Early-onset Group B Streptococcal Disease Prevention: For Clinicians

Overview of CDC Prevention Guidelines, 2010

National Center for Immunization and Respiratory Diseases
Division of Bacterial Diseases

November 19, 2010
Background on Group B Streptococcal (GBS) Disease and Prevention
Group B Streptococcus

- Gram positive, beta hemolytic bacteria
- Common colonizer of human gastrointestinal and genitourinary tracts
- Recognized as causing disease in humans in the 1930s
- Causes serious disease in young infants, pregnant women and older adults
- Emerged as most common cause of sepsis and meningitis in infants <3 months in the 1970s
Early-onset: 0-6 days of life

Late onset: 7-89 days of life

Early-onset GBS Disease (EOGBS)

• **Leading infectious cause of neonatal sepsis in U.S.**
  - Annual incidence in 2008: 0.28 cases / 1,000 live births
  - Estimated 1,200 cases in 2008

• **Clinical presentation**
  - Typically symptoms appear on day 0 or day 1 of life
  - Respiratory distress, apnea, signs of sepsis most common symptoms
  - Bacteremia most common form of disease (app. 80% of cases)
  - Pneumonia and meningitis less common

• **Case fatality rate**
  - 1970s: As high as 50%
  - 4-6% in recent years
Photo courtesy of Dr. Carol Baker Baylor College of Medicine, Houston, TX
GBS Maternal Colonization

- **GBS Carriers**
  - 10% - 30% of women
  - Higher proportion in African Americans and nonsmokers
  - GBS usually live in gastrointestinal tract but can spread to the genital tract
  - No symptoms or signs on examination
  - Colonization comes and goes over months
  - Not a sexually transmitted infection

- **Risk factor for early-onset disease: GBS colonization during labor and delivery**
  - Prenatal cultures late in pregnancy can predict delivery status
Mother to Infant Transmission of GBS

GBS colonized mother

- Non-colonized newborn (50%)
- Colonized newborn (50%)

- Asymptomatic (98%)
- Early-onset sepsis, pneumonia, meningitis (2%)
Additional Risk Factors for Early-onset GBS Disease

- **Obstetric risk factors:**
  - Preterm delivery
  - Prolonged rupture of membranes
  - Infection of the placental tissues or amniotic fluid / fever during labor

- **GBS in the mother’s urine during pregnancy** (marker for heavy colonization)

- **Previous infant with GBS disease**

- **Low maternal levels of anti-GBS antibodies**

- **Demographic risk factors**
  - African American
  - Young maternal age
Prevention of Early-onset GBS Disease

• **Intrapartum antibiotics (IAP)**
  – Highly effective at preventing early-onset disease in women at risk of transmitting GBS to their newborns
  – Efficacy in clinical trials: 100%
  – Effectiveness in observational studies: 86-89%

• **Challenge: How best to identify women who should receive IAP?**
1996 Consensus Guidelines for GBS Prevention

• **Screening-based approach:**
  – Vaginal-rectal culture at 35-37 wks
  – IAP for GBS carriers
  – IAP for preterm delivery (unless negative culture result available)

• **Risk-based approach:**
  – No vaginal-rectal culture
  – 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
Rate of Early-onset GBS Disease in the 1990s, United States

Group B Strep Association formed
1st ACOG & AAP statements
CDC draft guidelines published
Consensus guidelines

Cases per 1,000 live births


Year

Early-onset GBS disease

Screening for GBS Protects More Infants from Early-onset GBS than Relying on Risk Factors

- Infants whose mothers are screened for GBS are less than half as likely to develop early-onset GBS disease as mothers who are not screened.

- Screening identifies colonized women without obstetric risk factors (18% of all deliveries in 1990s).

