


Update: Perinatal Group B Streptococcal Disease

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Objectives

- Describe the epidemiology of Group B Streptococcus, including incidence and risk factors.
- Discuss the latest treatment & prevention guidelines for perinatal Group B streptococcal disease.

Group B Streptococcus (GBS)

- Leading bacterial infection associated with illness and death among newborns in the U.S.
  - *Prior to active prevention activities (1996):*
    - 8,000 – 12,000 cases of GBS sepsis & meningitis in newborns each year (U.S.)
    - Approximately 2,000 deaths
    - Direct medical costs: $300 million/year

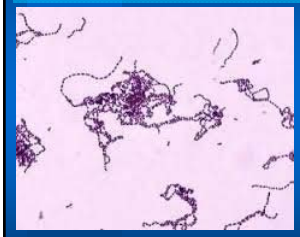
Group B Streptococcus (GBS)

- *Currently:* Remains the leading infectious cause of morbidity & mortality among newborns in the U.S.
  - CDC estimates 1,200 cases of GBS sepsis & meningitis in newborns each year (U.S.)
  - Approximately 70% of cases are among babies born at term (≥37 weeks gestation)

Group B Streptococcus

- *Streptococcus agalactiae*
- Gram positive cocci
  - Short chains in clinical specimens
  - Longer chains in culture
- Blood Agar plate
  - Gray-white mucoid colonies
  - Small zone of beta hemolysis

Gram Stain




S. agalactiae: Blood Agar Plate

Beta-Hemolysis

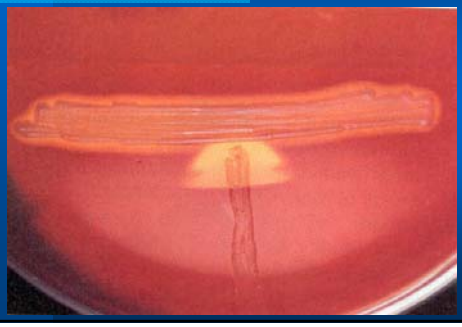
Streptococcus agalactiae

- Laboratory Tests:
  - Catalase: Negative
  - 6.5% NaCl: No growth
  - CAMP test: Positive
  - Bile Esculin: Negative
  - Hippurate hydrolysis: Positive

CAMP test

- Used to presumptively identify group B streptococci
- Named after the individuals who discovered the reaction
  - Christie, Atkins, & Munch-Petersen
- *Staphylococcus aureus* is inoculated onto blood agar plate
- Unknown streptococcal isolate inoculated perpendicularly to *S. aureus* inoculum

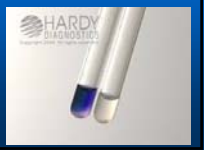
Positive CAMP test



Positive & Negative CAMP test

Hippurate Hydrolysis

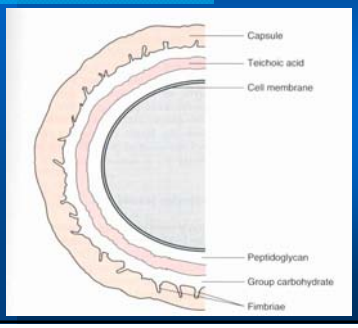
- Differentiates S. agalactiae from other beta-hemolytic streptococci
- Inoculate sodium hippurate with colony; incubate 2 hours at 35ºC; add ninhydrin reagent (indicator); incubate 10-15 min
- Deep purple color = positive result



Lancefield Classification

- Developed in the 1930's
- Rebecca Lancefield
- Differentiation of C carbohydrate in cell wall
- *Streptococcus agalactiae* – Group B
- Only one organism in Group B category
- Names used interchangeably

Schematic Representation: Streptococcal Cell Wall



Source & Transmission

- Normal flora of bowel, vagina, or throat
- Many "carriers" of GBS (asymptomatic)
- 10 - 30% of all pregnant women carry GBS in the rectum or vagina
- Fetus may come into contact with GBS before or during birth (vertical transmission)
- Cesarean section does NOT eliminate risk

Maternal to Infant Transmission

- If mother carries GBS:
  - 1 of every 100-200 babies will be affected
    - 1 in 4,000 chance if IAP is administered
  - 80% of the cases occur in the first week of life (Early-onset disease – EOD)
  - Most cases apparent a few hours after birth
  - Premature babies are more susceptible

