A Second-Tier Screening Approach for CAH: Oklahoma’s Experience

Kathy Kirk, RN, MSN
Theresa Steckel, BSN, RN
Pam King, MPA, RN
Debbie Kline, BS
Edd Rhoades, MD, MPH
Kenneth Copeland, MD
92% (46) states plus DC screen for CAH
- No CAH screening currently offered:
  - Arkansas
  - Kansas
  - West Virginia
- Limited CAH screening:
  - Montana (by request)
Anticipated Hurdles

- Endocrinologists in Oklahoma hesitant
  - False Positives (prematurity, sickness/stress at birth, rarely twins sharing blood *in utero*)
    - Increase the real cost of screening
    - Increase the workload of specialists
    - Desensitize providers to needed follow-up
    - Increase parental stress
  - Detection of “non-classics”
    - Not the primary goal of screening
    - Best treatment approach unclear
Expansion for CAH

- OGAC recommended expansion – 2000
- BOH mandated 2004

Newborn Screening Committee of OGAC established an Endocrine Workgroup:
- Pediatric endocrinologists in Oklahoma
- OSDH Lab
- OSDH Follow-up
Endocrine Workgroup
Recommendations

- Two-tier Screen
- Courier – screen result by 8th day of life
- Aggressive STFU Protocol with ER referral
- Long-term Endocrine Follow-up Nurse
Oklahoma CAH Screening Start Date

February 14, 2005
Screening

First-tier: OSDH performs 17-OHP assay
  – Perkin Elmer AutoDELFIA

Second-tier: Mayo performs steroid profile **ONLY** on 17-OHP values identified out-of-range by OSDH lab
  – OSDH overnights specimens to Mayo
  – Contract - $20.00 per specimen
Second-Tier Test
Mayo Medical Laboratories

17-OHP by LC-MS/MS
- Liquid chromatography-tandem mass spectrometry

If LC-MS/MS 17-OHP elevated
⇒ ratio performed

Test performed on the same OSDH filter paper
Mayo Medical Laboratories
Steroid Profiling

17-OHP
- Abnormal > 10.2 ng/ml

Ratio = \frac{17-\text{OHP} + \text{Androstenedione}}{\text{Cortisol}}
- Abnormal > 2.5
Mayo Reporting
# Business days

- 76% two days
- 19% one day
- 5% >= three days
Screen Results – Not Consistent with CAH as of January 1, 2007

<table>
<thead>
<tr>
<th>Birth Weight ≥ 2500 grams:</th>
<th>17-OHP ng/ml</th>
<th>Steroid Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 50 &amp;</td>
<td>Not performed</td>
<td></td>
</tr>
<tr>
<td>&lt; 90 &amp;</td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Birth Weight &lt; 2500 grams:</th>
<th>17-OHP ng/ml</th>
<th>Steroid Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 100 &amp;</td>
<td>Not performed</td>
<td></td>
</tr>
<tr>
<td>≥ 100 &amp;</td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>
### Screen Results – Referred to Follow-up as of January 1, 2007

#### Birth Weight > 2500 grams:

<table>
<thead>
<tr>
<th>17-OHP ng/ml</th>
<th>Steroid Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 90</td>
<td>&amp; pending, normal or abnormal</td>
</tr>
<tr>
<td>50 to 89</td>
<td>&amp; abnormal</td>
</tr>
</tbody>
</table>

#### Birth Weight < 2500 grams:

<table>
<thead>
<tr>
<th>17-OHP ng/ml</th>
<th>Steroid Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 190</td>
<td>&amp; pending, abnormal</td>
</tr>
<tr>
<td>&gt; 100</td>
<td>&amp; abnormal</td>
</tr>
</tbody>
</table>
Due to delays related to second-tier testing, providers notified of OSDH presumptive 17-OHP values before second-tier testing is available.

Due to the emergent nature of CAH screening, LTFU Staff are involved in the diagnostic process for discharged infants.

The Endocrine LTFU is on call 24 hours a day.

STFU Staff are on call 24 hours for Mayo reporting – including weekends.
<table>
<thead>
<tr>
<th>Short-Term Follow-Up Actions</th>
<th>Endocrine Long-Term Follow Up Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Contact PCP and provide detailed &amp; <strong>timed</strong> follow-up instructions.</td>
<td>☐ Contact PCP to assist with location of family and provide F/U guidance as needed.</td>
</tr>
<tr>
<td>☐ Contact Endocrine Long term Follow up Nurse (ELFU).</td>
<td>☐ Assist with referral to specialist.</td>
</tr>
<tr>
<td>☐ Monitor for completion of DX process.</td>
<td>☐ Assist with routing confirmatory testing to contracted OSDH Lab.</td>
</tr>
<tr>
<td>☐ Assist ELFU as needed to ensure timelines are met.</td>
<td>☐ Provide support and emergency education to families.</td>
</tr>
<tr>
<td>☐ Ends with DX and TX date (if applicable).</td>
<td>☐ Ensure diagnostic timelines are met.</td>
</tr>
<tr>
<td></td>
<td>☐ Follow confirmed cases into adulthood.</td>
</tr>
</tbody>
</table>
Diagnostic Workup