2002 GBS Guidelines: Key Changes

- Single strategy for identifying candidates for IAP: universal screening by culture at 35-37 wks
- IAP agents for penicillin-allergic
  - Cefazolin, except for women at high risk of anaphylaxis
- 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 and Impact of Early-onset GBS Disease Prevention Guidelines
Proportion of Women Screened for GBS Colonization

- Proportion of women screened increased from 48% to 85%
- 98% of women screened had available result at labor

Van Dyke et al., NEJM 2009 360: 2626-36
Proportion of Women with an Indication for GBS IAP Who Received GBS IAP

- Proportion of women with an indication for IAP who then received IAP increased from 74% to 85%

Van Dyke et al., NEJM 2009 360: 2626-36
Rate of Early- and Late-Onset GBS, 1990-2008

Source: Active Bacterial Core surveillance / Emerging Infections Program
Early-onset GBS Disease in the U.S., 2000-2008

Source: Active Bacterial Core surveillance / Emerging Infections Program
Implementation Challenges

• Missed prevention opportunities among infants born preterm
  – 50% screened prior to admission
  – Only 18% of GBS unknown screened on admission
  – Preterm 20% less likely to receive IAP when indicated than term
  – Receipt of ≥4 hours IAP protective (78% effective, 95% CI 44-91)

• Penicillin-allergic women
  – Only 14% at low risk for anaphylaxis received cefazolin
  – 70% at low risk for anaphylaxis received clindamycin even though
    • <5% had susceptibility testing
    • No data on efficacy/effectiveness of clindamycin to prevent EOGBS

GBS Resistance: Clindamycin and Erythromycin
All Ages, 2001-2008*

*Isolates are from CO, GA, MD, MN, NY, and OR. 2007 data excluded since only early-onset isolates were tested.

Source: Active Bacterial Core surveillance / Emerging Infections Program
Potential Unintended Consequences of GBS Prevention Guidelines

• **Adverse drug reactions**
  – Anaphylaxis among women receiving GBS IAP very rare
  – Two studies reviewing >12,000 births found one non-fatal case
  – Four published case reports in U.S. since 1996

• **Impact on non-GBS sepsis**
  – Stable or decreasing rates in most studies
  – *E.coli* sepsis may be increasing among pre-term infants, but trends not consistent across studies

• **Health services utilization for neonates**
  – Studies conducted during 1996-2002 reported increased, stable, or decreased use of health services for neonates whose mothers received IAP
  – No studies on the impact of the 2002 guidelines
2010 GBS Guidelines

Organizations Endorsing CDC’s 2010 GBS Guidelines

- American College of Obstetricians and Gynecologists
- American Academy of Pediatrics
- American College of Nurse-Midwives
- American Academy of Family Physicians
- American Society for Microbiology
2010 GBS Guidelines: Methods

- Key stakeholders convened late 2008
  - American Academy of Pediatrics, American Academy of Family Physicians, American College of Nurse-midwives, American College of Obstetricians and Gynecologists, Centers for Disease Control and Prevention, Society for Hospital Epidemiology of America, American Society for Microbiology, microbiologists, pharmacologists, state health departments, parent organizations

- Reviewed relevant data
- Identified areas of guidelines that needed changes or clarifications
- Made evidence-based revisions to guidelines
Prevention of Perinatal Group B Streptococcal Disease
Revised Guidelines from CDC, 2010

Continuing Education Examination available at http://www.cdc.gov/mmwr/cms/conted.html

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
Key Prevention Strategies Remain Unchanged in 2010

- **Universal screening of pregnant women for GBS at 35-37 weeks gestational age**
- **Intrapartum antibiotic prophylaxis for:**
  - GBS positive screening test
  - GBS colonization status unknown with
    - Delivery <37 weeks
    - Temperature during labor ≥100.4°F (>38.0°C)
    - Rupture of membranes ≥18 hours
  - Previous infant with GBS disease
  - GBS in the mother’s urine during current pregnancy
- **Penicillin preferred drug for IAP**
  - Ampicillin acceptable alternative
  - Cefazolin preferred for penicillin-allergic at low risk of anaphylaxis
Identification of Candidates for IAP in the 2010 GBS Guidelines
Indications for Intrapartum GBS Prophylaxis

- Previous infant with invasive GBS disease
- GBS bacteriuria during current pregnancy
- Positive GBS screening test during current pregnancy
- Unknown GBS status AND any of the following:
  - Delivery at $<37$ weeks’ gestation
  - Amniotic membrane rupture $\geq 18$ hours
  - Intrapartum temperature $\geq 100.4^\circ F$ ($\geq 38.0^\circ C$)
Intrapartum GBS Prophylaxis Not Indicated

