PERINATAL
GROUP B. STREPTOCOCCAL
DISEASE

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Outline
- Case presentation
- Introduction
- Epidemiology
- GBS invasive disease
  - Early-onset
  - Late-onset
  - Very late-onset
- MMWR 1996 Consensus Guidelines
- MMWR 2002 Consensus Guidelines
  - Differences between the guidelines
  - Algorithms

Case of BG D.
Birth History
2746g female infant born at 38 2/7 wks to a 19 y/o G1P1 mother via SVD. Maternal history significant for class C DM and LGSIL type II. Medications include glucophage and PNV. Mother's blood type is A+. Rubella immune, HepBlsAg neg, HIV neg. RPR, GBS, chlamydia and GC unknown.

Infant delivered via SVD with AROM about 7 ½ hrs PTD. Resuscitation included stimulation, drying and bulb suction. APGARs 6 at 1min and 8 at 5min. At 10min of life began with strong grunting. Noted to have coarse breath sounds and had a significant amount of thick secretions. Catheter suctioned, improved temporarily and resumed grunting. Taken to Level II NICU.

Case of BG D. continued
Initial Physical Exam pertinent findings
- T 97.5  P 170  BP 60/40  R 52  Sats 87% on RA
- Gen: mild-moderate respiratory distress, grunting
- Color: Pale
- HEENT: NC, AFSF
- CV: regular rhythm no murmur appreciated, pulses fair, cap refill 3-4sec
- Lungs: clear to auscultation, good air entry, intermittent retractions
- Given 10cc/kg NS bolus with immediate improvement in perfusion, color, and respiratory status.
- Grunting resolved quickly, no retractions, 97-100% saturations room air

Initial Labs:
- ABG: 7.22/38/72/16.8/-11.4 on room air (prior to completion of bolus)
- ABG: 7.32/45/40/23/-3 about 2 hours of life
- CBC: 13.7/15.6/45/159  S18  B 11 L61  M6  IT:0.37

CXR First 30min of Life

How would you manage this patient?
Introduction

- Group B. Streptococcus (GBS) emerged in 1970s as the leading cause of neonatal sepsis and meningitis in the US
  - Prior to use of intrapartum antibiotic prophylaxis (IAP)
    - 8,000 cases of early-onset GBS disease annually
    - 1.7 cases per 1,000 live births
    - 4-6% of affected infants died
    - Women with prenatal GBS colonization were 25X more likely to deliver infants with early-onset GBS

Maternal Complications

- GBS accounted for more than 50,000 maternal infections per year
  - Bacteremia
  - Endometritis
  - Chorioamnionitis
  - Urinary tract infections
  - Early fetal loss, stillbirth
  - Premature rupture of membranes
  - Preterm delivery

Invasive GBS Disease 1993-98

- Early-Onset Neonatal 20%
- Late-Onset Neonatal 8%
- Pregnant Women 4%
- Childhood Disease 2%
- Non-Pregnant Adults 33%

Virulence Factors of GBS

- Capsular polysaccharides
  - Complex carbohydrates
  - Confer virulence in part by inhibiting complement in absence of serotype specific antibody
  - Serotypes known are: Ia, Ib, Ic, II, III, IV, V, VI, VII, and VIII
- Invasion associated gene (iagA)
  - Anchor for lipoteichoic acid
  - Participates in invasion of blood brain barrier
- Surface proteins/substances
  - C proteins
  - Pilins
  - Hemolysins, protease, CAMP factor, complement factor 5a
Early-Onset Invasive GBS Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Septicemia</td>
<td>25-40%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>35-55%</td>
</tr>
<tr>
<td>Meningitis</td>
<td>5-10%</td>
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</table>

- Mortality
  - 4% term
  - 6% preterm
- Meningitis Survivors
  - Hearing loss, vision loss, mental retardation, seizures

Mortality:
- 4% term
- 6% preterm

Meningitis Survivors:
- Hearing loss, vision loss, mental retardation, seizures

Early-Onset Invasive GBS Disease

- 75% of GBS infections are early-onset
- Presents at 0-6 days of life
- Most become ill within first 24 hrs

Early-Onset Invasive GBS Disease

- Acquired through vertical transmission
  - Colonized birth canal
  - Ascending infection after rupture of membranes
  - Aspiration of contaminated fluid
  - Hematogenous dissemination
- 50% of infants born vaginally to colonized mothers become colonized
- 1-2% of colonized infants develop invasive disease.