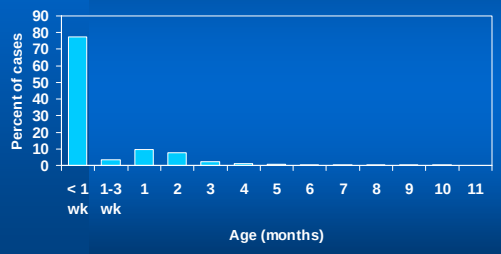
Clinical Disease

- Sepsis – most dramatic & devastating complication
- Pneumonia - early-onset only; 0-5 days
- Meningitis – can be early-onset or late-onset (5-90 days)
- Neurologic - hearing and/or visual loss; impaired mental abilities

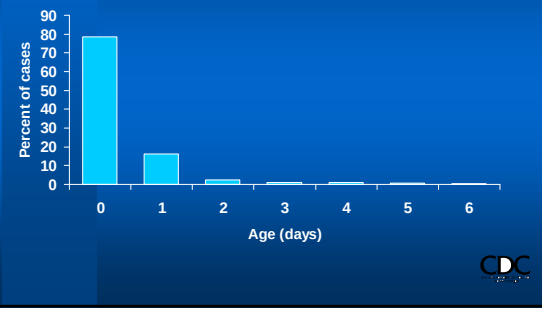
Signs & Symptoms – Early Onset

- Asymptomatic at birth
- Within first 24 hours of life:
  - Tachypnea
  - Lethargy
  - Irritability
  - Jaundice
  - Cyanosis
  - Mottling of skin
  - Hypotension
  - Decreased feeding
- 60 – 80% of infections occur within 12 hours of life
- Mechanical ventilation often required

GBS Disease in Infants



Early-Onset Neonatal GBS Disease

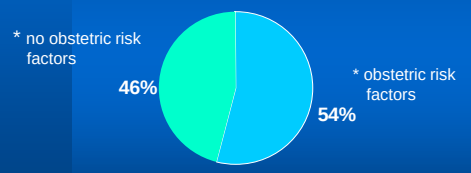


Risk Factors for Early-Onset GBS Disease

- Maternal GBS colonization – primary risk
- Obstetric: prolonged rupture of membranes (>18 hours), preterm labor (<37 weeks), intrapartum fever (100.4º F)
- Previous infant with GBS disease
- Demographic (age < 20 yrs, African-American)

Obstetric Risk Factors Among Women with GBS Infants

n = 245



* premature < 37 wk, ROM ≥ 18 hr, temp ≥ 100.4º F (38º C)

Prevention Strategies: 1992-96

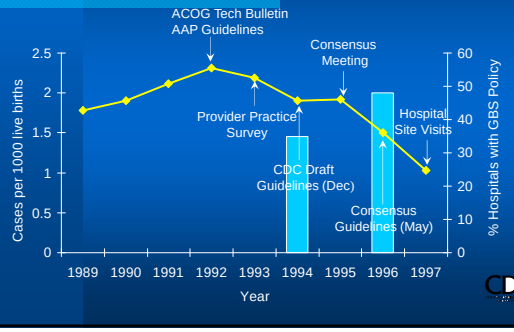
- American College of Ob & Gyn (ACOG)
  - No prenatal screening
  - Prophylaxis for women with OB risk factors
- American Academy of Pediatrics (AAP)
  - Universal prenatal screening
  - Prophylaxis for carriers with OB risk factors
- EITHER approach expected to prevent 60-75% of early-onset disease

Prevention: Intrapartum Antibiotic Prophylaxis (IAP)

- Antibiotics administered IV after onset of labor or membrane rupture, but before delivery
- Most likely method for preventing GBS
- Penicillin is drug of choice; ampicillin also used

Impact of Prevention

Early-Onset GBS Disease by Year and Percent Hospitals with a GBS Policy -- Atlanta, GA



Prevention Statistics

- CDC and Prevention's surveillance data indicate that early-onset GBS disease declined by 65% between 1993 and 1998 (in areas with continuous data)
- In 1998, an estimated 3,900 neonatal infections and 200 deaths were prevented

Barriers to Effective GBS Disease Prevention - Initially

- 63% of clinicians collected prenatal cultures for GBS

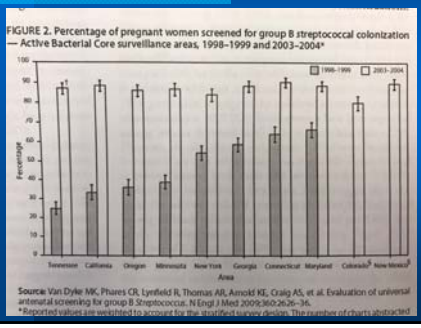
  BUT:
- 91% used suboptimal sites (not vag/rectal)
- Few clinicians knew what media their labs used
- <10% of 200 labs surveyed were using optimal media (selective broth)

Jafari et al., Pediatr Infect Dis J 1995;14:662-7.
Whitney et al., OB GYN 1997;89:28-32.

