2010 Guidelines for GBS Prophylaxis

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Hypothetical Case #1

- Primagravida.
- Low risk PNC at Kaiser, routine.
- Active labor at term, good dates.
- Afebrile, membranes intact.
- GBS screen was not performed during PNC.
- Would you start antibiotics?
- Which antibiotic would you start?
Hypothetical Case #2

- Primagravida. Prenatal records available.
- Low risk PNC at an outside clinic, routine.
- Active labor at term, good dates.
- Afebrile, membranes intact.
- GBS screen was not performed during PNC.
- Would you start antibiotics?
- Which antibiotic would you start?

Hypothetical Case #3

- Primagravida at 36 weeks.
- Will undergo cesarean section for Severe Preeclampsia.
- Not in PTL, membranes intact.
- GBS unknown.
- Would you start antibiotics?
Hypothetical Case #4

- Primagravida at 36 weeks.
- Will undergo cesarean section for Severe Preeclampsia.
- Not in PTL, membranes intact.
- GBS positive.
- Would you start antibiotics?

Neonatal Sepsis

- In the early 20th century, Group A Streptococcus was the leading cause of neonatal and maternal peripartum infection in the U.S.
- Group B Streptococcus (GBS), or *Streptococcus agalactiae*, a gram-positive coccus.
- First identified in 1887.
- Originally known as a leading cause of bovine mastitis.

(Schrag and Stoll, Pediatr Infect Dis J., 2006)
Neonatal Sepsis (cont.)

- 1938: Fry reports 3 fatal cases of maternal postpartum sepsis from GBS.

![Image of Dr. Lancefield from Rockefeller University](image1.png)

Neonatal Sepsis (cont.)

- 1964: First study of perinatal GBS infections published.
- 1970s: GBS is the leading cause of neonatal sepsis.
- Incidence was 1.5 to 2 cases per 1,000 births.
- Fatality rates were 20% to 50%.
- Vertical transmission recognized as early as 1970s.
- 1980s: Early trials showed efficacy of intrapartum antibiotics.
- No large-scale programs aimed at reducing GBS infection, so incidence and mortality rates remained static into 1990s. (Baltimore, Semin Perinatol, 2007)
Neonatal Sepsis (cont.)

- GI tract is natural human reservoir.
- Likely source of vaginal colonization.
- Approximately 10-30% of pregnant women are colonized vaginally or rectally.
- Colonization can be transient, chronic or intermittent.
  (CDC, 2010)

Neonatal Sepsis (cont.)

- GBS colonized mothers
- Non-colonized infants
  - 50%
- GBS colonized infants
  - 50%
- Asymptomatic infants
  - 98%
- Early onset GBS Disease
  - 2%

(www.cdc.gov)
Neonatal Sepsis (cont.)

- GBS disease classified as early onset and late onset.
  - Early onset: first week of life.
  - Late onset: after first week to 3 months.
- Early disease from ascending spread from vagina into amniotic fluid.
- Fetal aspiration can lead to stillbirth, pneumonia or sepsis.
- Transmission occurs primarily after onset of labor or rupture of membranes.

(CDC, 2010)
Neonatal Sepsis (cont.)

- Transmission can occur through intact membranes.
- Pathogenesis of late disease less well-understood. (Stade, et al., Cochrane review, 2004)
- Infant may contract GBS during passage through birth canal, but most often this results in only asymptomatic colonization. (Dermer, et al., Jrnl Ped Nurs, 2004)

Morbidity and Mortality

- GBS meningitis: 50% rate of long-term neurodevelopmental delays at 5 years of life.
- Well-recognized cause of stillbirth. (Heath and Schuchat, 2007)
- Mortality rate of early onset disease declined to 4% due to improved neonatal care. (Baltimore, 2007)
Risk Factors, Racial Disparity

- Gestational age < 37 weeks.
- Longer duration of membrane rupture.
- Maternal age < 20.
- African-American race.
- Maternal fever / intra-amniotic infection.
- Previous delivery of infant with invasive GBS disease.
- Low maternal levels of anti-CPS IgG.
- GBS colonization.
  - Heavy colonization.
  (CDC, 2010)

Dueling Protocols

- July, 1992: ACOG issues first guidelines: intrapartum antibiotic prophylaxis (IAP) for known GBS carriers and ≥ 1 risk factor. ACOG stated that IAP may have benefit in cases of GBS unknown status and risk factors.
  - PTL
  - PPROM < 37 weeks
  - Prolonged rupture ≥ 18 hours
  - Prior infant with symptomatic GBS infection
  - Maternal fever during labor (99.5º)
  (Towers, et al., AJOG 1999)
Dueling Protocols (cont.)

