Effective Prevention of GBS Sepsis in the Neonate

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Financial Disclosures

- I have no financial disclosures
Objectives

- Review what GBS is and why we should be aware of it as OB/GYNs
- Review the history of GBS in obstetrics in the United States
- Review the most recent GBS prevention guidelines
- Review the status of GBS infections in pregnant women and infants worldwide
- Discuss future prevention strategies for GBS disease
What is GBS?

- Group B Streptococcus or Streptococcus agalactiae
- Encapsulated Gram + diplococcus
- Normal bacterial flora colonizing GI and GU tract
- Ten serotypes with varying degree of pathogenesis
  - Ia, Ib, II, III, V
Why are we concerned about GBS?
Pregnant women

- Urinary tract infections (asymptomatic bacteriuria)
- Chorioamnionitis
- Postpartum endometritis
- Peripartum bacteremia
Neonates

**Early Onset Disease**
0-6 days of life (most commonly within 24 hrs of birth)
Bacteremia w/o a focus, sepsis (80-85%), pneumonia (10%), and/or meningitis (7%).

**Late Onset Disease**
7-89 days of life (usually 28-35 days)
Bacteremia w/o focus (65%), meningitis (32%), focal infections
Serotype III GBS

**Late Late Onset Disease**
>3 months of life
Incidence

- EOD: 0.24/1000 live births
- LOD 0.35/1000 live births
Putting it in perspective

- BUMCP 5500 deliveries a year
  - 1.3 EOD cases annually
  - 1.9 LOD cases annually
  - 5.3 EOD cases over 4 years
  - 7.7 LOD cases over 4 years
  - (2.6 cases of invasive GBS in pregnant women over 4 years)
Case Fatality Rates

- **EO D**
  - 2-3% of term infants w/o meningitis
  - 20% of preterm infants w/o meningitis

- **LO D**
  - 1-2% for term infants
  - 5-6% for preterm infants
Long Term Outcomes of those with meningitis

Long-term Outcomes of Group B Streptococcal Meningitis
Romina Libster, Kathryn M. Edwards, Fatma Levent, Morven S. Edwards, Marcia A. Rench, Luis A. Castagnini, Timothy Cooper, Robert C. Sparks, Carol J. Baker, Prachi E. Shah
Pediatrics Jul 2012, 130 (1) e8-e15; DOI: 10.1542/peds.2011-3453
Risk Factors for Transmission

Maternal colonization
Prior to 1970s

- bovine mastitis pathogen
- 1930s: cases of puerperal sepsis in humans
- 1930-1960s: Coliform/enterococcus/staphylococcus bacteria
1970s

- GBS emerges as leading cause of early neonatal morbidity and mortality in US
- Incidence of infection 2/1000 live births
- Mortality rate of 1/1000 live births (initial case-fatality ratios as high as 50%)
- 1977: NIH Workshop on perinatal infections due to GBS
1992 – AAP Guidelines

- Screen all pregnant women at 26-28 wks.
- Do NOT recommend antepartum treatment of asymptomatic GBS
  except GBS bacteriuria
- Maternal GBS carriers WITH intrapartum RF
  - Preterm labor
  - PPROM
  - Fever in labor
  - Multiple births
  - ROM beyond 18 hrs
- Treat with Amp (2g/1g), PCN (5mU), or if allergy, clinda OR erythro
- IAP for prior invasive GBS disease in infant
1993 ACOG guidelines


- Risk based screening
1996 CDC Statement

- Culture based OR risk based screening is acceptable
- IAP regimen: Penicillin, Ampicillin, Clindamycin, or Erythromycin
- Encouraged providers, laboratories, Labor and Delivery facilities develop strategy for GBS prevention
- No oral antibiotics in antepartum period because does not eliminate colonization carriage or preventing neonatal disease

ACOG and AAP both endorsed this statement
2002 CDC Statement
Endorsed by AAP and ACOG

- Universal culture based screening between 35-37 wks
- No routine IAP for GBS colonized women undergoing planned cesarean section who have not begun labor or had ROM
- New prophylaxis regimens for women with PCN allergy: PCN/Amp, cefazolin, clinda/erythro, vancomycin
- Antimicrobial susceptibility testing for Clindamycin and Erythromycin for women with PCN allergy
- Suggested algorithm for management of pts with threatened PT delivery
- Updated algorithm for management of newborns exposed to IAP
- GBS bacteriuria of any quantity recommended to receive IAP
2010 CDC Consensus Statement
Endorsed by ACOG and AAP