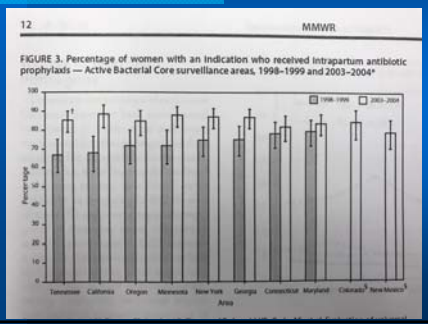
Prevention Strategies: 2002

- Universal culture screening for all pregnant women at 35-37 weeks gestation
- Implementation was rapid & widespread
- However, only 50.3% of women delivering preterm had known GBS status
- Only 63.4% received prophylaxis
- Population of women not receiving prenatal medical care

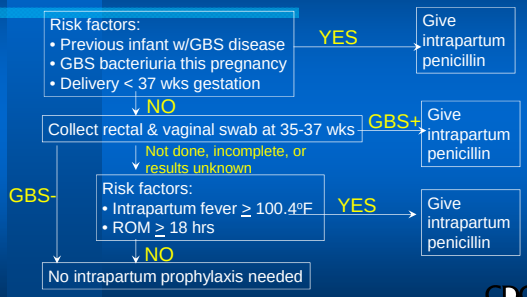
Women Screened for GBS (1998-9) vs. (2003-4)



Women Who Received IAP (1998-9) vs. (2003-4)



Prevention Strategy: 2010



Advantages of Prevention Strategy

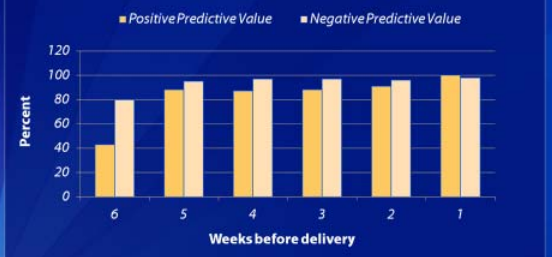
- Optimizes prenatal screening
  - Fewer false negatives
  - Less pressure on physicians to treat
- Antibiotics to all GBS carriers
  - Antibiotics start earlier before development of risk factors
  - Adequate time for antibiotic effectiveness

CDC's Recommendations for Prenatal GBS Cultures

Optimize cultures:

- Site: vagina and rectum
  - Single swab or two swabs
  - Through anal sphincter
- Cervical, perianal, & perineal – NOT acceptable
- Timing: 35 to 37 weeks
- Processing: selective broth medium

When to Culture?



N=826
Yancey et al., OB GYN 1996;88:811-5.

Specimen Transport

- Inoculate swabs into non-nutritive transport medium
  - Commercially available (Stuart's or Amie's)
- Specimens in media may remain viable at RT for up to 4 days, *however*…
  - Results most sensitive when processed within 24 hours & refrigerated
- Specimens should be properly labeled
  - GBS specimen, penicillin allergy status

Laboratory Testing

- Inoculate swabs into selective broth
  - Todd-Hewitt broth with nalidixic acid (15 µg/ml) and EITHER colistin (10 µg/ml) or gentamicin (8 µg/ml)
  - Commercially: SBM or LIM broth
- Incubate broth 18-24 h. Subculture to sheep blood agar plate

Laboratory Testing

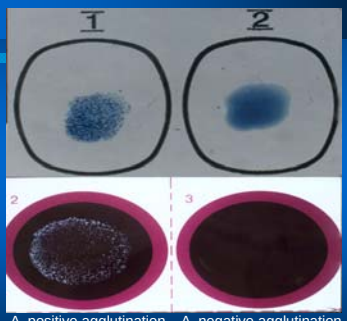
- Pigmented enrichment broth
  - StrepB Carrot Broth
  - Concern: 5-8% of GBS isolates don't produce granadaene (orange carotenoid pigment)