- Serum 17-OHP (by an OSDH approved lab)
- BMP
- Clinical assessment:
  - Ambiguous genitalia (females)
  - Adrenal insufficiency
    - Change feeding patterns
    - Vomiting
    - Diaphoresis
    - Tachypnea
    - Pale mucus membranes
    - Dehydration
Emergency Protocol

- Locate infant within 24 hours
- Office or ER visit within 24 hours for clinical assessment
- Pediatric Endocrinology consult after assessment and review of BMP
- Parent Education - ELFU
Hospitalized Protocol

- Monitor BMP daily
- Repeat filter paper within 24 to 48 hours
- Monitor for S&S of adrenal insufficiency
- Consult Pediatric Endocrinologist (within 24 hours) for:
  - Abnormal BMP
  - Ambiguous genitalia
  - S/S adrenal insufficiency
  - Abnormal repeat filter paper
20 months of screening  
Feb 14, 2005 to October 31, 2006

94,044 Specimens tested by OSDH

689 (0.7%) specimens
Out-of-Range 17-OHP

518 (75%)
NORMAL Steroid profile  
(Not Recalled)

31 (5%)
ABNORMAL Steroid profile  
(Recalled)

140 (20%)
OSDH 17-OHP and NORMAL Steroid profile  
(Recalled)

4
Salt wasting CAH

148
Not consistent with classical salt-wasting CAH

15 expired unrelated to CAH
Reduction of Recall Utilizing Second-Tier

Out-of-Range 17-OHP on filter paper, includes repeats
Using Second-Tier, Newborns recalled for further testing
Potential reduction of recall i.e., stop recalling ALL normal steroid profiles

2/14/05 to 10/31/06
# Cases – Confirmed Salt wasting CAH

<table>
<thead>
<tr>
<th>Case</th>
<th>OSDH Filter Paper 17-OHP (ng/ml)</th>
<th>MML 17-OHP (ng/ml)</th>
<th>MML Ratio</th>
<th>Treatment Initiated (DOL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>227</td>
<td>672</td>
<td>55.21</td>
<td>7 days</td>
</tr>
<tr>
<td>Case 2</td>
<td>68.7</td>
<td>27.3</td>
<td>4.31</td>
<td>10 days</td>
</tr>
<tr>
<td>Case 3</td>
<td>251</td>
<td>129</td>
<td>2.64</td>
<td>&lt; 1 day</td>
</tr>
<tr>
<td>Case 4</td>
<td>207</td>
<td>242</td>
<td>26.8</td>
<td>3 days</td>
</tr>
</tbody>
</table>
Second-Tier Lessons Learned

- Learning curve for providers, including reporting of pending results
- Maternal or neonatal steroid treatment *may* result in false negatives – mailer modified and follow-up nurse inquiry
- 27 specimens of the 689 (4%) had an abnormal steroid profile, but normal confirmatory testing
  - All confirmed cases had abnormal steroid profiles
- Weekend communication – Mayo tests when OSDH program is closed
Lessons Learned

Fall 2005: Presumptive cut-offs adjusted for low birth weight infants and protocol for hospitalized newborns established, recommending repeat filter paper if clinically stable.

Spring 2006: For discharged infants, follow-up nurse has discretion (in collaboration with provider) to repeat filter paper, if clinically stable (all infants referred to ELFU for parent education).

January 2007: Discontinued recommending follow-up testing for low birth weight infants with normal steroid profile (OSDH stills calls provider on cases with significantly elevated 17-OHP, while steroid profile is pending)
In Conclusion...

- Oklahoma successfully implemented newborn screening for CAH in February, 2005
- Second state to utilize CAH second-tier screening:
  - Avoided unnecessary diagnostic and/or repeat filter paper testing costs
  - No false negatives have been reported
  - 518 families avoided parental stress related to recall
  - Follow-up rates decreased from 1:137 to 1:563

Future confidence in normal second tier results would further reduce recall rates to 1:3,034.
Acknowledgements

- OGAC
- Pam King, MPA, RN
- Kenneth Copeland, MD
- Edd Rhoades, MD, MPH
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- Debbie Kline, OSDH Lab
- OSDH STFU Staff
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  - Paula Vann, RN
  - Terry Geisler, LPN
  - Mary Beth Wilhelm, AA

Oklahoma State Department of Health (OSDH) Newborn Screening Program

www.health.ok.gov/program/gp
(405) 271-6617
Thank you!