- Universal culture based screening between 35-37wks gestational age
  - POSITIVE – intrapartum antibiotic prophylaxis*
  - NEGATIVE – no prophylaxis
- POSITIVE GBS Urine culture at any time in pregnancy (greater than or equal to $10^4$ cfu/ml) – intrapartum antibiotic prophylaxis
- Prior infant with invasive GBS disease - intrapartum antibiotic prophylaxis
- Unknown GBS status at the onset of labor and any of the following:
  - Delivery at <37wks
  - ROM 18 hours or greater
  - Intrapartum temperature >100.4F (38.0 C)
  - Intrapartum NAAT positive for GBS
Instructions for the collection of a genital swab for the detection of a group B streptococcus (GBS)

1. Remove swab from packaging. Insert swab 2cm into vagina, (front passage). Do not touch cotton end with fingers.

   me, u.r. number, date and time of collection. Place swab container into transport bag and hand it to a staff member.
2010 CDC Consensus Statement
Special Considerations

- **PTL**
  - Swab on admission if no GBS swab in last 5 wks
  - Start intrapartum GBS prophylaxis if prior culture result + or if GBS status unknown

- **PPROM**
  - Swab on admission if no GBS swab in last 5 wks
  - Latency Abx (ampicillin IV) - adequate GBS coverage
  - **Not in labor and no Latency Abx** - treat x 48 hrs
  - Penicillin/Cephalosporin allergy
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
“Data are not sufficient to make recommendations regarding the timing of procedures intended to facilitate progression of labor, such as amniotomy, in GBS-colonized women. **Intrapartum antibiotic prophylaxis is optimal if administered for at least 4 hours before delivery; therefore, such procedures should be timed accordingly, if possible.**”

Prevention of Perinatal Group B Streptococcal Disease Revised Guidelines from CDC, 2010
ACOG 2011/2015

- Number 485, April 2011
- (Replaces No. 279, December 2002, Reaffirmed 2015)
GBS Prevention in the US and World wide
### Estimated GBS disease incidence among infants with disease onset 0–89 days, by region (adapted from 3).

<table>
<thead>
<tr>
<th>Region (year of publication of included studies)</th>
<th>Countries included in review (number of studies)</th>
<th>Pooled estimate of incidence per 1,000 live births (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe (2001–2011)</td>
<td>Czech Republic (1), Denmark (2), France (1),</td>
<td>0.57 (0.44–0.71)</td>
</tr>
<tr>
<td></td>
<td>Germany (1), Italy (1), Netherlands (2), Norway (2),</td>
<td></td>
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<tr>
<td></td>
<td>Portugal (1), Slovakia (1), Spain (3), Sweden (1),</td>
<td></td>
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<tr>
<td></td>
<td>UK (4)</td>
<td></td>
</tr>
<tr>
<td>The Americas (2002–2009)</td>
<td>Antigua and Barbuda (1), Brazil (1), Jamaica (2),</td>
<td>0.67 (0.54–0.80)</td>
</tr>
<tr>
<td></td>
<td>USA (12)</td>
<td></td>
</tr>
<tr>
<td>Eastern Mediterranean (2002–2009)</td>
<td>Iraq (1), Kuwait (1), Saudi Arabia (1), Tunisia (1)</td>
<td>0.35 (0.07–0.62)</td>
</tr>
<tr>
<td>Western Pacific (2004–2009)</td>
<td>Australia (1), Australia and New Zealand (2),</td>
<td>0.15 (0.04–0.27)</td>
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<tr>
<td></td>
<td>Macau (1), Malaysia (1), South Korea (1),</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Singapore (1)</td>
<td></td>
</tr>
<tr>
<td>Southeast Asia (2002–2009)</td>
<td>Bangladesh (1), India (2), Thailand (2)</td>
<td>0.02 (-0.03–0.07)</td>
</tr>
<tr>
<td>Africa (2005–2009)</td>
<td>Kenya (1), Malawi (1), Nigeria (1), South Africa (1)</td>
<td>1.21 (0.50–1.91)</td>
</tr>
</tbody>
</table>
Future interventions

- Rapid test
- Vaccine
  - Racial disparities
  - Late onset dx
- Long acting antibiotics
Rapid Tests