Laboratory Testing continued

- Inspect and ID suggestive organisms
  - B-hemolytic or nonhemolytic, Gram+, catalase-
- If GBS not identified after 18-24h on sheep BAP, reincubate and inspect at 48h
- Various GBS Ag detection tests (slide agglutination, genetic probes, fluorescent antibodies) may be used for specific identification or CAMP test for presumptive identification

Slide Agglutination Tests

Results: Agglutination Commercial Tests



A positive agglutination
GBS is present

A negative agglutination
GBS is not present

Photo courtesy of Dr. Richard Facklam, CDC

PCR (Nucleic acid amplification tests – NAAT)

- Can be used for GBS screening at 35-37 weeks if performed from an enrichment broth (incubated for 18-24 hours)
- Cannot be performed directly from vaginal-rectal swab unless woman with unknown GBS status presents in active labor & has no risk factors

PCR (Nucleic acid amplification tests – NAAT)

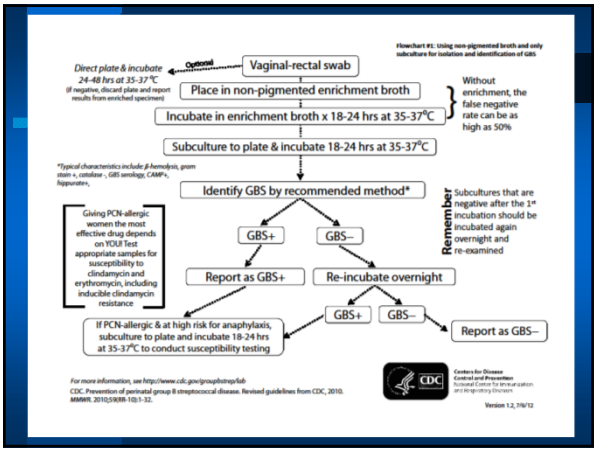
- Concerns:
  - Despite simplicity and rapid turnaround time (1-4 hours), the pre-enrichment step is still required (18-24 hours)
  - An isolate may not be recoverable for antimicrobial susceptibility testing (required for penicillin-allergic women at high risk for anaphylaxis)

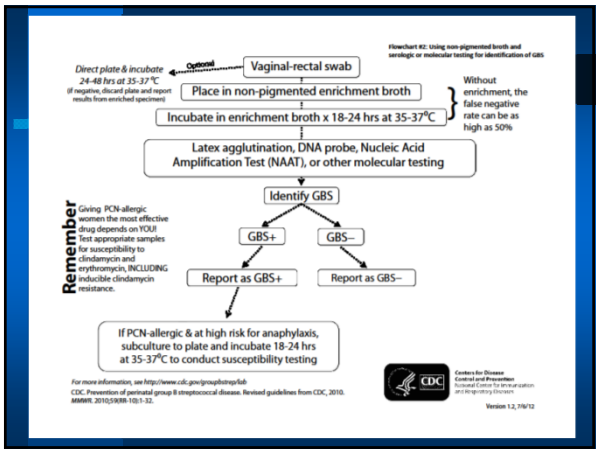
PCR (Nucleic acid amplification tests – NAAT)

- As molecular technologies continue to evolve:
  - Expect NAATs or more sophisticated methods to emerge as the standard for detection of GBS carriers
  - May even replace cultures as test sensitivity improves
  - Recent studies show 90% sensitivities for NAAT vs. 54% for culture testing

Laboratory Testing - Urine

- GBS bacteriuria
  - A marker for heavy colonization
  - A risk factor for having an infant with early-onset GBS disease
  - Colony count cutoff of 10^4 cfu/mL or higher
    - New guidelines
    - Prevents burden of reporting all colony counts





GBS Carriage by Culture Site

Women in study (#)	Vagina (%)	Anorectum (%)	Both (%)
789	10	18	21
94	18	28	31
301	11	14	18

GBS Carriage by Culture Method

Women in study (#)	Selective broth (%)	Blood agar plate (%)
166	34	14
952	17	9
383	20	13

Intrapartum Prophylaxis

- Penicillin
  - 5 million units IV load, then 2.5 million units IV every 4h until delivery
- Ampicillin
  - 2 g IV load, then 1g IV every 4h until delivery
  - Acceptable alternative, but broader spectrum may select for resistant organisms
- Penicillin allergy
  - Clindamycin or Erythromycin (increase in resistance)
  - Vancomycin - if resistant