- Colonization with GBS during a previous pregnancy
  - Unless another indication during the current pregnancy
- GBS bacteriuria during a previous pregnancy
  - Unless another indication during the current pregnancy
- Negative vaginal and rectal GBS screening test during the current pregnancy
  - Regardless of intrapartum risk factors
- Cesarean delivery performed before labor onset on a woman with intact amniotic membranes
  - Regardless of maternal GBS test status
  - Regardless of gestational age
Bacteriuria

- **GBS in urine during pregnancy**
  - GBS found in urine of 2%-7% of pregnant women
  - Marker of heavy vaginal-rectal colonization
  - Risk factor for early-onset GBS disease in the newborn
  - Antibiotic treatment of GBS bacteriuria during pregnancy does not eliminate GBS from the genitourinary and gastrointestinal tracts, and recolonization after a course of antibiotics is typical

- **Clinicians must inform laboratories when submitted urine specimens are from pregnant women**
- **Women with symptomatic or asymptomatic GBS urinary tract infections detected during pregnancy should be treated according to current standards of care**
- **Women with GBS isolated from the urine at any time during the current pregnancy should receive IAP**
Prenatal GBS Sample Collection

• **Site:** vagina and rectum
  – Single swab or two swabs
  – Lower 1/3 of vagina
  – Through anal sphincter
  – Collection: NOT by speculum
  – Self collection an option

• **Timing:** 35 to 37 weeks

• **Transport:** Nonnutritive transport medium
  – Examples - Stuart’s or Amies
  – With or without charcoal
  – Results most sensitive if processed within 24 hours of collection
  – Results most sensitive if refrigerated before processing
Antimicrobial Susceptibility Testing for Penicillin-Allergic Women at High Risk of Anaphylaxis

• Many isolates from invasive GBS disease are resistant to clindamycin or erythromycin
  – Resistance to erythromycin is associated frequently but not always with resistance to clindamycin
  – Some isolates susceptible to clindamycin but resistant to erythromycin may have inducible clindamycin resistance

• Antimicrobial susceptibility testing should be performed on antenatal GBS isolates from penicillin-allergic women at high risk for anaphylaxis
  – Should include testing for inducible resistance (e.g. D-zone test)

• Specimens from penicillin allergic women at high risk for anaphylaxis should be clearly labeled
Intrapartum testing for GBS

- Nucleic acid amplification tests (NAAT) such as PCR an option for intrapartum GBS testing for women who are GBS unknown at labor onset and have no risk factors
- Lower sensitivity for direct specimens (no enrichment)
  - Positive result: Administer IAP
  - Negative result and patient does not develop intrapartum temperature \( \geq 100.4^\circ F \) (\( \geq 38.0^\circ C \)) or have ROM \( \geq 18 \) hours: No IAP
  - Negative result and patient develops intrapartum temperature \( \geq 100.4^\circ F \) (\( \geq 38.0^\circ C \)) or has ROM \( \geq 18 \) hours: Administer IAP

- Additional slides on changes affecting laboratories in the 2010 GBS prevention guidelines can be found at: www.cdc.gov/groupbstrep/lab.html
FIGURE 7. Algorithm for recommended laboratory testing for prenatal screening for group B streptococcal (GBS) colonization*

Vaginal rectal swab

Enrichment broth (can use nonpigmented or pigmented broth)
   Incubate 18–24 hrs at 35°–37°C

Nonpigmented broth

Further testing (can subculture or use rapid tests)

Pigmented broth

No indicator color growth

GBS indicator color observed

Subculture to appropriate media; incubate 18–24 hrs at 35°–37°C

Identify GBS by recommended method*

GBS-

Reincubate overnight

GBS+

Report as GBS+

GBS-

Report as GBS-

DNA probe, latex agglutination or nucleic acid amplification test (NAAT)

GBS-

Report as GBS-

GBS+

Report as GBS+

Antimicrobial susceptibility testing if penicillin-allergic and at high risk for anaphylaxis*
Threatened Preterm Delivery

