HYDROCORTISONE SEPSIS: WHY AND WHEN?

Eduardo Juan Troster, MD, PhD
Cristiane Freitas Pizarro, MD
USE OF CORTICOSTEROID THERAPY IN SEPSIS/SEPTIC SHOCK IS BASED IN SEVERAL ASPECTS:

- Current epidemiology of septic shock;
- Anti-inflammatory properties of corticosteroids;
- Diagnosis of adrenal insufficiency: baseline cortisol and post corticotropin-stimulated test;
- Incidence of adrenal insufficiency and relative adrenal insufficiency;
- Relation between cathecolamine-dependent septic shock and relative adrenal insufficiency.
CURRENT EPIDEMIOLOGY OF SEPTIC SHOCK

- Septic shock remains a common condition associated with substantial morbidity, mortality and economic cost in intensive care units (ICUs) world-wide;

- An estimated 750,000 cases of severe sepsis occur annually in the United States and the mortality rate is about 30%; (Angus et al. - 2001);
Data suggest that sepsis is a major public health problem, with an incidence density of about 57 per 1000 patients/day;

PEDIATRIC ICU OF SÃO PAULO UNIVERSITY

Septic shock incidence

2002  2003

Mortality

2002  2003

Sá, Kalil, Oliveira, Vaz, 2003
SEVERE SEPSIS/SEPTIC SHOCK MORTALITY IN CHILDREN - USA

Ano  | %  
---   | ---
1963  | 97% 
1985  | 57% 
1991  | 12% 
1999  | 9%  

Crit Care Med 2003; 19
Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock*

Joseph A. Carcillo, MD; Alan I. Fields, MD; Task Force Committee Members

Pediatric considerations

Margaret M. Parker, MD, FCCM; Jan A. Hazelzet, MD; Joseph A. Carcillo, MD
Recognize decreased mental status and perfusion. Maintain airway and establish access according to PALS guidelines.

Push 20cc/Kg isotonic saline or colloid boluses up to and over 60cc/Kg.
Correct hypoglycemia and hypocalcemia.

**Fluid refractory-dopamine/dobutamine resistant shock**

Titrate epinephrine for cold shock and norepinephrine for warm shock to normal MAP-CVP difference for age and SVCO2 saturation > 70%
Catecholamine-resistant shock

At risk of adrenal insufficiency?

Draw baseline cortisol level then give hydrocortisone

Normal blood pressure
Cold shock
SVCO₂ Sat < 70%

Add vasodilator or type III PDE inhibitor with volume loading

Low blood pressure
Cold shock
SVCO₂ Sat < 70%

Titrated volume resuscitation and epinephrine

Not at risk?

Draw baseline cortisol level or perform ACTH stim test. Do not give hydrocortisone

Low blood pressure
Warm shock
SVCO₂ Sat ≥ 70%

Titrated volume and norepinephrine

Persistent Catecholamine-resistant shock

Start cardiac output measurement and direct fluid, inotrope, vasopressor, vasodilator, and hormonal therapies to attain normal MAP-CVP and CI > 3.3 and < 6.0L/min/m².

Refactory shock
Consider ECMO
ANTI-INFLAMMATORY PROPERTIES OF CORTICOSTEROIDS
SCHEMATIC SUMMARY OF GLUCOCORTICOID PROPERTIES

![Diagram showing the effects of glucocorticoids on various immune and inflammatory pathways.]

Keywords: Chemokines, Chemotaxis, IL-1, TNF, IL-6, CRF, ACTH, iNOS, NO, NADPH oxidase, O₂⁻, COX2, PGE₂, MIF, IL-10, IκB, Lipocortin 1, Acute Phase proteins (including IL-1ra).

What are the criteria to be used in diagnoses of adrenal insufficiency and relative adrenal insufficiency in critically ill patients?
### Different Criteria Utilized to Define Adrenal Insufficiency According to Several Authors

<table>
<thead>
<tr>
<th>Author</th>
<th>Cortisol Level (μg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rothwell <em>et al.</em> (1991)</td>
<td>Increment cortisol &lt; 9 after ACTH stimulated test</td>
</tr>
<tr>
<td>Soni <em>et al.</em> (1995)</td>
<td>Cortisol &lt; 18 after ACTH stimulated test</td>
</tr>
<tr>
<td>Hatherill <em>et al.</em> (1999)</td>
<td>Increment cortisol &lt; 7.5 after ACTH stimulated test</td>
</tr>
<tr>
<td>Menon e Clarson (2002)</td>
<td>Baseline Cortisol &lt; 7 and/or cortisol &lt; 18 after ACTH stimulated test</td>
</tr>
<tr>
<td>Marik e Zaloga (2003)</td>
<td>Baseline cortisol &lt; 25</td>
</tr>
<tr>
<td>Pizarro <em>et al.</em> (2005)</td>
<td>Increment cortisol ≤ 9 after ACTH stimulated test</td>
</tr>
</tbody>
</table>
What are the appropriate plasma cortisol concentrations in patients with sepsis and septic shock?

