Objectives

- Review the 2010 Centers for Disease Control and Prevention (CDC) Guidelines for the Prevention of Perinatal GBS
- Discuss the process for developing and evidence base for the new guidelines
  - Highlight local research that contributed
- Review the new Neonatal Algorithm

Incidence of GBS Disease 1990-2008

Early-onset GBS Disease (EOGBS)

- Guidelines introduced in 1996 and revised in 2002
- There has been an ~80% reduction in EOGBS following introduction of the guidelines
  - Remains leading cause of early-onset neonatal sepsis in US
  - Estimated 1,200 cases per year
- Clinical presentation
  - Typically within 24-48 hours
  - Respiratory distress, apnea, signs of sepsis
  - Sepsis and pneumonia most common
    - Meningitis less common
- Case fatality rate
  - 1970s: >50%
  - 4-6% in recent years
1996 Consensus Guidelines for GBS Prevention

- Screening-based approach:
  - Vaginal-rectal culture at 35-37 wks gestation
  - Intrapartum antibiotic prophylaxis (IAP) for GBS carriers
  - IAP for preterm delivery (unless negative culture result available)
- Risk-based approach:
  - IAP for preterm deliveries, membrane rupture >18 hours, or intrapartum fever (T >38°C)
- Both strategies: IAP to women with
  - GBS bacteriuria during pregnancy
  - Previous infant with GBS disease

2002 Guidelines: Key Changes

- Universal Screening
  - Culture at 35-37 wks gestation
- IAP agents for penicillin-allergic
- No routine IAP for planned cesarean deliveries
- GBS screening and IAP for threatened preterm deliveries
- More detail on specimen collection and handling
- Neonatal management
  - Addition of chorioamnionitis

Implementation Challenges

- Missed prevention opportunities among preterm
  - 50% screened prior to admission
  - 18% of GBS unknown screened on admission
  - Preterm less likely to receive IAP when indicated than term;
    • RR 0.81 (95% CI: 0.75-0.87)
- Penicillin-allergic women
  - At low risk for anaphylaxis:
    - 14% receive cefazolin (preferred agent)
    - 70% receive clindamycin
  - Only 5% have susceptibility testing
    - 25-30% of isolates are resistant
  - Reports of EOGBS in infants born to women receiving clindamycin
- False Negative Culture-based Screens
  - ~80% of infants with EOGBS are born to women with negative screens

GBS Guidelines Revision

- Key stakeholders convened early 2009
  - AAP, AAFP, ACNM, ACOG, ASM, SHEA, pharmacologists, state health departments, parent organizations
- Meeting June 22-23, 2009
  - Review relevant data
  - Published literature
  - Surveillance data
- Identify areas of guidelines that should be changed or clarified
- Make evidence-based revisions to guidelines
2010 GBS Prevention Guidelines: Maintain Primary Prevention Strategies

- Universal screening at 35-37 weeks
- IAP for:
  - GBS positive
  - GBS unknown with
    - Delivery <37 weeks
  - Intrapartum temperature ≥100.4
  - Rupture of membranes ≥18 hours
  - Previous infant with GBS disease
  - GBS bacteriuria
- Penicillin preferred agent
  - Ampicillin acceptable alternative

2010 GBS Prevention Guidelines: Important Changes

- Laboratory methods
  - Use of pigmented media to detect GBS
  - Role of PCR testing
  - Prenatal (requires enrichment step)
- Obstetric management
  - Revised cut-off for reporting GBS bacteriuria (>10^3)
  - Updated, more directive recommendations for threatened preterm delivery
- Neonatal Management: revised algorithm

Obstetrical Management

- New algorithms for
  - Preterm Labor
  - Preterm Premature Rupture of Membranes
- Stress collection of GBS screens at presentation
- Recommend antibiotics that cover GBS and are aligned with antibiotics given for latency

