Adjunctive Hydrocortisone Therapy For Pediatric Sepsis: Rationale for Community/Practitioner Equipoise

UW Medicine Pacific Northwest Sepsis Conference
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Current State

The dearth of rigorous data to guide prescribing decisions for the critically ill results in “off-label” use of nearly half the medications that do get prescribed.

Lat I, Mloek S, Janzen J, et al.
Off label medication use in adult critical care patients.
J Crit Care 2011; 26: 89-94.
2014 Clinical Practice Parameters For Hemodynamic Support of Pediatric And Neonatal Septic Shock

- Microbes
  - PAMPS
  - Inflammation
  - Intestinal Translocation
  - Mitochondrial Injury
  - Secondary Infection
  - Recovery
  - Death
- Collateral Damage
- Sepsis
  - DAMPS
  - Bacterial DNA
  - Excess CARS
  - Balanced SIRS/CARS
  - Excess SIRS/IR


Hemodynamic Instability in Sepsis
- Compromised endothelial integrity
- Systemic vasoplegia
- Impaired cardiac contractility
- Mitochondrial/cytotoxic dysoxia

- Microbe
- Cytokine
- NO'
- Shock
- MODS
- Cortisol
Waterhouse-Friderichsen Syndrome

- Petechial rash
- Coagulopathy
- Cardiovascular collapse
- Bilateral adrenal hemorrhage

Waterhouse R. A case of suprarenal apoplexy. Lancet 1911; 1: 577-578

Cortisol

ACTH

The Pragmatic View of Adjunctive Hydrocortisone In Dire Straits Sepsis

Critical care for sepsis is focused on preventing, minimizing, and hastening resolution of organ dysfunction.

Corticosteroid Hemodynamic Actions
- Modulation of signal transduction
- Augmentation of catecholamine, angiotensin, endothelin, and mineralocorticoid receptor numbers and attenuation of down regulation
- Inhibition of prostaglandin metabolism
- Alteration of Na and Ca transport
- Decreased microvascular permeability
- Increased erythrocyte 2, 3 diphospho-glycerate


Adrenal Steroids Effect On The Cardiovascular System

Pressor Response to Hydrocortisone

9 Septic Patients
60 Minutes After 50 mg Hydrocortisone
(p = 0.032)

Baseline

Increase in MAP (mm Hg)
Norepinephrine (ug/kg/min)


Impact of Corticosteroids Among Critically Ill Children With Vasopressor Dependent Shock

Dopamine
Norepinephrine


IL-6/IL-8 Response to Hydrocortisone

**Effect of Low Dose Hydrocortisone and Fludrocortisone on Adult Septic Shock Mortality**

- Performed in 19 ICUs in France
- Enrolled within 8 hrs of shock onset
- Randomized centrally in blocks of 4
- Screened 1326; ineligible, 1026
- Randomized 300: 149 placebo, 151 hydrocortisone
- Employed parallel-group study design
- Utilized intent-to-treat principle

Annane D, et al. JAMA 2002; 288: 862-871

300 adult patients with septic shock enrolled after a corticotropin stimulation test
- 50 mg hydrocortisone IV, Q 6 hrs + 50 ug fludrocortisone daily or placebo
- In corticotropin test non-responders: mortality → 63% in placebo group vs 53% in steroid group (HR 0.67, [0.47-0.95], p=0.02)
- Adverse events similar in the two groups

Median Time to VIS Withdrawal

<table>
<thead>
<tr>
<th></th>
<th>Placebo (115)</th>
<th>Steroid (114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-responders</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Responders</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>HR</td>
<td>1.91</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>1.29-2.84</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.001</td>
<td></td>
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</tbody>
</table>

28-Day Mortality

<table>
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<tr>
<th></th>
<th>Placebo (115)</th>
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<tbody>
<tr>
<td>Non-responders</td>
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<td>53%</td>
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<tr>
<td>Responders</td>
<td>53%</td>
<td>61%</td>
</tr>
<tr>
<td>OR</td>
<td>0.54</td>
<td>0.91</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.31-0.97</td>
<td>0.32-2.99</td>
</tr>
<tr>
<td>p</td>
<td>0.04</td>
<td>0.96</td>
</tr>
</tbody>
</table>