- November, 1992: AAP publishes guidelines recommending all pregnant women be cultured at 26-28 weeks.
- IAP for women in labor with (+) culture and ≥ 1 risk factor.
  - Risk factors similar to ACOG, with the addition of GBS bacteriuria.
  (Towers, et al., 1999)

Dueling Protocols (cont.)

- May, 1993: ACOG stated that routine cultures are not recommended.
- May, 1996: CDC publishes new guidelines recommending either the risk factor approach or the culture approach.
  - June, 1996: ACOG adopts CDC guidelines.
  (Towers, et al., 1999)
After 1996

- 70% decline in incidence by 1999. (CDC, 2002)

After 1996 (cont.)

- Series of small, single-center studies showed culture approach superior to risk-based approach.
- Other persuasive findings:
  - Towers, et al. found that only 30% of documented cases of term GBS sepsis had evidence of maternal intrapartum risk factors. (AJOG 1999)
  - CDC-sponsored multistate comparison found culture approach 50% more effective than risk-based approach. (CDC, 2002).
After 1996 (cont.)

- 2 additional reasons why culture-only approach is superior:
  - Communication of a single strategy is simpler, more consistent than communicating 2 strategies.
  - Culture-based approach has clear metrics that can be followed to evaluate implementation.

(CDC, 2002)

2002 Guidelines

Vaginal and rectal GBS screening cultures at 35–37 weeks' gestation for ALL pregnant women (unless patient had GBS bacteriuria during the current pregnancy or a previous infant with invasive GBS disease)

- Previous infant with Invasive GBS disease
- GBS bacteriuria during current pregnancy
- Positive GBS screening culture during current pregnancy (unless a planned cesarean delivery, in the absence of labor or amniotic membrane rupture, is performed)
  - Unknown GBS status, culture not done, incomplete, or results unknown and any of the following:
    - Delivery at <37 weeks gestation*
    - Amniotic membrane rupture ≥18 hours
    - Intrapartum temperature ≥100.4°F (≥38.0°C)

Intrapartum *prophylaxis indicated

- Previous pregnancy with a positive GBS screening culture (unless a culture was also positive during the current pregnancy)
- Planned cesarean delivery performed in the absence of labor or membrane rupture (regardless of maternal GBS culture status)
- Negative vaginal and rectal GBS screening culture in late gestation during the current pregnancy, regardless of intrapartum risk factors

Intrapartum *prophylaxis not indicated

*If onset of labor or rupture of amniotic membranes occurs at <37 weeks' gestation and there is a significant risk for preterm delivery (as assessed by the clinician), a suggested algorithm for GBS prophylaxis management is provided (Figure 3).

1If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis.

(CDC, 2002)
2002 Guidelines (cont.)

- October, 2002: AAP endorsed CDC guidelines.
- December, 2002: ACOG endorsement.
- From 2002 to 2004 (after universal screening), 33% further decline in incidence of early-onset GBS disease.
- 0.34 per 1,000 births.
  - Incidence among black infants still more than 2x higher than white infants.
  (Schrag and Stoll, 2006)
- Approximately 1,600 cases of GBS sepsis and 80 deaths annually.
  (ACOG, 2002)

(CDC, 2002)
2002 Guidelines (cont.)

(Baltimore, 2007, reprinting CDC Data)

After 2002...

(CDC, 2010)
…Room for Improvement

- 85% of pregnant patients were screened for GBS.
- Of those, 98% had results available at delivery.
- 85% needing IAP received prophylaxis.
- "Suboptimal" GBS screening rates with threatened PTL:
  - 18% of women who progressed to delivery.
  - 31% of women who did not deliver.

(CDC, 2010)

…Room for Improvement

- Only 13.8% of patients with a low risk PCN allergy needing IAP received Cefazolin.
  - 70% of this group received Clindamycin.
  - No studies establishing efficacy of Clindamycin and Erythromycin.
  - Limited data suggests that Clindamycin and Erythromycin do not reach fetal tissues reliably.
  - Increasing resistance of GBS to Clindamycin.

