30</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>35</td>
<td>31</td>
<td>18</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td></td>
<td>98</td>
<td>61</td>
<td>32</td>
</tr>
</tbody>
</table>
42 RCTs, 10194 patients over 56 years
What guidance exists for clinicians?
H. CORTICOSTEROIDS

1. We suggest against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg per day (weak recommendation, low quality of evidence).
## The Big 2

<table>
<thead>
<tr>
<th></th>
<th>ADRENAL</th>
<th>APROCCHSS</th>
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<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>Adults with septic shock (Sepsis-2) + IMV</td>
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<td><strong>Intervention</strong></td>
<td>Hydrocortisone 200mg IV daily -given for 7 days w/o tapering</td>
<td></td>
</tr>
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<td><strong>Control</strong></td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Primary = 90 day mortality</td>
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<td>3800 patients across 69 sites</td>
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<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>Adults with septic shock (Sepsis-2) + IMV</td>
<td>Adults with septic shock &lt;24 hrs (Sepsis-3)</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Hydrocortisone 200mg IV infusion daily -given for 7 days w/o tapering</td>
<td>Hydrocortisone 50mg IV q6h Fludrocortisone 50ug PO daily -given for 7 days w/o tapering</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Primary = 90 day mortality</td>
<td>Primary = 90 day mortality</td>
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<tr>
<td></td>
<td>3800 patients across 69 sites</td>
<td>1241 patients across 34 sites</td>
</tr>
</tbody>
</table>
90-Day Mortality

ADRENAL

APROCCHSS
Shock Reversal

ADRENAL

APROCCHSS
Updated Guidance
Updated MA & BMJ Rapid Recommendation

Corticosteroids in Sepsis: An Updated Systematic Review and Meta-Analysis

Bram Rochwerger, MD, MSc; Simon J. Oczkowski, MD, MSc, MHS; Reed A. C. Siemieniuk, MD; Thomas Agoritsas, MD, PhD; Emilie Belley-Cote, MD; Frédérique D’Aragon, MD, MSc; Erick Duan, MD, MSc; Shane English, MD, MSc; Kira Gossack-Keenan, BSc; Mashari Alghuroba, MSc; Wojciech Szczeklik, MD, PhD; Kusum Menon, MD, MSc; Walied Alhazzani, MD, MSc; Jonathan Sevransky, MD; Per Olav Vandvik, MD, PhD; Djillali Annane, MD, PhD; Gordon Guyatt, MD, MSc

Corticosteroid therapy for sepsis: a clinical practice guideline


Crit Care Med. 2018 Sep;46(9):1411-1420
BMJ. 2018 Aug 10;362:k3284
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk</th>
<th>GRADE certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0.93 (95% CI 0.84-1.03)</td>
<td>Low</td>
</tr>
<tr>
<td>Shock reversal at 1 week</td>
<td>1.26 (95% CI 1.12-1.42)</td>
<td>High</td>
</tr>
<tr>
<td>SOFA score at 1 week</td>
<td>-1.39 (95% CI -1.88 to -0.89)</td>
<td>High</td>
</tr>
</tbody>
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Crit Care Med. 2018 Sep;46(9):1411-1420
### Is there Harm?

<table>
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<tr>
<th>Outcome</th>
<th>Pooled Relative Risk</th>
<th>GRADE certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypernatremia</td>
<td>1.64 (95% CI 1.32-2.03)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1.16 (95% CI 1.08-1.24)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Neuromuscular Weakness</td>
<td>1.21 (95% CI 1.01-1.45)</td>
<td>Low</td>
</tr>
</tbody>
</table>
Subgroup effect?

• No evidence of credible subgroup effect
  – Relative effect consistent across all subgroups
    • Control group mortality
    • Pulmonary source
    • Duration/Dose of corticosteroids
    • Corticosteroid molecule (including HC + Flud)
    • Risk of bias
Should we give corticosteroids to patients with sepsis?

Corticosteroid therapy for sepsis: a clinical practice guideline


BMJ. 2018 Aug 10;362:k3284
Mortality
Less shock
Less organ dysfunction

ICUAW
Metabolic derangements
BMJ Recommendation

• The BMJ Rapid Recommendation panel makes a **weak/conditional recommendation to give corticosteroids** to people with all types and severity of sepsis
Sepsis of any severity?

Risk ratio

Control group mortality (%)

P = 0.26
### Absolute Effect increases with Severity

<table>
<thead>
<tr>
<th>Risk of Death at 30 days</th>
<th>Relative Effect of Steroids</th>
<th>Absolute Effect of Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% (sepsis)</td>
<td>RR 0.93</td>
<td>0.7% reduction</td>
</tr>
<tr>
<td>20%</td>
<td>RR 0.93</td>
<td>1.4% reduction</td>
</tr>
<tr>
<td>30% (septic shock)</td>
<td>RR 0.93</td>
<td>2.1% reduction</td>
</tr>
<tr>
<td>40%</td>
<td>RR 0.93</td>
<td>2.8% reduction</td>
</tr>
<tr>
<td>50%</td>
<td>RR 0.93</td>
<td>3.5% reduction</td>
</tr>
</tbody>
</table>
Only to the sickest patients?

Risk vs. benefit of stress-dose steroids in septic shock?

Side-effects from steroid

Risk > Benefit
Steroids *harmful*

Benefit > Risk
Steroids *beneficial*

Farkas J. http://emcrit.org/pulmcrit
Risk vs. benefit of stress-dose steroids in septic shock?

- Lower Reward, Lower Risk
- Side-effects from steroid
- Benefit of steroid ??
- Higher Reward, Higher Risk

Severity of Septic Shock
Take-away

• The majority of patients with sepsis will probably benefit from a short course of steroids
  – If you give to patients with septic shock, it probably also makes sense to give to patients with less severe disease

• It may not matter what you give but Hydrocortisone 100-200mg/day IV bolus is the most common regime used in the literature

• Future RCTs may not bring any further clarity in regards to effect on mortality
Future Steroid RCTs?

Relative Risk for 90-Day Mortality

APROCCHSS

ADRENAL
Targeted Immunotherapy?

The Cytokine Cascade

Inflammatory Stimulus

Antibodies

Anti-Inflammatory Mediators
- BPI
- IL-4, 10, 11, 13
- IL-1ra, TNF Receptors
- G-CSF
- Activated Protein C

TNF \rightarrow IL-1

(-) 

IL-8, Chemokines

Neutrophil
- Adhesion
- Migration
- Prime & burst
- O₂ free radicals

Interleukins
- Interferons
- Leukotrienes
- Thrombin

Nitric Oxide
- Myocardial Depression
- Hypotension
- Metabolic Block
Thank you

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