CORTICUS
Corticosteroid Therapy of Septic Shock

- Prospective, randomized, double-blinded, placebo-controlled
- 52 participating ICUs, 9 countries
- Enrollment March 2002-November 2005
- Independent DSMB
- Hydrocortisone: 50 mg IV dosed every 6 hours for 5 days (or placebo); then weaning dosing. No fludrocortisone

CORTICUS: Time to Reversal of Shock


Cardiovascular Dysfunction Resolution In CORTICUS Subjects


Septic Shock Reversal By 7 Days: Role of Corticosteroids

Patients randomized to treatment with hydrocortisone demonstrated a faster decrease in total organ dysfunction/failure determined by the SOFA score, primarily driven by a faster improvement in cardiovascular organ dysfunction/failure.


**Changes in the 21st Century**

- Immunizations for common childhood bacterial pathogens
  - *Neisseria meningitidis*
  - *Hemophilus influenzae*
  - *Streptococcus pneumoniae*

- Universal screening for 21-hydroxylase deficiency, responsible for 95% of cases of congenital adrenal insufficiency
On Further Review of Annane’s Initial Clinical Trial . . .

- Unexpectedly 76.6% of subjects demonstrated non-responsiveness to corticotropin
- Role of fludrocortisone unclear
- Etomidate, an inhibitor of 11β-hydroxylase, that catalyzes a rate-limiting step in cortisol synthesis, was administered to 24% of subjects


CORTICUS Mortality Data

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Hydrocortisone</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>78/248</td>
<td>31.5%</td>
<td>(25.6, 37.3)</td>
</tr>
<tr>
<td>Corticotropin Non-responders</td>
<td>39/108</td>
<td>36.1%</td>
<td>(26.9, 45.3)</td>
</tr>
<tr>
<td>Corticotropin Responders</td>
<td>39/136</td>
<td>28.7%</td>
<td>(21.1, 36.3)</td>
</tr>
</tbody>
</table>

Hydrocortisone cannot be recommended for routine care of severe sepsis.

Nor can the corticotropin stimulation test be recommended to guide hydrocortisone therapy.

Hydrocortisone should not be given if SBP > 90 can be achieved with aggressive fluid and vasoactive-inotropic resuscitation.

Adjunctive cortisol therapy may have a role for septic shock persisting > 1 hour despite adequate fluid and high dose vasoactive-inotropic resuscitation.


Sepsis 28 Day All Cause Mortality
Role of Corticosteroids

Although low-dose hydrocortisone therapy ameliorates septic shock at 7 and 28 days, it does not reduce 28-day mortality.


Low-Dose Hydrocortisone Therapy Attenuates Septic Shock in Adult Patients But Does Not Reduce 28-Day Mortality: A Meta-Analysis of Randomized Controlled Trials
Adjunctive Corticosteroid Therapy For Pediatric Septic Shock

- PHIS Database Investigation
- RESOLVE Database Investigation
- PERSEVERE Database Investigation
- Pediatric Septic Shock Personalized Medicine
- SPROUT Point Prevalence Investigation
- PERSEVERE Database Investigation

**Adjunctive Corticosteroid Therapy in Pediatric Severe Sepsis: RESOLVE Study Observations**

Follow-up analysis of the investigation data base for RESOLVE (REsearching severe Sepsis and Organ dysfunction in children: a gLObal perspective) trial (NCT00049764)