- Separate algorithms are presented for GBS prophylaxis in the setting of threatened preterm delivery, one for spontaneous preterm labor (PTL) and one for preterm premature rupture of membranes (pPROM).
- Women with PTL or pPROM should all receive:
  - Screening on admission for GBS if GBS status unknown
  - Antibiotics for GBS prophylaxis
- Antibiotics to prolong latency in pPROM can serve as GBS IAP if certain criteria are met
  - Ampicillin 2 g IV followed by 1 g IV every 6 hours for 48 hours
  - Delivery occurs while the mother is receiving that antibiotic regime
FIGURE 5. Algorithm for group B streptococcus (GBS) intrapartum prophylaxis for women with preterm* labor (PTL)

1. Patient admitted with signs and symptoms of preterm labor

2. Obtain vaginal-rectal swab for GBS culture† and start GBS prophylaxis§

3. Patient entering true labor??
   - Yes: Continue GBS prophylaxis until delivery**
   - No: Discontinue GBS prophylaxis

4. Obtain GBS culture results
   - Positive: GBS prophylaxis at onset of true labor
   - Not available prior to labor onset and patient still preterm: No GBS prophylaxis at onset of true labor;†† repeat vaginal-rectal culture if patient reaches 35–37 weeks’ gestation and has not yet delivered‡‡
   - Negative: No GBS prophylaxis at onset of true labor
FIGURE 6. Algorithm for group B streptococcus (GBS) intrapartum prophylaxis for women with preterm* premature rupture of membranes (pPROM)

1. Obtain vaginal-rectal swab for GBS culture† and start antibiotics for latency§ OR GBS prophylaxis¶.

2. Patient entering labor?
   - Yes: Continue antibiotics until delivery.
   - No: Continue antibiotics per standard of care if receiving for latency or continue antibiotics for 48 hours** if receiving for GBS prophylaxis.

3. Obtain GBS culture results.
   - Positive: GBS prophylaxis at onset of labor.
   - Not available prior to labor onset: No GBS prophylaxis at onset of true labor; †† repeat vaginal-rectal culture if patient reaches 35–37 weeks’ gestation and has not yet delivered§§.
   - Negative: No GBS prophylaxis.
Antibiotic Selection in the 2010 GBS Guidelines
Antibiotics for IAP

- **Penicillin** the first-line agent for IAP
  - Dosage: 5 million IU IV then 2.5-3.0 million IU IV every 4 hours
  - Revised dose (2.5-3.0 million IU) consistent with available penicillin formulations

- **Ampicillin** an acceptable alternative
# Data on Antibiotics for Intrapartum GBS Prophylaxis

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Efficacy (clinical trials)</th>
<th>Effectiveness (observational studies)</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>
Antibiotics for IAP in Women Allergic to Penicillin

• Cefazolin best option for a woman allergic to penicillin but not at high risk for anaphylaxis

• Drugs with less evidence for effectiveness (e.g. clindamycin, vancomycin) only for women at high risk of anaphylaxis
  – High risk for anaphylaxis defined as history of anaphylaxis, angioedema, respiratory distress or urticaria following penicillin

• Erythromycin no longer included as option
Antibiotics for IAP in Women Allergic to Penicillin

• **Women at high risk for anaphylaxis following penicillin or a cephalosporin may receive CLINDAMYCIN for GBS IAP if:**
  – Their GBS isolate is susceptible to clindamycin and erythromycin OR
  – Their GBS isolate is susceptible to clindamycin but resistant to erythromycin and testing for inducible resistance is negative

• **Women at high risk for anaphylaxis following penicillin or a cephalosporin may receive VANCOMYCIN for GBS IAP if:**
  – Their GBS isolate is intrinsically resistant to clindamycin OR
  – Their GBS isolate shows inducible resistance to clindamycin OR
  – Their GBS isolate’s susceptibility to clindamycin and erythromycin is unknown
2010 GBS Guidelines: Algorithm for Selecting IAP Regimens

FIGURE 8. Recommended regimens for intrapartum antibiotic prophylaxis for prevention of early-onset group B streptococcal (GBS) disease*