• The value of baseline cortisol and post corticotropin stimulated test in critically ill patients remains a controversial issue;

• “Normal” or “high normal” plasma cortisol concentrations may represent relative adrenal insufficiency or unresponsiveness in sepsis and septic shock and an insufficient response to stress;

• The rapid corticotropin stimulation test has been suggested to be useful in evaluating adrenocortical function and as a predictor of mortality in sepsis;
## Incidence of Adrenal Insufficiency According to Various Published Definitions

<table>
<thead>
<tr>
<th>Author (Yr)</th>
<th>Cortisol Level (µg/dl)</th>
<th>According bibliography references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rothwell et al. (1991)</td>
<td>Increment &lt; 9 after ACTH stimulated test</td>
<td>40%</td>
</tr>
<tr>
<td>Soni et al. (1995)</td>
<td>Cortisol &lt; 18 after ACTH stimulated test</td>
<td>24%</td>
</tr>
<tr>
<td>Hatherill et al. (1999)</td>
<td>Increment cortisol &lt; 7,5 after ACTH stimulated test</td>
<td>52%</td>
</tr>
<tr>
<td>Loisa et al. (2002)</td>
<td>Cortisol baseline &lt; 25 and increment ≤ 9</td>
<td>15%</td>
</tr>
<tr>
<td>Menon e Clarson (2002)</td>
<td>Cortisol baseline &lt; 7 and/or cortisol &lt; 18 after ACTH stimulated test</td>
<td>31%</td>
</tr>
<tr>
<td>Marik e Zaloga (2003)</td>
<td>Cortisol baseline &lt; 25</td>
<td>61%</td>
</tr>
<tr>
<td>Pizarro et al. (2005)</td>
<td>Increment ≤ 9 after ACTH stimulated test</td>
<td>44%</td>
</tr>
</tbody>
</table>
INCIDENCE OF ADRENAL INSUFFICIENCY IN CHILDREN
### Summary of published studies on adrenal stimulation testing in critically ill pediatric patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>n</th>
<th>Dose of ACTH for stimulation test</th>
<th>Definition of adrenal insufficiency</th>
<th>Proportion with AI/RAI</th>
<th>Clinical Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hatherill</td>
<td>Pediatric Septic shock</td>
<td>33</td>
<td>145 µg/ m² To max 250 µg</td>
<td>Poststimulation increase &gt; 9 µg/dl</td>
<td>525</td>
<td>Increased vasopressor requirements</td>
</tr>
<tr>
<td>1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menon</td>
<td>Pediatric Critical illness</td>
<td>13</td>
<td>&gt;10Kg: 250 µg &lt; 10 Kg: 125 µg</td>
<td>Basal cortisol &lt; 7 µg/dl or Poststimulation cortisol &lt; 18 µg/dl</td>
<td>31%</td>
<td>Not assessed</td>
</tr>
<tr>
<td>2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>Pediatric Sepsis</td>
<td>42</td>
<td>0.5 µg/m²</td>
<td>Basal cortisol &lt; 5 µg/dl or poststimulation cortisol &lt; 18 µg/dl</td>
<td>17%</td>
<td>Increased vasopressor requirements</td>
</tr>
<tr>
<td>2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pizarro</td>
<td>Pediatric Setic shock</td>
<td>57</td>
<td>250µg</td>
<td>Basal cortisol&lt; 20 µg/dl Poststimulation increase &lt; 9 µg/dl</td>
<td>AI – 18% RAI – 26%</td>
<td>Unresponsive shock</td>
</tr>
<tr>
<td>2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Adapted by Curr Opin Pediatr 18:448-453
Absolute and relative adrenal insufficiency in children with septic shock*
Cristiane F. Pizarro, MD; Eduardo J. Troster, MD, PhD; Durval Damiani, MD, PhD; Joseph A. Carcillo, MD
Crit Care Med 2005 Vol. 33, No. 4