**Corticosteroids for Pediatric Sepsis: RESOLVE Study Observations**

<table>
<thead>
<tr>
<th></th>
<th>Yes, Adjunctive Corticosteroids (n=193)</th>
<th>No, Adjunctive Corticosteroids (n=284)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>Mean ± SD or % 5.45 ± 5.54 4.7, 6.2 4.68±5.10 4.1, 5.3</td>
<td>0.1229</td>
</tr>
<tr>
<td>Males (%)</td>
<td>Mean ± SD or % 51.8 44.8, 58.8 55.6 49.9, 61.4</td>
<td>0.4112</td>
</tr>
<tr>
<td>PRISM III</td>
<td>Mean ± SD or % 17.2 ± 8.1 16.0, 18.3 16.5 ± 8.2 15.6, 17.5</td>
<td>0.4065</td>
</tr>
<tr>
<td># ODs</td>
<td>Mean ± SD or % 3.8 ± 1.2 3.7, 4.0 3.6 ± 1.2 3.5, 3.8</td>
<td>0.0605</td>
</tr>
<tr>
<td>POPC</td>
<td>Mean ± SD or % 1.5 ± 0.9 1.4, 1.6 1.5 ± 1.0 1.4, 1.6</td>
<td>0.7882</td>
</tr>
</tbody>
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Corticosteroids for Pediatric Sepsis: RESOLVE Study Observations

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<tbody>
<tr>
<td>Mortality</td>
<td>15.1 ± 10.0, 20.2</td>
<td>18.8 ± 14.2, 23.4</td>
<td>0.297</td>
</tr>
<tr>
<td>MV Days</td>
<td>8.3 ± 7.4</td>
<td>7.4 ± 6.8</td>
<td>0.370</td>
</tr>
<tr>
<td>VIS Days</td>
<td>4.5 ± 3.9</td>
<td>4.3 ± 3.7</td>
<td>0.589</td>
</tr>
<tr>
<td>PICU Days</td>
<td>12.1 ± 10.0, 13.3</td>
<td>11.0 ± 10.0, 12.0</td>
<td>0.156</td>
</tr>
<tr>
<td>Hosp Days</td>
<td>18.1 ± 16.9, 19.4</td>
<td>15.9 ± 14.8, 17.0</td>
<td>0.011</td>
</tr>
</tbody>
</table>

“Children with severe sepsis enrolled in the RESOLVE trial who received corticosteroids demonstrated similar illness severity compared with those children who did not. Outcomes (mortality, days of vasoactive-inotropic infusion and mechanical ventilation, organ failure resolution, change in POPC score, and PICU and hospital length of stay) were similar in children who did or did not receive corticosteroids as adjunctive therapy in the largest pediatric sepsis clinical trial conducted to date”.


“Physicians often believe that it is best to err on the side of treatment, and they likely unintentionally underestimate the harms of treatment”.

Corticosteroid Side Effects

- Hypertension
- Hyperglycemia
- Reduced somatic growth
- Impaired wound healing
- Neuromuscular weakness
- Hospital acquired infection
- Altered neurodevelopment

Actions of Corticosteroids On Immune Cell Gene Expression


Repression of Gene Programs Corresponding to Adaptive Immunity Among Children With Sepsis

- T cell receptor signaling
- T and B cell functioning
- Antigen presentation
- Glucocorticoid receptor
- Peroxisome proliferator facilitated receptor-α activation
- Such repression is further enhanced with corticosteroid prescription.

Corticosteroid Treatment and Repression of Adaptive Immunity In Pediatric Septic Shock


Top Ten (of 319) Gene Network Signaling Pathways Differentially Regulated By Corticosteroids

<table>
<thead>
<tr>
<th>Signaling Pathway</th>
<th>Number of Genes</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-cell receptor signaling</td>
<td>11</td>
<td>1.9 x 10^-7</td>
</tr>
<tr>
<td>CD30 signaling in T-helper cells</td>
<td>14</td>
<td>2.5 x 10^-7</td>
</tr>
<tr>
<td>Role of NFAT in regulation of the immune response</td>
<td>13</td>
<td>5.7 x 10^-7</td>
</tr>
<tr>
<td>CD28 signaling in T helper cells</td>
<td>10</td>
<td>7.2 x 10^-7</td>
</tr>
<tr>
<td>NOD signaling in T lymphocytes</td>
<td>9</td>
<td>6.3 x 10^-7</td>
</tr>
<tr>
<td>CTLA-4 signaling in cytotoxic T lymphocytes</td>
<td>7</td>
<td>6.3 x 10^-7</td>
</tr>
<tr>
<td>DMSO-activated receptor signaling</td>
<td>12</td>
<td>7.3 x 10^-7</td>
</tr>
<tr>
<td>NOD signaling</td>
<td>5</td>
<td>6.3 x 10^-7</td>
</tr>
<tr>
<td>Non T receptor signaling</td>
<td>5</td>
<td>7.3 x 10^-7</td>
</tr>
</tbody>
</table>