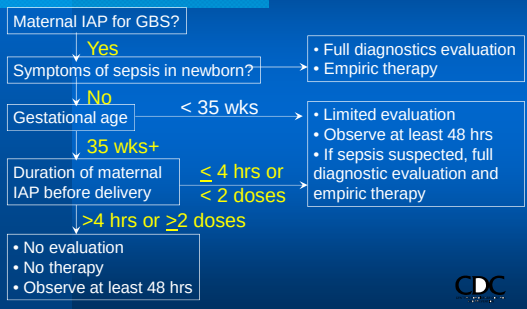
Timing of Intrapartum Ampicillin and Transmission of GBS

Interval between Ampicillin and birth	No. of GBS carrier mothers	No. (%) GBS colonized babies
Controls (no Ampicillin)	209	98 (47)
< 1 hour	30	13 (43)
1-2 hours	36	7 (19)
2-4 hours	80	2 (2.4)
>4 hours	105	1 (0.9)

Diagnostic Evaluation of Infants Born to Mothers with IAP

- Full Evaluation
  - CBC & Differential
  - Blood culture
  - +/- Chest X-ray
  - +/- Lumbar puncture
- Limited Evaluation
  - CBC & Differential
  - Blood culture

Sample Algorithm for Management of Newborn if Maternal IAP



Concerns with Prophylaxis

- Adverse effects from antibiotics
  - Mild allergic reactions
  - Anaphylaxis
  - Consequences for newborn treatment (observe for 48 hours)

Concerns with Prophylaxis

- Antimicrobial-resistant pathogens
  - 27% of pregnant women in U.S. receive antibiotics during labor & delivery
  - 15% of GBS isolates resistant to Clindamycin or Erythromycin (no longer recommended w/o susceptibility testing)
  - Ampicillin-resistant *Escherichia coli* is increasing as cause of neonatal sepsis due to GBS-associated IAP

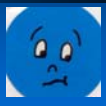
Possible Solutions

- Vaginal Disinfectants
  - Less invasive approach
  - Chlorhexidine investigated in randomised trial in Sweden
  - Less effective than antibiotic prophylaxis
  - Does not lead to an increase in resistant pathogens
  - Clinical trials have found no protection against early-onset GBS disease - 2014

Possible Solutions

- Vaccine development
  - No licensed vaccine currently available
  - Clinical trials are in progress
    - Healthy, nonpregnant adults
    - Have shown vaccines to be well tolerated and immunogenic

Concerns about Vaccination



- Vaccination during pregnancy
- Optimal timing of vaccination
- Proposed target group: include non-pregnant women and even adolescent girls
- Shift in serotypes of strains causing GBS disease

Vaccination During Pregnancy

- Most women reluctant to accept vaccine during pregnancy
  - Warned to avoid smoking, alcohol & drugs
  - Concerned about adverse effects of vaccine on developing fetus

Timing of Vaccination

- Timing is crucial to minimize potential harm to fetus while allowing adequate time for GBS antibodies to be produced
- Health care professionals agree that early in 3rd trimester is most appropriate time to vaccinate (low risk to fetus; enough time to produce antibodies & cross placenta)

Proposed Target Group

- Addition of GBS vaccine to adolescent series (when booster doses are administered)
  - Duration of protection is unknown
  - Need to protect women over all of their reproductive years
  - Many booster doses may be necessary and complicate vaccination programs
  - Many countries do not immunize at this age

Other Suggestions: Natural Remedies

- Boost competitive & healthy bacteria
  - Probiotics (yogurt & aged cheeses)
- Boost the immune system
  - Avoid sugars & refined carbohydrates
  - Increase vitamin C and D
  - Increase proteins & vegetables in diet
- Kill the bacteria
  - Garlic, tea tree oil, colloidal silver

Other Suggestions: Natural Remedies

- No studies regarding the effectiveness of these remedies
- However, many women have experienced a reversal from positive to negative cultures for GBS after following one or more of these remedies
- Many websites with suggestions of herbal remedies to prevent GBS

Case Study #1

- 28 year old female
- First pregnancy
- Vaginally delivers 5 pound, 15 ounce male
- 37 weeks gestation
- Normal apgar scores at birth
- Mother & baby discharged 24 hours later

Case Study #1

- 24 hours after discharge (48 hours after birth):
  - Difficulty nursing and breathing
  - Lethargic
  - Irritable
- Baby brought to emergency room
  - Fever
  - Hypotension
  - Ventilator