Editorials

One step forward: An advance in understanding adrenal insufficiency in the pediatric critically ill*
Michael Agus, MD
Pediatric Critical Care and Endocrinology
Children’s Hospital Boston Harvard Medical School Boston, MA
Crit Care Med 2005 Vol. 33, No. 4

Adrenal insufficiency in the critically ill neonate and child
Monica Langer, Biren P. Modi and Michael Agus
INCIDENCE OF ABSOLUTE AND RELATIVE ADRENAL INSUFFICIENCY IN PATIENTS WITH SEVERE SEPSIS AND SEPTIC SHOCK

Cristiane F Pizarro; Eduardo Juan Troster

Durval Damiani and Joseph A Carcillo

PICU – CHILDREN INSTITUTE – SÃO PAULO - BRAZIL
1. To determine the incidence of absolute adrenal insufficiency and relative adrenal insufficiency in children with septic shock and severe sepsis;

2. To evaluate their effect on vasopressor requirements and mortality.
The patients were classified in four groups according to adrenal function:

**GROUP 1**
**ABSOLUTE ADRENAL INSUFFICIENCY**
Baseline cortisol < 20µg/dl and an increment = 9µg/dl

**GROUP 2**
**RELATIVE ADRENAL INSUFFICIENCY**
Baseline cortisol ≥ 20µg/dl and an increment = 9µg/dl

**GROUP 3**
**ADEQUATE ADRENAL RESPONSE**
(with elevated baseline cortisol)
Baseline cortisol ≥ 20µg/dl and an increment > 9µg/dl

**GROUP 4**
**ADEQUATE ADRENAL RESPONSE**
(without an elevated baseline cortisol)
Baseline cortisol < 20µg/dl and an increment > 9µg/dl
CLASSIFICATION OF ADRENAL FUNCTION

- Absolute Adrenal Insufficiency
- Relative Adrenal Insufficiency
- Adequate Adrenal Response (baseline cortisol ≥ 20 μg/dL)
- Adequate Adrenal Response (baseline cortisol < 20 μg/dL)
VASOPRESSOR AND FLUID REQUIREMENTS IN THE FOUR GROUPS

CATHECOLAMINE REFRACTORY SHOCK

FLUID RESPONSIVE SHOCK

DOPAMINE/DOBUTAMINE REFRACTORY SHOCK
MORTALITY RATES IN THE FOUR ADRENA L FUNCTION GROUPS

- **Group 1 - AAI**
  - Survivors: 50%
  - Non-Survivors: 50%

- **Group 2 - RAI**
  - Survivors: 47%
  - Non-Survivors: 53%

- **Group 3 - AAR**
  - Survivors: 67%
  - Non-Survivors: 33%

- **Group 4 - AAR**
  - Survivors: 76%
  - Non-Survivors: 24%
SHOULD HYDROCORTISONE BE PREFERRED TO OTHER GLUCOCORTICOIDS IN PATIENTS WITH SEPSIS / SEPTIC SHOCK? YES.
1. MOST OF THE EXPERIENCE WITH LOW-DOSE CORTICOSTEROID TREATMENT IN SEPTIC SHOCK HAS BEEN WITH THE USE OF HYDROCORTISONE
BEFORE EUROPEAN’S META-ANALYSIS - 1995