Cortisol Downregulation Of HLA-DR Transcription During Septic Shock

“We observed a transcriptional regulatory effect of cortisol through a mechanism involving the main major histocompatibility complex type II transactivator CIITA and particularly the isoforms I and III.”

The Sepsis Seesaw: Tilting Towards Immunosuppression

It makes little sense to administer potent anti-inflammatory agents to treat sepsis patients who are in a state of immune suppression and may well benefit from immune reconstitution instead.


Anti-Inflammatory Sepsis Therapy

It makes little sense to administer potent anti-inflammatory agents to treat sepsis patients who are in a state of immune suppression and may well benefit from immune reconstitution instead.


Adjunctive Hydrocortisone Therapy For Pediatric Septic Shock: Equipoise Arguments
‘Anecdotes’ is Not the Plural of ‘Evidence’.  
“In the absence of facts we tell ourselves stories.”  
*Noah Hawley. Before the Fall*

“Therapeutic Illusion”  
“When physicians believe that their actions or tools are more effective than they actually are, the results can be unnecessary and costly care.  
“And their therapeutic illusion facilitates continued use of inappropriate tests and treatments”.  

**Conscious Heuristics Can Help Counteract Therapeutic Illusion**  
❖ Before concluding that a treatment is effective, look for other explanations.  
❖ If there exists evidence for success, look also for evidence of failure.  
❖ Acknowledge that ‘evidence’ is not the plural of ‘anecdotes’.  
❖ Practice with intellectual honesty.  
Hydrocortisone Rx Septic Shock
Winning the Battle; Losing the War?

-SIRS
Augmented Hemodynamics

+CARS
Suppressed Immunity


“Last Ditch” Interventions
May Increase Risk of Mortality

- Sodium Bicarbonate

- Calcium

- Hyperoxia

- Therapeutic Hypothermia

Science

“...requires testing of its ideas ... to see if predictions are borne out by experiment ... the testing of theories can be considered to distinguish science from other creative fields.”

ADRENAL Study Protocol:

ADjunctive corticosteroid tREatment iN criticAlly iiL patients with septic shock

As corticosteroids may produce either benefit or harm, there is a scientific, ethical and health economic imperative to conduct such a trial.


True Minimal Risk

- Both interventions fall within the scope of community practice
- No definitive evidence for the superiority of either treatment

In the absence of a well defined clinical practice (wide variation that is largely unexplained), it is reasonable to randomize two well founded yet competing beneficial treatment strategies that lie within the boundaries of competent or good care.
“The Committee continues to maintain equipoise on the question of adjunctive steroid therapy for pediatric sepsis, pending prospective randomized clinical trials.”


Science

“...requires testing of its ideas ... to see if predictions are borne out by experiment ... the testing of theories can be considered to distinguish science from other creative fields.”


"It is said: medicine is the art of healing. Rather, one should say that medicine is the science of healing. The aim of medicine is to arrive at a cure scientifically and not empirically. The problem that medical practice must resolve is thus immense, for it is necessary to embrace both physiology and pathology before one can achieve a scientifically valid treatment."

Adjunctive hydrocortisone For Pediatric Septic Shock: Why Equipoise is Essential

There are two ways to be fooled. One is to believe what isn’t true; the other is to refuse to believe what is true.

--Soren Kierkegaard

jerry.zimmerman@seattlechildrens.org