Case Study #1

- Laboratory tests were ordered:
  - Urine culture (suprapubic aspiration)
  - Blood cultures (from 2 different sites)
  - CSF culture
  - Gram stains on all fluids
  - Direct Antigen Test (DAT) on CSF and urine

Case Study #1

- Laboratory results:
  - CSF Gram stain
    - Gram positive cocci in chains
  - CSF Culture
    - Group B Streptococcus
  - Direct Antigen Test
    - Group B Streptococcus

Case Study #1

- Baby treated successfully with Penicillin
- Future pregnancies:
  - Risk factor category
  - Automatic Intrapartum Prophylaxis before delivery
  - Delay discharge of infant for 48 hours

Case Study #2 : 1995-96

- 27 year old female
- First pregnancy
- At 32 weeks gestation, urine culture reveals 10,000 – 50,000 CFU/mL beta-hemolytic streptococci, Group B
- Ob/Gyn prescribes 250 mg oral Amoxicillin 2x for 10 days

Case Study #2 : 1995-96

- At 39 weeks gestation, vaginal culture reveals growth of normal flora
- 6 days later, female is admitted to hospital for labor induction
- Vaginal culture is repeated: negative
- 7 pound, 4 ounce female is vaginally delivered; apgar score = 9
- Mother & baby discharged 48 hours later
- No complications with GBS

Case Study #2 : 1998-99

- 30 year old female
- Second pregnancy
- Previous GBS carrier; infant not affected
- At 13 weeks gestation, vaginal culture reveals no GBS present
- At 21 weeks gestation, urine culture reveals 1,000 – 10,000 CFU/mL GBS

Case Study #2 : 1998-99

- Ob/Gyn prescribes 250 mg oral Amoxicillin 2x for 10 days
- At 36 weeks gestation, vaginal culture repeated; reveals no GBS present
- Admission to hospital 30 days later for labor induction

Case Study #2 : 1998-99

- Upon admission (8:00 am):
  - IV Penicillin G (5 mu) administered
  - Four hours later (12:00 pm) :
    - Dosage lowered to 2.5 mu
  - At 3:07 pm:
    - 8 pound male vaginally delivered; apgar score = 9
  - Mother & baby discharged 48 hours later
  - No complications with GBS

Case Study #3

- 1938
- 6 month old male
- Diagnosed with streptococcal meningitis
- Grave prognosis
- 7 other babies in isolation with same diagnosis

Case study #3

- Dr. offered “experimental treatment”
- Mother had to sign consent
  - Treatment could:
    - Kill baby
    - Have no effect
    - Treat disease
- Only 1 of 8 mothers signed consent
- Treated baby survived; other 7 died

Case Study #3

“Experimental Treatment”

Penicillin

Case Study #3

- Penicillin
  - Very experimental in 1938
  - Had not gone to clinical trials / no studies yet
  - Extremely hard to acquire

Case Study #3

- Age 21 (after MT school)
- Returned to hospital & met Dr. that treated him
- Dr. located patient's medical chart
- Cause of patient's GBS:
  - Breach baby
  - Long labor
    - ROM >18 hours

The Advocate, May 16, 2001

- "Child gets $107.8 million malpractice award"
  - 10 year old male
  - Brain damage due to delayed treatment for bacterial meningitis
  - 1990, New York hospital
  - Test result showed that mother was positive for GBS

The Advocate, May 16, 2001

- However,
  - Test was ordered a day later than should have been
  - Delay of one day in returning test results from lab (sent out)
  - Another 24 hours elapsed before patient was given antibiotics
- Jury ruled in favor of patient

Case Study #4

- Woman delivered baby who developed severe GBS disease
- Remembered being cultured for GBS & results were negative
- Attorney subpoenaed her medical records
- Indicated patient was screened for GBS in 35th & 37th week of pregnancy
- Results were negative

