Adrenal Insufficiency in Pediatric and Neonatal Intensive Care Units
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The Issue
- Pediatric Endocrinologists get a number of consults for adrenal insufficiency for patients in the PICU and NICU
- There has been some disagreement
  - Endocrinologists and intensivists
  - Endocrinologists and neonatologists
  - Endocrinologists
- Dr. Sukumaran – QA/QI project evaluate consults from 7/1/07-12/30/10

Adrenal Insufficiency in PICU
- Individuals with known primary or central adrenal insufficiency
- Critical Illness Related Cortisol Insufficiency – CIRCI
  - Poorly understood
  - Difficult to diagnose

Adrenal Insufficiency in NICU
- Better understood
- Related to development of adrenal gland

Adrenal Gland History
- Adrenals first recognized as separate from the kidney in 1552 by Eustachius
  - Function unknown
- 1849 – Addison noted adrenal function important for survival
- 1949- Cortisone first isolated
Activation of HPA axis
- Normal response to stress to maintain homeostasis
  - Cardiovascular Function
  - Intermediary Metabolism
  - Immune-mediated Inflammation
  - During critical illness essential for survival

HPA in Critical Illness
- Individuals with known primary or central adrenal insufficiency
  - Treat with additional steroids
  - 25-100 mg/M²/day of hydrocortisone depending on level of stress
  - Individuals with presumed normal adrenal function prior to critical illness

Functional Adrenal Insufficiency
- Mid-1980s- Adrenal dysfunction in critical illness
- Mid-1990s- Use of steroids in septic shock controversial
- 2000 Renewal of concept of functional adrenal insufficiency in septic shock
- Diagnosis is controversial

Factors Affecting HPA Axis in Critical Illness
- Inflammatory Cytokines
  - IL-1
  - IL-6
  - TNFα
- Autonomic System
- Innate Immune Response
  - Toll-like Receptors
  - MIF
Activity of the Hypothalamic–Pituitary–Adrenal Axis under Normal Conditions (Panel A), during an Appropriate Response to Stress (Panel B), and during an Inappropriate Response to Critical Illness (Panel C).

Problems with Assessing HPA Axis in Critical Illness
- Variability in contributing factors
- Polymorphisms
- Response to acute critical illness differs from prolonged critical illness
- Transcortin levels may decrease
  - >90% cortisol is bound to transcortin and albumin

Assessment of HPA Axis in Critical Illness
- Ideally, would measure free cortisol but not readily available
- Most readily available cortisol assay is immunoassay, which exhibits non-uniformity that is exaggerated during critical illness
  - Kaleida Health uses chemiluminescence (immunoassay)
  - Studies on adrenal insufficiency during critical illness use variable criteria for defining AI

Consensus- American College of Critical Care Medicine 2008
- CIRCI
  - Adrenal insufficiency OR
  - Tissue cortisol resistance
  - Not relative adrenal insufficiency
  - Hypotensive individuals
  - Respond poorly to fluids & vasopressors
Consensus- 2

- Diagnosis with free cortisol may be preferable but not widely available
- Best diagnosed by EITHER
  - Delta cortisol of < 9 mcg/dL after 250 mcg Cosyntropin OR
  - Baseline cortisol < 10 mcg/dL

RESOLVE Study

- Researching severe Sepsis & Organ dysfunction in children a Global prospective study
- Prospective randomized double-blinded placebo-controlled trial on efficacy (or not) of activated protein C in pediatric severe sepsis
- 104 pediatric centers in 18 countries
- November, 2002- April, 2005
- n = 477

Retrospectively Examined Outcomes and Steroid Use

- Mechanical ventilation for sepsis associated-pulmonary function
- Vasoactive inotropic support to support hemodynamics
- During 1st 6 days of post-study entry
  - 193 steroids
  - 284 no steroids

Table 1. Comparison of baseline characteristics among children in the RESOLVE trial who received or did not receive adjunctive corticosteroids

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Received Adjuvant Corticosteroids (n = 193)</th>
<th>Did Not Receive Adjuvant Corticosteroids (n = 284)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± 10 or %</td>
<td>4.45 ± 0.55</td>
<td>4.98 ± 0.39</td>
<td>.0229</td>
</tr>
<tr>
<td>CI</td>
<td>4.86 ± 0.82</td>
<td>5.51 ± 0.62</td>
<td>.4112</td>
</tr>
<tr>
<td>PRISM-III, I&lt;1 1st day -score</td>
<td>17.2 ± 4.1</td>
<td>16.0 ± 4.3</td>
<td>.0410</td>
</tr>
<tr>
<td>PRISM-III, I&lt;1 1st day -score</td>
<td>17.2 ± 4.1</td>
<td>16.0 ± 4.3</td>
<td>.0410</td>
</tr>
<tr>
<td>Organ dysfunction, n</td>
<td>3.8 ± 1.5</td>
<td>3.5 ± 1.2</td>
<td>.0060</td>
</tr>
<tr>
<td>Baseline POPC score</td>
<td>1.5 ± 0.9</td>
<td>1.6 ± 0.9</td>
<td>.7802</td>
</tr>
</tbody>
</table>