- Patient allergic to penicillin?
  - No
    - Penicillin G, 5 million units IV initial dose, then 2.5–3.0 million units† every 4 hrs until delivery or Ampicillin, 2 g IV initial dose, then 1 g IV every 4 hrs until delivery
  - Yes
    - Patient with a history of any of the following after receiving penicillin or a cephalosporin?:
      - Anaphylaxis
      - Angioedema
      - Respiratory distress
      - Urticaria
        - No
          - Cefazolin, 2g IV initial dose, then 1 g IV every 8 hrs until delivery
        - Yes
          - Isolate susceptible to clindamycin and erythromycin?*
            - No
              - Vancomycin, 1 g IV every 12 hrs until delivery
            - Yes
              - Clindamycin, 900 mg IV every 8 hrs until delivery
Newborn Management in the 2010 GBS Guidelines
Revised Neonatal Management Algorithm

- Applies to all newborns
  - Regardless of whether mother received IAP

- Management based on clinical appearance, risk factors (maternal chorioamnionitis, prolonged rupture of membranes, preterm), and adequacy of IAP if indicated for mother

- Adequate IAP clarified
  - \( \geq 4 \) hours of IV penicillin, ampicillin, or cefazolin before delivery
  - All other agents or durations are considered inadequate for purposes of neonatal management

- Aims to reduce unnecessary evaluations and antibiotics in newborns at relatively low risk for early-onset GBS disease
FIGURE 9. Algorithm for secondary prevention of early-onset group B streptococcal (GBS) disease among newborns

- Signs of neonatal sepsis?
  - Yes: Full diagnostic evaluation* Antibiotic therapy†
  - No
    - Maternal chorioamnionitis?§
      - Yes: Limited evaluation¶ Antibiotic therapy†
      - No
        - GBS prophylaxis indicated for mother??
          - Yes
            - Mother received intravenous penicillin, ampicillin, or cefazolin for ≥4 hours before delivery?
              - Yes: Observation for ≥48 hours††§§
              - No
                - ≥37 weeks and duration of membrane rupture <18 hours?
                  - Yes: Observation for ≥48 hours††¶¶
                  - No
                    - Either <37 weeks or duration of membrane rupture ≥18 hours?
                      - Yes: Limited evaluation¶ Observation for ≥48 hours††
                      - No
## Recommended Management: 2002 vs. 2010

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>2002</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn with signs of sepsis, no IAP</td>
<td>No guidance</td>
<td>Full evaluation +antibiotics</td>
</tr>
<tr>
<td>Well appearing newborn, maternal chorioamnionitis</td>
<td>No guidance</td>
<td>Limited evaluation +antibiotics</td>
</tr>
<tr>
<td>Well appearing newborn, GBS+ mother, no IAP</td>
<td>No guidance</td>
<td>Depends on GA and ROM</td>
</tr>
<tr>
<td>Well appearing newborn, mother w/ indication for IAP, received clindamycin or vancomycin</td>
<td>No guidance</td>
<td>Depends on GA and ROM</td>
</tr>
<tr>
<td>Well appearing newborn, mother w/ indication for IAP, received ampicillin, penicillin or cefazolin ≤4 hrs</td>
<td>Limited evaluation</td>
<td>Depends on GA and ROM</td>
</tr>
<tr>
<td>Well appearing newborn, mother w/ indication for IAP, received ampicillin, penicillin or cefazolin ≥4 hours, GA 35-36 weeks</td>
<td>Limited evaluation</td>
<td>Observation for ≥48 hours</td>
</tr>
</tbody>
</table>
What Can You Do to Help?

• Make sure your OB, Peds, FP, Midwife, and Microbiology colleagues know the new guidelines are out

• Check to see if your lab is following the new guidelines for laboratory methods

• Form a committee to plan steps needed for implementation in your facility
Early-onset GBS Disease Web Resources

- Centers for Disease Control and Prevention
  - [www.cdc.gov/groupbstrep](http://www.cdc.gov/groupbstrep)
- American College of Obstetricians and Gynecologists
  - [http://www.acog.org](http://www.acog.org)
- American Academy of Pediatrics
  - [http://www.aap.org](http://www.aap.org)
- American College of Nurse-Midwives
  - [http://www.midwife.org](http://www.midwife.org)
- American Academy of Family Physicians
  - [http://www.aafp.org](http://www.aafp.org)
- American Society for Microbiology
  - [http://www.asm.org/](http://www.asm.org/)
- Group B Strep Association
  - [http://www.groupbstrep.org](http://www.groupbstrep.org)
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