Mortality rate ~ 11%

Log Odds Ratio

<table>
<thead>
<tr>
<th>Study</th>
<th>Favors Treatment</th>
<th>Favors Control</th>
<th>Relative Risk</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luce et al (1988)</td>
<td></td>
<td></td>
<td>1.07</td>
<td>(0.72 - 1.60)</td>
</tr>
<tr>
<td>VASSCg (1987)</td>
<td></td>
<td></td>
<td>0.95</td>
<td>(0.57 - 1.58)</td>
</tr>
<tr>
<td>Bone et al (1987)</td>
<td></td>
<td></td>
<td>1.35</td>
<td>(0.98 - 1.84)</td>
</tr>
<tr>
<td>Sprung et al (1984)</td>
<td></td>
<td></td>
<td>1.11</td>
<td>(0.74 - 1.67)</td>
</tr>
<tr>
<td>Thompson et al (1976)</td>
<td></td>
<td></td>
<td>1.01</td>
<td>(0.77 - 1.31)</td>
</tr>
<tr>
<td>Lucas et al (1984)</td>
<td></td>
<td></td>
<td>1.09</td>
<td>(0.36 - 3.27)</td>
</tr>
<tr>
<td>Schumer et al (1976)</td>
<td></td>
<td></td>
<td>0.30</td>
<td>(0.13 - 0.72)</td>
</tr>
<tr>
<td>Klastersky et al (1971)</td>
<td></td>
<td></td>
<td>0.97</td>
<td>(0.65 - 1.45)</td>
</tr>
<tr>
<td>CS group (1963)</td>
<td></td>
<td></td>
<td>1.72</td>
<td>(1.23 - 2.41)</td>
</tr>
<tr>
<td>Common Relative Risk</td>
<td></td>
<td></td>
<td>1.13</td>
<td>(0.99 - 1.29)</td>
</tr>
</tbody>
</table>
BEFORE EUROPEAN’S META-ANALYS

Large, RCT of High-dose corticosteroids in septic shock are not effective, and might even be harmful ...

<table>
<thead>
<tr>
<th>Author (Yr)</th>
<th>N</th>
<th>Drug</th>
<th>Dose / Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooperative Study Group</td>
<td>194</td>
<td>Hydrocortisone</td>
<td>300mg followed by 50mg/day (6 days)</td>
</tr>
<tr>
<td>(1963)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klastersky et al.</td>
<td>85</td>
<td>Betamethasone</td>
<td>1mg/kg daily (3days)</td>
</tr>
<tr>
<td>(1971)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schumer (1976)</td>
<td>172</td>
<td>Methylprednisolone Dexamethasone</td>
<td>30mg/kg 3mg/kg Repeated after 4hrs (x1) if necessary</td>
</tr>
<tr>
<td>Thompson et al.</td>
<td>60</td>
<td>Methylprednisolone</td>
<td>30mg/kg (Up to 4hrs in 24 hrs)</td>
</tr>
<tr>
<td>(1976)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sprung et al.</td>
<td>59</td>
<td>Methylprednisolone Dexamethasone</td>
<td>30mg/kg 6mg/kg Repeated after 4hrs (x1) if necessary</td>
</tr>
<tr>
<td>(1984)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lucas &amp; Ledgerwood</td>
<td>48</td>
<td>Dexamethasone</td>
<td>2mg, 6mg/kg for 48hrs by continuous infusion</td>
</tr>
<tr>
<td>(1984)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veterans Administration</td>
<td>223</td>
<td>Methylprednisolone</td>
<td>30mg/kg followed by 5mg/kg (9hrs)</td>
</tr>
<tr>
<td>(1987)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone et al.</td>
<td>381</td>
<td>Methylprednisolone</td>
<td>30mg/kg (24hrs)</td>
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<tr>
<td>(1987)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luce et al.</td>
<td>75</td>
<td>Methylprednisolone</td>
<td>30mg/kg (x4) (24hrs)</td>
</tr>
<tr>
<td>(1988)</td>
<td></td>
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</tr>
</tbody>
</table>
1. Short courses of high dose corticosteroids do not affect mortality from severe sepsis and septic shock;

2. Long courses of low dose corticosteroids:
   a) Improve systematic haemodynamics and reduce the time on vasopressor treatment;
   b) Reduce mortality at 28 days, in intensive care units, and in hospital;
   c) Do not significantly alter risk of gastroduodenal bleeding, superinfections or hyperglycemia.

Annane et al. (2004) ⇒ meta-analysis
(16 trials 1955 - 2003)

### SUMMARY OF STUDY DESIGNS - 1998 - 2003

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Drug</th>
<th>Dose Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bollaert et al. (1998)</td>
<td>41</td>
<td>Hydrocortisone</td>
<td>100mg EV 8/8h 5 days, then 50mg 8/8h for 3 day and 25mg 8/8h for 3 day for responders</td>
</tr>
<tr>
<td>Briegel et al. (1999)</td>
<td>40</td>
<td>Hydrocortisone</td>
<td>100mg EV then 0,18mg/Kg/h until shock reversed, then 0.08mg/kg/h for 6 days, then tapered by 24mg/day</td>
</tr>
<tr>
<td>Chawla et al. (1999)</td>
<td>44</td>
<td>Hydrocortisone</td>
<td>100mg EV 8/8hs during 3 days</td>
</tr>
<tr>
<td>Annane et al. (2002)</td>
<td>299</td>
<td>Hydrocortisone</td>
<td>50mg EV 6/6hs during 7days plus fludrocortisone 50μg oral tablet 7 days</td>
</tr>
<tr>
<td>Keh et al. (2003)</td>
<td>40</td>
<td>Hydrocortisone</td>
<td>100mg EV 30min following 10mg/h during 3 days</td>
</tr>
</tbody>
</table>
2. Hydrocortisone is the synthetic equivalent to the physiologic final active cortisol;