(CDC, 2010)
New 2010 Guidelines

Previous Indications

Vaginal and rectal GBS screening cultures at 35–37 weeks' gestation for ALL pregnant women (unless patient had GBS bacteriuria during the current pregnancy or a previous infant with invasive GBS disease)

Intrapartum prophylaxis indicated
- Previous infant with invasive GBS disease
- GBS bacteriuria during current pregnancy
- Positive GBS screening culture during current pregnancy (unless a planned cesarean delivery, in the absence of labor or amniotic membrane rupture, is performed)
- Unknown GBS status (culture not done, incomplete, or results unknown) and any of the following:
  - Delivery at <37 weeks' gestation
  - Amniotic membrane rupture ≥18 hours
  - Intrapartum temperature ≥100.4°F (≥38.0°C)

Intrapartum prophylaxis not indicated
- Previous pregnancy with a positive GBS screening culture (unless a culture was also positive during the current pregnancy)
- Planned cesarean delivery performed in the absence of labor or membrane rupture (regardless of maternal GBS culture status)
- Negative vaginal and rectal GBS screening culture in late gestation during the current pregnancy, regardless of intrapartum risk factors

* If onset of labor or rupture of amniotic membranes occurs at <37 weeks’ gestation and there is a significant risk for preterm delivery (as assessed by the clinician), a suggested algorithm for GBS prophylaxis management is provided (Figure 3).

1 If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis.

(CDC, 2002)
New Indications

TABLE 3. Indications and nonindications for intrapartum antibiotic prophylaxis to prevent early-onset group B streptococcal (GBS) disease

<table>
<thead>
<tr>
<th>Intrapartum GBS prophylaxis indicated</th>
<th>Intrapartum GBS prophylaxis not indicated</th>
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</thead>
<tbody>
<tr>
<td>- Previous infant with invasive GBS disease</td>
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<tr>
<td>- GBS bacteriuria during any trimester of the current pregnancy*</td>
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<tr>
<td>- Positive GBS vaginal-rectal screening culture in late gestation* during current pregnancy*</td>
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<tr>
<td>- Unknown GBS status at the onset of labor (culture not done, incomplete, or results unknown) and any of the following:</td>
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<tr>
<td>- Delivery at ≤37 weeks gestation*</td>
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<tr>
<td>- Amniotic membrane rupture ≥18 hours</td>
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<tr>
<td>- Intrapartum temperature ≥39.4°C (103°F)</td>
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<tr>
<td>- Macrolide antibiotic susceptibilities of GBS isolate</td>
<td>- Conization with GBS during a previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)</td>
</tr>
<tr>
<td>- GBS bacteriuria during previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)</td>
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</tr>
<tr>
<td>- Negative vaginal and rectal GBS screening culture in late gestation* during the current pregnancy, regardless of intrapartum risk factors</td>
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<tr>
<td>- Caesarean delivery performed before onset of labor on a woman with intact amnion membranes, regardless of GBS colonisation status or gestational age</td>
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</tr>
</tbody>
</table>

Abbreviation: NAAT = nucleic acid amplification test

* Optimal timing for prenatal GBS screening is at 35–37 weeks gestation.

** NAAT testing for GBS is optimal and might not be available in all settings. Recommendations for the use of intrapartum antibiotics for prevention of early-onset GBS disease in the setting of threatened preterm delivery are presented in Figures 3 and 4.

(CDC, 2010)

Old Preterm Algorithm

(CDC, 2002)

(CDC, 2010)
Summary of Changes in 2010

- Rapid GBS testing incorporated into the algorithm.
- Preterm c-sections treated the same as term.
- Separate algorithms for PTL and PPROM.
- Preterm GBS culture valid for 5 weeks.
- Dosage of PCN changed to a range.
- If PCN allergic, give Cefazolin (Ancef) unless at high risk for anaphylaxis.
- Erythromycin no longer acceptable for IAP.
- Erythromycin resistance testing not needed with Clindamycin D-Testing.
Hypothetical Case #1

- Primagravida.
- Low risk PNC at Kaiser, routine.
- Active labor at term, good dates.
- Afebrile, membranes intact.
- GBS screen was not performed during PNC.
- Would you start antibiotics?
- Which antibiotic would you start?

Medicolegal Concerns

- CDC, ACOG and AAP all specify universal screening.
- KP has a protocol in place for universal screening.
- Hypothetical #1: Patient did not receive her 35-37 week GBS screen.
- Possible that the infant may develop early-onset GBS sepsis without any risk factors.
- 2010 guidelines are clear: No prophylaxis without risk factors.
- Plaintiff's attorney: GBS sepsis developed due to absence of prophylaxis due to improper prenatal care.
Hypothetical Case #2

- Primagravida. Prenatal records available.
- Low risk PNC at an outside clinic, routine.
- Active labor at term, good dates.
- Afebrile, membranes intact.
- GBS screen was not performed during PNC.
- Would you start antibiotics?
- Which antibiotic would you start?

On the Other Hand

- 3 concerns in the IAP era:
  - GBS resistance.
  - Shift in flora.
  - Allergy / Anaphylaxis.
GBS Resistance

- No reported resistance to penicillin or ampicillin. (Baltimore, 2007)
- Increasing MICs noted in > 5,000 cases.
- Resistance to Clindamycin and Erythromycin has increased since 1996.
  - Erythromycin: 25-32%.
  - Clindamycin: 13-20%.
  (CDC, 2010)
- This is an important concern and a reason to use antibiotics only where indicated.