Algorithm for GBS intrapartum prophylaxis for women with PTL

- Patient admitted with signs and symptoms of preterm labor
  - Obtain vaginal-rectal swab for GBS culture* and start GBS prophylaxis
    - Yes
      - Patient entering true labor?
        - No
          - Discontinue GBS prophylaxis
        - Yes
          - Obtain GBS culture results
            - Positive
              - Not available prior to labor or patient still premature
            - Negative
              - GBS prophylaxis at onset of true labor
  - No GBS prophylaxis; repeat vaginal-rectal culture if patient reaches 35–37 weeks' gestation and has not yet delivered

Algorithm for GBS intrapartum prophylaxis for women pPROM

- Patient entering labor?
  - Yes
    - Continue antibiotics until delivery
  - No
    - Continue antibiotics per standard of care if receiving for latency OR GBS prophylaxis
      - Positive
        - Not available prior to labor or patient still premature
      - Negative
        - GBS prophylaxis at onset of labor
  - No GBS prophylaxis; repeat vaginal-rectal culture if patient reaches 35–37 weeks' gestation and has not yet delivered
Caesarean Section

- GBS prophylaxis is not indicated for C-section delivery prior to onset of labor and rupture of membranes at any gestational age

Antibiotic Prophylaxis

- Penicillin is preferred
- Dosing has been increased to accommodate commercially available drug formulations
  - 5 million units IV initially
  - 2.5-3 million units IV every 4 hours until delivery

Antibiotics Selection for Intrapartum GBS Prophylaxis

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Efficacy</th>
<th>Effectiveness</th>
<th>Favorable pharmacokinetics in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>no</td>
<td>no</td>
<td>limited</td>
</tr>
</tbody>
</table>

Penicillin Allergy

- Specific risks for anaphylaxis are identified
  - Previous anaphylaxis, angioedema, respiratory distress, or urticaria
- Cefazolin is emphasized for all PCN allergic without above risk factors
- Clindamycin should only be used if susceptibility testing documented
- Erythromycin is recognized as ineffective

Regimens for IAP for prevention of EOGBS

- Patient allergic to penicillin?
  - Yes: Cefazolin, 2g IV initial dose, then 1 g IV every 4 hrs until delivery
  - No: Penicillin G, 5 million units IV initial dose, then 2.5–3.0 million units† every 4 hrs until delivery or Ampicillin, 2g IV initial dose, then 1 g IV every 4 hrs until delivery

‘False Negative’ EOGBS Cases

- False negative = negative prenatal GBS screen
  - Some false negative cases are expected
  - Imperfect test with imperfect timing
- Majority of EOGBS cases are ‘false negative’
  - 82% of term cases in Boston, 1997-2003
  - 79% of term cases in Utah, 2002-2006
  - 61% of term cases in 10 states, 2003-2004
  - Expected: 23-46% of cases

Puopolo et al, Pediatrics 2005;115;1240-1246
Laboratory Testing

- Vaginal/rectal swab
  - Enrichment broth (pigmented or non-pigmented)

- Once in enrichment media, can use
  - culture-based
  - nucleic acid based algorithm

New Research

- Evaluation of GBS in the microbiome of Healthy Pregnant Women
  - Weekly variation in healthy non-pregnant women in overall microbiome
- Collaboration with OB/Gyn, Pediatrics and Microbial Ecology at University of Idaho
- Better understanding of what a GBS screen means

Revision of the Neonatal Algorithm: Secondary EOGBS Prevention

- Broaden the scope
  - Recognize that majority of cases are now infants born to women with negative GBS screen
  - Provide recommendations for management of infants born to GBS positive woman with no IAP

- Clarify algorithm
  - Eliminate algorithm “dead ends”
  - Clarify adequate IAP

- Reduce unnecessary evaluations and antibiotics
  - Encourage rigorous definition of chorioamnionitis
  - Recommend clinical observation for well-appearing, low-risk infants with inadequate IAP

Concerns about the Algorithm

- Focus only on newborns with IAP
- No recommendations for newborns exposed to clindamycin or vancomycin
- Chorioamnionitis
- Potentially unnecessary neonatal diagnostic evaluations
  - Limited yield of the limited evaluation
Limited Data on Limited Evaluation