3. Hydrocortisone has intrinsic mineralocorticoid activity, whereas methylprednisolone or dexamethasone does not;

4. 20mg of hydrocortisone is equivalent to 0.05mg of fludrocortisone, and 0.05-2mg of fludrocortisone is recommended as mineralocorticoid replacement dosage after treatment of adrenal insufficiency.
WHEN

SHOULD HYDROCORTISONE BE USED

?
HYDROCORTISONE THERAPY

Carcillo JA, Task Force Committee Members - 2002

• Should be reserved for use in children with cathecolamine resistance and suspected or proven adrenal insufficiency. Patients at risk include:

1. *Purpura fulminans*;

2. *Children with severe septic shock*;

3. Children with pituitary or adrenal abnormalities;

4. Children who have previously received steroid therapies for chronic illness;

Dose recommendation vary from ⇒ 1-2mg/kg for stress coverage to 50mg/Kg for empirical therapy of shock followed by the same dose as a 24-hr infusion.

Crit Care Med.2003;30:1365-78
Hildebrandt et al., 2005

- There is no agreed consensus for the use of steroids in sepsis in UK practice at the moment.
  - Steroids are regularly used in 76% PICUs;
  - Only one Unit has a written protocol;
  - 84% units who use steroids gave as their main indication persistent hypotension despite the use of inotropes;
  - 79% units use hydrocortison / 21% dexamethasone;
  - 42% units perform a short synacthen test and 25% units performing synacthen tests used low-dose synacthen.
• Relative adrenal insufficiency and its clinical implications have come in focus with studies demonstrating a high prevalence in septic shock patients and a significant associated morbidity;

• This state of “relative” adrenal insufficiency is characterized by an inadequate production of cortisol in relation to an increased demand during periods of severe stress.
CLINICAL MANIFESTATIONS
RELATIVE ADRENAL INSUFFICIENCY

CARDIOVASCULAR INSTABILITY, WITH
HYPOTENSION AND SHOCK THAT IS
UNRESPONSIVE TO FLUID OR VASOPRESSOR
THERAPY
RELATIVE ADRENAL INSUFFICIENCY

• INCREASED MORBIDITY AND MORTALITY

• ASSOCIATION BETWEEN ADRENAL INSUFFICIENCY AND A REFRACTORY SEPTIC SHOCK
VASOPRESSOR AND FLUID REQUIREMENT IN THE FOUR GROUPS

Group 1 - AAI
- 100%

Group 2 - RAI
- 80%

Group 3 - AAR
- 60%

Group 4 - AAR
- 30%
  - 35%
  - 35%

FLUID RESPONSIVE SHOCK
CATHECOLAMINE REFRACTORY SHOCK
DOPAMINE/DOBUTAMINE REFRACTORY SHOCK
MORTALITY RATES IN THE FOUR ADRENAL FUNCTION GROUPS

- **Group 1 - AAI**: 50% SURVIVORS, 50% NON SURVIVORS
- **Group 2 - RAI**: 47% SURVIVORS, 53% NON SURVIVORS
- **Group 3 - AAR**: 67% SURVIVORS, 33% NON SURVIVORS
- **Group 4 - AAR**: 76% SURVIVORS, 24% NON SURVIVORS
Relative adrenal insufficiency as a predictor of disease severity, mortality, and beneficial effects of corticosteroid treatment in septic shock

Margriet F. C. de Jong, MSc; Albertus Beishuizen, MD, PhD; Jan-Jaap Spijkstra, MD, PhD;
A. B. Johan Groeneveld, MD, PhD, FCCP, FCCM

Crit Care Med 2007 vol. 35, 8
CONCLUSIONS

Doubts still persist regarding the efficacy of replacement therapy with low-dose steroids in children with catecholamine-resistant septic shock, and further randomized studies are needed to determine whether treatment of such patients changes morbidity and/or mortality.