- Approved by CDC to use if available
- Issues: cost, availability, timeliness, accuracy

Diagram:

- Transcription-mediated amplification (TMAY) / Nucleic acid sequence-based amplification (NASBA)
- Signal-mediated amplification of RNA technology (SMART)
- Helicase-dependent amplification (HDA) / Recombinase polymerase amplification (RPA)
- Rolling circle amplification (RCA)
- Loop-mediated amplification (LAMP) / Cross-priming amplification (CPA) / Smart amplification (Smart-AMP)

Key:
- DNA polymerase (DNA pol)
- Reverse transcriptase (RT-pol)
- RNA polymerase
- Helicase
- Ligase
- Single strand binding (SSB) proteins
- DNA fingerprint
- RNA fingerprint
- Main primers or probe
- Auxiliary (bumper) primers
- T7 promoter
Vaccines

- Polysaccharide
- Polysaccharide-Protein Conjugate
- Protein Based

### Potential antigens of group B streptococcus for use as vaccines

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Virulence factor</th>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbohydrates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B antigen</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Ia CPS</td>
<td>yes</td>
<td>yes</td>
<td>Phases 1 and 2</td>
</tr>
<tr>
<td>Ib CPS</td>
<td>yes</td>
<td>yes</td>
<td>Phases 1 and 2</td>
</tr>
<tr>
<td>II CPS</td>
<td>yes</td>
<td>yes</td>
<td>Phases 1 and 2</td>
</tr>
<tr>
<td>III CPS</td>
<td>yes</td>
<td>yes</td>
<td>Phases 1 and 2</td>
</tr>
<tr>
<td>V CPS</td>
<td>yes</td>
<td>yes</td>
<td>Phase 1</td>
</tr>
<tr>
<td>VI CPS</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>VIII CPS</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>Proteins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C proteins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Beta</td>
<td>?</td>
<td>yes</td>
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</tr>
<tr>
<td>Epilin</td>
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<td>no</td>
<td>no</td>
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<tr>
<td>Rib</td>
<td>?</td>
<td>yes</td>
<td>no</td>
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<tr>
<td>R-proteins</td>
<td>?</td>
<td>no</td>
<td>no</td>
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<tr>
<td>Type V/VIII alpha-like proteins</td>
<td>?</td>
<td>yes</td>
<td>no</td>
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<tr>
<td>C3a peptidase</td>
<td>?</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Ssp</td>
<td>?</td>
<td>yes</td>
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</tr>
<tr>
<td>LtrG</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>P1b</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>

CPS: capsular polysaccharide.
## Development status of current vaccine candidates (adapted from 329).

<table>
<thead>
<tr>
<th>Developer</th>
<th>Candidate name/identifier</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>POC</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH</td>
<td>Tetanus toxoid-CPS conjugates: monovalent (multiple studies), bivalent (one study); CRM 197-CPS conjugate: monovalent (one study)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X (trial in pregnant women)</td>
<td></td>
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<tr>
<td>Novartis/GSK</td>
<td>CRM 197-CPS conjugate: monovalent (multiple), trivalent (several)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X (trial in pregnant women)</td>
<td></td>
</tr>
<tr>
<td>Minervax</td>
<td>N-terminal domains of the Rib ad AlphaC surface proteins</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Novartis/GSK</td>
<td>Pilus proteins</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Various academic groups</td>
<td>Other protein(s) and/or protein-CPS conjugates</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CPS: capsular polysaccharide, GSK: GlaxoSmithKline, NIH: National Institutes of Health, POC: proof of concept
Long acting Abx

Benzathine Penicillin
600,000 I.U.
Sterile Benzathine Penicillin
B.P./USP
Use immediately after reconstitution.
For IM use only

NDC 01570-148-10
FOR DEEP IM INJECTION ONLY
2,400,000

Monarch Pharmaceuticals
Summary

- GBS is **BAD**
- *Universal culture screening* with IAP has helped tremendously
- There are still areas for improvement
- IAP does not affect LOD incidence
Thank you to my fellow OB/GYN residents for allowing me to use photos of their precious babies in my presentation.
References

6. CDC. Prevention of perinatal group B streptococcal disease: a public health perspective. MMWR 1996;45 (no. RR-7)
7. CDC. Prevention of perinatal group B streptococcal disease: revised guidelines from CDC. MMWR 2002, 51 (No. RR-11)