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sepsis cases N</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>PPV %</th>
<th>PVN %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerdes, 1987</td>
<td>13</td>
<td>46</td>
<td>92</td>
<td>27</td>
<td>96</td>
</tr>
<tr>
<td>Greenberg, 1990</td>
<td>19</td>
<td>63-68</td>
<td>45-55</td>
<td>43-46</td>
<td>70-71</td>
</tr>
<tr>
<td>Initial (0-7 hrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeat (12-24 hrs)</td>
<td>17</td>
<td>100</td>
<td>50-73</td>
<td>56-73</td>
<td>100</td>
</tr>
<tr>
<td>Ottolini, 2003</td>
<td>17</td>
<td>41</td>
<td>73</td>
<td>1.5</td>
<td>99</td>
</tr>
</tbody>
</table>

* varying sepsis definitions of abnormal CBC were applied


Clinical Signs of Sepsis: Sensitive Indicator

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
<th>+PV</th>
<th>-PV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of clinical signs</td>
<td>92%</td>
<td>53%</td>
<td>4%</td>
</tr>
<tr>
<td>Baby critically ill</td>
<td>31%</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>ANC &lt;10th percentile</td>
<td>48%</td>
<td>73%</td>
<td>4%</td>
</tr>
<tr>
<td>ANC &lt;10th percentile</td>
<td>16%</td>
<td>96%</td>
<td>8%</td>
</tr>
<tr>
<td>Manroe et al</td>
<td>I:T ratio, &gt;= .25 cutoff</td>
<td>45%</td>
<td>84%</td>
</tr>
<tr>
<td>I:T ratio, &gt;= .30 cutoff</td>
<td>35%</td>
<td>89%</td>
<td>7%</td>
</tr>
</tbody>
</table>


Health Services Utilization for Neonates

- Concern that GBS chemoprophylaxis may lead to excessive evaluations and antibiotics in neonates
- Population-based study in CT, 1996
  - Infants exposed to IAP were not more likely to receive antibiotics and did not have increased length of stay
- Administrative data from 19 hospitals in UT, ‘98-’02
  - Infants whose mother received any IV antibiotic were more likely to receive antibiotics >72 hrs and had increased length of stay


Glasgow et al, Paed and Perinatal Epidemiology, 21, 338–346.

Neonatal Algorithm

- Applies to all newborns
- Adequate prophylaxis is defined as PCN, Ampicillin, or Cefazolin for at least 4 hours prior to delivery
- Definition of Term and Preterm now are >/= 37 weeks and < 37 weeks
- Well appearing infants at 35-36 weeks with adequate prophylaxis do not need laboratory evaluation

1. Full diagnostic evaluation includes: blood culture, CBC, chest radiograph (if respiratory abnormalities are present), and lumbar puncture (if patient is stable enough to tolerate procedure and sepsis is suspected).
2. Antibiotic therapy should be directed toward the most common causes of neonatal sepsis, including intravenous ampicillin for GBS and coverage and should take into account local antibiotic resistance patterns.
3. Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis.
4. Limited evaluation includes: blood culture (at birth) and CBC with differential and platelets (at birth and/or at 6–12 hours of life).
5. If signs of sepsis develop, a full diagnostic evaluation should be conducted and antibiotic therapy initiated.
6. If ≥37 weeks’ gestation, observation may occur at home after 24 hours. If other discharge criteria have been met, access to medical care is readily available, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until discharge criteria are achieved.
Summary: 2010 GBS Guidelines

• Major strategies remain the same
  – Universal screening and IAP for GBS-colonized

• Key changes in 2010
  – New laboratory options for detection of GBS
  – Refined recommendations for obstetric providers
    • EDGBS prevention among preterm
    • Antibiotic choices for penicillin-allergic
  – Revised neonatal algorithm
    • Broaden scope
    • Increase clarity
    • Decrease unnecessary evaluations and antibiotics for low-risk infants

QUESTIONS!