Early-Onset Septicemia

- 25-40% of early-onset GBS disease
- Non-specific signs
  - Irritability
  - Lethargy
  - Respiratory symptoms
  - Temperature instability
  - Poor perfusion
  - Hypotension
- Most newborns do not have fever

Pneumonia

- 35-55% of early-onset GBS disease
- Respiratory signs (apnea, grunting, tachypnea etc.) are the presenting feature in more than 80% of patients
- CXR may mimic RDS, retained fetal lung fluid or lobar pneumonia
- PPHN may complicate GBS pneumonia
Meningitis

- 5-10%
- 80% of GBS isolates from neonates with meningitis are serotype III
- Presenting S/S may be identical to those of a baby without meningeal involvement
- Pathology shows very limited inflammatory response

Early-onset Invasive GBS and Fatality Rates by Gestational Age 1993-1998

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>No. (%) of Early-onset Cases</th>
<th>Case Fatality Rate (%)</th>
</tr>
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<tbody>
<tr>
<td>&lt;33 wk</td>
<td>137 (9)</td>
<td>30</td>
</tr>
<tr>
<td>34 to 36 wk</td>
<td>116 (7)</td>
<td>10</td>
</tr>
<tr>
<td>&gt;37 wk</td>
<td>1,247 (83)</td>
<td>2</td>
</tr>
</tbody>
</table>

*Data on both gestational age and outcome were available for 1,584 infants who had early-onset disease (96%). Reproduced with permission from Schrag S, et al. N Engl J Med. 2000;342:15–20.

Multiple Births

- The non-affected sibling(s) of a multiple birth with invasive GBS should be evaluated empirically
- Increased risk of early and late onset disease

Late-Onset GBS Disease

- Late-onset infection 7 days to 3 months
  - Typically presents 3-4wks after birth
  - Presents with bacteremia without a focus
  - Meningitis occurs in about 25% of cases
  - Majority horizontally transmitted
    - From colonized mother, hospital, community
    - <50% from vertical transmission
  - Serotype III accounts for 65-75% of late onset disease
  - Prognosis is good; case fatality rates of 2-6%
  - Focal infections
    - Osteomyelitis, septic arthritis, cellulitis

Bone and Joint Infection

- 5% of late-onset disease
- Septic arthritis tends to present earlier than osteomyelitis (mean age 20 d v. 31 d)
- Onset tends to be indolent
- Lack of movement of involved extremity or pain with movement are common
- Hip is most common site of arthritis; humerus is the most common site of osteomyelitis

Unusual Manifestations

- Facial Cellulitis
- Submandibular or parotid adenitis
- Endophthalmitis
- Ethmoiditis
- Scalp Abscess
- Brain Abscess
- Cerebritis
- Supraglottitis
- Delayed onset of right-sided CDH
- Endocarditis
- Pericarditis
- Peritonitis
- Adrenal abscess
- Breast Abscess
- Bursitis
- Omphalitis
Very Late-Onset Disease

- Onset after 3 months of age
- Most cases occur in premature infants
- Bacteremia without a focus of infection is common
- Very late-onset infections may be the initial manifestation of an immune deficiency such as HIV

Antimicrobial Management

- Ampicillin plus an aminoglycoside for empiric treatment
  - Ampicillin - coverage for listeria monocytogenes
  - Gentamicin - in vitro synergy
- Definitive
  - Pencillin G
    - Narrow spectrum and active agent in vitro
      - Meningitic doses
        - < 7 DOL 250-450,000 units/kg IV q 8hrs
        - > 7 DOL 400-500,000 units/kg IV q 4-6hrs