Shift in Flora

- Isolated reports of increased incidence in gram negative sepsis, specifically *E. coli*.
- Large multistate studies have not shown an overall increase in *E. coli* or other forms of sepsis.
- 2 studies from the NICHD, however, have found increases in early-onset *E. coli* sepsis in VLBW (< 1,500 g) infants.
  - Increased from 3.2 to 6.8 cases per 1,000 births.
  - 85% of infections were Ampicillin resistant.
  (Schrag and Stoll, 2006)
Shift in Flora (cont.)

- Baltimore: difficult to discern whether this reflects effect of IAP or part of community-wide trends of ampicillin-resistance in all *E. coli* infections.
- Moore, et al: limited data on causality argues for not modifying current IAP recs.
  - Data does suggest need for continuing assessment of IAP in VLBW context.
    (Lancet, 2003)
- Argument for use of penicillin instead of ampicillin.
  - Penicillin is the preferred agent of choice for IAP.
  - Ampicillin is acceptable but penicillin is preferred for its narrow spectrum of activity.
  (CDC, 2010)

Shift in Flora (cont.)

- Recent case reports of early onset sepsis due to MRSA.
  (Schrag and Stoll, 2006).
- Impossible to attribute causality to IAP.
- General principle still remains: the more we use antibiotics, the faster we change the ecology of early-onset sepsis.
Allergy / Anaphylaxis

- Rate of anaphylaxis from PCN estimated to range from 4 / 10,000 to 4 / 100,000.
- As of 2010, only a single case of anaphylaxis to GBS prophylaxis known to CDC. (CDC, 2010)
- Medicolegal concern:
  - If intrapartum anaphylaxis occurs with death or other serious or permanent sequelae, and infant born with no GBS sepsis, easy case for plaintiff's attorney.

Medicolegal Concerns (cont.)

- Common practice to give antibiotics.
- No ambiguity in the CDC guidelines.
- Sound medical reasons not to give antibiotics.
- Purpose of the antibiotics is not to prophylax against GBS but to prophylax against litigation.
  - If antibiotics are started, discuss with the patient and document informed consent.
  - Hypothetical #2 should be handled identically as #1.
- If you are unlucky and anaphylaxis occurs, there is absolutely no defense.
Medicolegal Concerns (cont.)

Hypothetical No. 1

(-) Abx

99.8%

(+) GBS

Sepsis

0.2%

(-) GBS

Sepsis

(-) Anaphylaxis

99.96%

(+) Anaphylaxis

(+ ) Abx

0.04%

(+ ) Anaphylaxis

Medicolegal Concerns (cont.)

Hypothetical No. 2

(-) Abx

99.8%

(+) GBS

Sepsis

0.2%

(+) GBS

Sepsis

(-) Anaphylaxis

99.96%

(+) Anaphylaxis

(+ ) Abx

0.04%

(+) Anaphylaxis
Rapid GBS Testing

- Picard and Bergeron developed a PCR based assay for GBS detection.
- Targets \( cfb \) gene.
- Simple vagino-rectal swab.
- PCR assay takes < 1 hour to run.
- Sensitivity of 97.0%.
- Specificity of 100%.
  - PPV of 100% and NPV of 98.8%.

(Picard and Bergeron, Eur J Clin Microbiol Infect Dis, 2004)

Rapid GBS Testing (cont.)

- Picard and Bergeron transferred the PCR technology to Infectio Diagnostic, Inc.
- Approved by FDA in 2002.
- Sensitivity: ranges from 62.5% - 98.5%
- Specificity: 64.5% - 99.6%
- Sensitivity equivalent to standard culture with the use of an enrichment step.
  - Time-consuming, not practical for intrapartum decision-making.
- Does not provide sensitivities.
Conclusions

- Screening and IAP initially produced an impressive decline in early-onset GBS sepsis. This decline has flattened.
- Possibility that E. coli and other pathogens may displace GBS as the leading cause of neonatal sepsis in the future.
- Possibility that this is occurring now for VLBW infants.
- GBS unknown status at term poses a dilemma.
- Decision not to treat is perhaps more beneficial from a public health point of view, but exposes the institution to medicolegal risk.
- Use of antibiotics in the absence of risk factors may cause anaphylaxis, thus also creating a medicolegal risk.
- Rapid GBS testing is effective, approved by the FDA and CDC, and would resolve this dilemma.

References

- Image of Rebecca Lancefield from Rockefeller University website: http://www.rockefeller.edu/vaf.
References (cont.)


New Neonatal Algorithm

(CDC, 2010)