POPC= Pediatric Overall Performance Category  PRISM-III= Pediatric Risk of Mortality Score
10- normal, 0- brain death
17 variables or signs in 1st 12 hrs

Summary CIRCI

- Unclear what diagnosis criteria should be
- Unclear benefits from treatment

### Adrenal Insufficiency in Preterm Infants
- Prior to 30 weeks gestation minimal fetal cortisol
- Absence of 3β-hydroxysteroid dehydrogenase until 23 weeks
- Suppression of fetal HPA axis by maternal cortisol
- Later in gestation placental 11β-hydroxysteroid dehydrogenase-2 begins to inactivate maternal cortisol
- Several studies demonstrate lower basal & stimulated cortisol in preterm infants with hypotension

### Adrenal Insufficiency in Term Neonates
- Placenta produces CRH, increasing with gestation
- Placental CRH is stimulated by cortisol (differs from hypothalamic CRH)
- At birth, placental CRH is suddenly withdrawn
- HPA axis may be suppressed during transition
- Critically ill newborns may have relative adrenal insufficiency

### NICU Consults
- From January, 2005 - December, 2006 24 consults (1 per month)
- Quality Improvement Protocol Initiated November, 2007
- From July, 2007 - October 2010 (40 months) 20 consults (1 per 2 months)

### NICU Steroid Protocol
- November, 2007 NICU and Endocrine Protocol
- Cortisol level is NOT part of protocol
- Conditions that may require steroids
  - Airway edema
  - Hypotension
  - Rescue treatment in BPD to extubate
  - Extreme hypoxemia
  - CAH
**Decrease in NICU Consults**
- Established criteria for starting steroids
- Most importantly if steroids not helping than d/c
- Attempt to get all neonates off steroids by 9 days
- Protocols depending on time on steroids
  - 10-14 days: F/U with PMD, no Endocrine
  - 14-28 days: +/- Endocrine
  - >28 days: +Endocrine consult
- Steroid wean protocol

**Quality Assurance/ Improvement Project**
- All patient charts with the ICD-9 code of 255.41 from 7/1/07-31/10 were reviewed
- 65 inpatient consults
- 52 unique patients
- 7 with known adrenal insufficiency
  - Brain tumor
  - X-linked adrenal leukodystrophy
  - Addison's disease (2)
  - Neuroblastoma
  - Chronic steroids – Diamond-Blackfan Anemia
  - Adrenalectomy

**Patient Locations**
- 32 PICU or s/p PICU
- 20 NICU

**Adrenal Test**
- Random/Fasting Cortisol
- Cosyntropin 250 mcg IV
- Cosyntropin 250 mcg IM
- Cosyntropin 10 mcg IV
- Cosyntropin 10 mcg IM
- Cosyntropin 1 mcg SubQ
- Cosyntropin other

**Testing HPA Axis**
- Insulin Induced Hypoglycemia
  - Too dangerous
  - Too labor intensive
- Metyrapone
  - Dangerous if true adrenal insufficiency
  - Takes too long
- Standard Cosyntropin test
  - 250 mcg
  - Measure levels at 30 and 60 minutes
  - High rate false negative

**Low Dose Cosyntropin**
- 1 mcg Cosyntropin IV
- Widely used starting around 2000
- Cortisol peaks at 30 minutes
- More sensitive for central adrenal insufficiency than standard dose
Delivered ACTH1–24 concentration as a function of the surface area of the delivery equipment and the composition of the diluent.

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Adrenal Insufficiency Consult Outcomes

- 7 adrenal insufficiency
- 1 patient died
- 32 cleared based on pre-treatment labs/stimulation test
  - 21 were cleared before discharge
  - 11 were cleared as outpatients
- 12 patients either failed testing or were lost to F/U
  - 2 on maintenance steroids
  - 9 on stress dose steroids
  - 1 on “natural” steroids for “adrenal fatigue”
Problems with Overdiagnosing or Overtreating CIRCI

- May take months to years to resolve
- Parental anxiety
- Unnecessarily treating during future illness-potential to impede recovery
- Misunderstanding leading to iatrogenic adrenal insufficiency

Goals

- Consensus within Endocrine
  - Diagnostic test to use
  - Criteria for pass/fail
- Treatment protocol consensus between Endocrine and PICU
  - Labs prior to treatment
  - Criteria for treatment
  - Criteria for discontinuation
  - Criteria for further follow-up

Conclusions

- Temporary adrenal insufficiency in the NICU occurs because of
  - Adrenal immaturity
  - Critical illness that occurs during the transition phase
- By working as a team we can
  - Identify patients at highest risk for adrenal insufficiency
  - Reduce parental anxiety

Conclusions- 2

- CIRCI in the PICU much harder to diagnose
- We can and should do a better job identifying and treating patients at risk for adrenal insufficiency post-PICU