Duration of Antimicrobial Management

- Uncomplicated bacteremia 7-10 days
- Uncomplicated meningitis 14 days
- Meningitis with ventriculitis/abscess 21-28 days
- Osteomyelitis/Endocarditis 4-6 weeks

Neonatal GBS Prevention

- Early 1990s AAP and ACOG established guidelines for GBS prevention
- 1996 CDC Consensus Guidelines

Screening for colonization

Culture all pregnant women at 35-37wks gestational age

Advantages

- 87% sensitivity
- 97% specificity
- 5% false negative rate
- Maximizes prevention of invasive disease

Disadvantages

- More expensive
- More women treated with IAP compared to risk based strategy
- Higher risk of abx reactions
- Risk of overtreatment and antibiotic resistance
Risk-Factor Based Strategy

- Intrapartum fever >100.4 (≥38˚)
- Delivery before 37 wks gestation
- Rupture of membranes >18hrs
- Previous delivery of an infant affected by GBS disease
- GBS bacteriuria during current pregnancy

Administer intrapartum antibiotics to women who have any risk factors

Advantages

- Avoids excessive use of intrapartum antibiotics
- Less expensive
- Less labor intensive

Disadvantages

- 60% of term infants who develop GBS disease are born to asymptomatic mothers without risk factors
- Waiting for risk factor
  - Such as >18hrs for rupture of membranes or waiting for fever to begin IAP


Events leading to revision of guidelines

- Persistence of early-onset GBS disease
- CDC sponsored multistate study comparing screening and risk factor based strategies
  - 5,144 births with 312 having early-onset GBS disease
  - Screening approach >50% more effective
  - 18% of all deliveries were to mothers colonized but with no risk factors

2002 Key Changes in Recommendations

- Screening of all pregnant women 35-37wks for GBS colonization
- Updated IAP regimens for women with PCN allergy
- Instructions on GBS specimen collection and culture
- No IAP for GBS colonized women undergoing cesarean section who have not labored or had rupture of membranes
- Algorithm for management of pts with threatened preterm delivery
- Updated algorithm for management of newborns exposed to IAP
Who to screen?

- Obtain cultures of all pregnant women at 35-37 wks gestation
  - Except:
    - GBS bacteriuria in current pregnancy
    - Previous infant with invasive GBS disease

Cultures

- Cultures from both the lower vagina and rectum
- Inoculate in a non nutrient transport media
- Grow in selective broth medium
- Then sub-culture on a blood agar plate
  - Combined cultures increase recovery rate of GBS by 25%
  - 50% higher rate of GBS isolation with selective media
- Screening cultures require 24-48hrs.

Intrapartum Antibiotic Prophylaxis Is Indicated

- Positive screening culture
- History of infant with early onset GBS disease
- GBS bacteriuria during current pregnancy
- Culture status unknown and intrapartum fever \( \geq 100.4 \) \(^{\circ}\text{F} \) (>\(38\) \(^{\circ}\text{C}\)), preterm labor, or prolonged rupture of membranes \(>18\) hrs

Antibiotic Prophylaxis Not Indicated

- Recent negative screening culture
- Positive GBS culture in previous pregnancy but no neonatal GBS infection
- GBS positive culture but planned cesarean delivery without labor or ROM
- GBS negative at 35-37wks with intrapartum fever, preterm labor or prolonged rupture of membranes
  - Maternal antibiotics for treatment if evidence of chorioamnionitis

Planned Cesarean Section Delivery

- Retrospective study and a review of CDC surveillance data showed an extremely low risk of GBS transmission
- If planned, mother not in labor and membranes intact do not need IAP but should undergo routine screening
- GBS colonization not an indication for cesarean section
- GBS can cross intact amniotic membranes

Threatened Preterm Delivery

- Onset of labor or rupture of membranes at <37 weeks gestation with risk of delivery
  - Obtain screening cultures
  - Administer IV PCN
  - If GBS negative (no growth at 48hrs)
    - discontinue antibiotics
  - If GBS positive continue PCN IV for 48hrs
    - PCN should be reinitiated when labor likely to proceed to delivery
Recommended Maternal Antibiotic Regimens

- **Recommended**
  - Penicillin G: 5 million units IV initial, then 2.5 million units q 4hrs
- **Alternative**
  - Ampicillin: 2 grams IV initial then 1 g IV q 4hrs

Patients with PCN Allergy

- **If “low risk” for anaphylaxis**
  - Cefazolin 2 g IV, then 1 g IV q8hrs
  - (Reaches bactericidal conc after 3 hrs)
- **If “high risk” for anaphylaxis**
  - Clindamycin 900mg IV q8hrs
  - or Erythromycin 500mg IV q 6hrs
  - If resistant to clindamycin:
    - Vancomycin 1g IV q 12hrs

Timing of Intrapartum Ampicillin Administration and Rate of Vertical Transmission

<table>
<thead>
<tr>
<th>Time Between Ampicillin Administration and Delivery</th>
<th>Number of Group B Streptococci Carriers</th>
<th>Number of Colonized Newborns (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 h</td>
<td>24</td>
<td>11 (46)</td>
</tr>
<tr>
<td>1 to 2 h</td>
<td>21</td>
<td>6 (28)</td>
</tr>
<tr>
<td>&gt;2 to 4 h</td>
<td>70</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>4-8 h</td>
<td>86</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Control group (no ampicillin)</td>
<td>253</td>
<td>120 (47)</td>
</tr>
</tbody>
</table>

So where are we now?

- **Active Bacterial Core Surveillance (ABCs)**
  - Conducts population and laboratory based surveillance for all cases of invasive GBS in select counties of 10 states
    - California (3 county San Francisco Bay area); Colorado (children < 1 year in 5 county Denver area); Connecticut (children < 1 year); Georgia (children < 1 year); Maryland; Minnesota; New Mexico; New York (15 county Rochester and Albany areas); Oregon (3 county Portland area); Tennessee (11 urban counties)
    - represent 32,806,285 persons and 542,607 live births
  - Since 1990s the incidence of early-onset GBS disease has decreased by 80%

Rate of Early-Onset invasive GBS Disease by Race 2000-2006

- Black infants (n = 428)
- Overall (N = 1,199)
- White infants (n = 656)

Rates of Early Onset Disease in Preterm and Term Newborns

- Preterm black infants (n = 149)
- Preterm white infants (n = 122)
- Term black infants (n = 534)
- Term white infants (n = 534)
Future Directions in Prevention

- Real-time PCR and other rapid detection tests
  - Allow for rapid identification of GBS status in women with no prenatal care, imminent delivery
  - Possible delay in IAP, lack of isolate for susceptibility testing, sensitivity/specificity

- Vaccines
  - Targeted against the capsular polysaccharide
    - Multivalent, including the five most common serotypes
  - Potentially could prevent GBS related stillbirths
  - Provide longer duration of immunity to the newborn
  - Protect mother against invasive GBS infection
  - Immunogenicity of candidate vaccines have been demonstrated (monovalent)

Back to Case of BG D.

- Assessment
  - Term AGA female born via SVD with APGARs of 6 and 8 at one and five minutes respectively admitted for respiratory distress, hypoperfusion and metabolic acidosis

- Plan
  - Neuro: monitor
  - Resp: monitor, currently stable room air
  - CV: s/p NS bolus, monitor
  - Fen/GI: IVF at 80cc/kg. Chem in am. Glucose protocol
  - Heme/ID: hct stable 47. CBC as above, blood cx. Begin Ampicillin and Gentamycin

Case of BG D. cont

- Blood culture + for GBS within 16 hours
  - Resistant to erythromycin, clindamycin

- Repeated blood culture

- Lumbar puncture performed
  - Gram stain-no leukocytes or bacteria
  - CSF culture negative

- Mother GBS +, urine negative

Management of newborn whose mother received IAP

- Antibiotic treatment for GBS?
- Signs of neonatal sepsis?
- Gestational age (<32 weeks)?
- Duration of IAP before delivery <45 min? No therapy if sepsis is suspected, full diagnostic evaluation and empiric therapy?
- No evaluation for suspect GBS+ mother

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