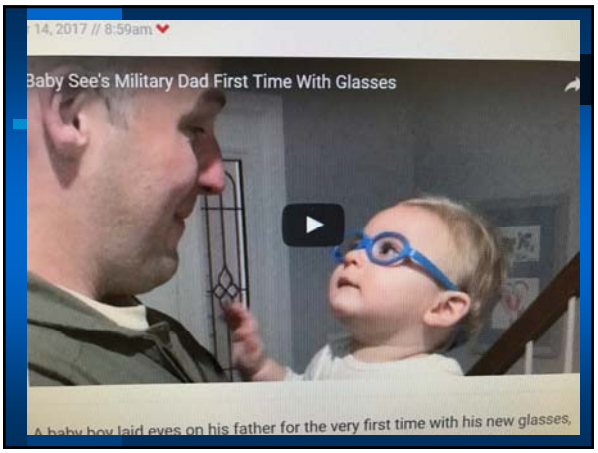
Case Study #4

- So, what happened???
- Medical records revealed the collection site was the cervix
  - Suboptimal site
  - Should be rejected & physician notified
- Physician was sued for inappropriate site collection
- Hospital sued for accepting & processing the specimen

Medical Laboratory Observer, April 1, 2012

Case Study #5

- Caldwell family in New York
- 9 month old Reagan
- Received new glasses right after father left on a 2 month deployment to Antarctica for the Air Force
- Video shows Reagan seeing his father for the first time
  - http://abc7ny.com/health/watch-baby-sees-military-dad-for-1st-time-with-glasses-after-homecoming/1793497/



Case Study #5

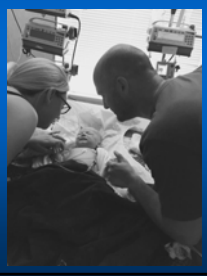
- Tough year for the Caldwell's
  - Reagan needed glasses due to GBS infection
  - Mother was GBS +; received antibiotics during delivery
  - Reagan began showing symptoms of meningitis 20 days after delivery

Case Study #5

- Symptoms included:
  - Very fussy
  - Lack of appetite
  - Fever (103.1ºF) 24 hours later
- Brought to emergency room
  - CSF contained bacteria; glucose level extremely low
  - Septic
  - Began having seizures

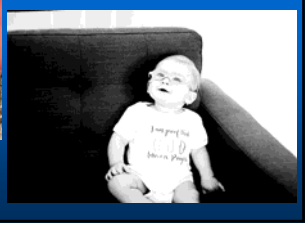
Case Study #5

- Diagnosed with GBS meningitis
- Poor prognosis

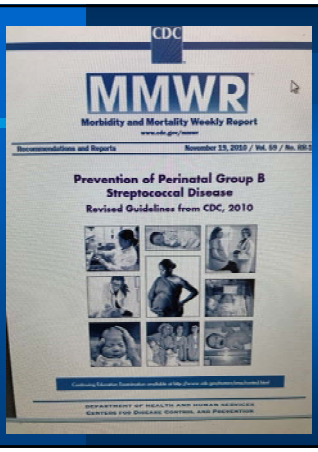


Case Study #5

- Reagan survived & continues therapy



Facebook page: GBS/Strep B Streptococcus: Reagan's Journey



2010 Revised Guidelines

MMWR, Vol. 59 (RR-10) Nov. 19, 2010

Organizations Endorsing the 2010 GBS Guidelines

- American College of Obstetricians & Gynecologists
- American Academy of Pediatrics
- American College of Nurse-Midwives
- American Academy of Family Physicians
- American Society for Microbiology

Major Differences in New Guidelines

- Expanded options for lab detection of GBS, including use of pigmented media & PCR assays
- Revised colony count threshold for labs to report GBS in urine of pregnant women

Minor Differences in New Guidelines

- Recommendations for IAP agents to promote the most appropriate antibiotic for penicillin-allergic women (clindamycin & erythromycin)
- Penicillin dosing changed to facilitate the implementation in facilities with different pre-packaged penicillin products

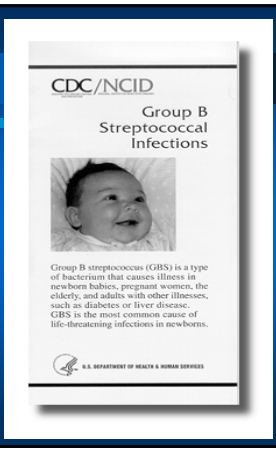
What Can You Do to Help?

- Make sure your OB, Peds, and Microbiology colleagues keep up with the new guidelines
- Ensure your lab is using selective broth medium
- Plan steps needed for implementation in your facility

Educational Methods

- Communication between Ob/Gyn and patient
- Public Awareness
  - Literature (brochures, advertising, posters)
  - Videos
  - Web Sites

Brochures



Posters

Pre-natal Facilities

Posters

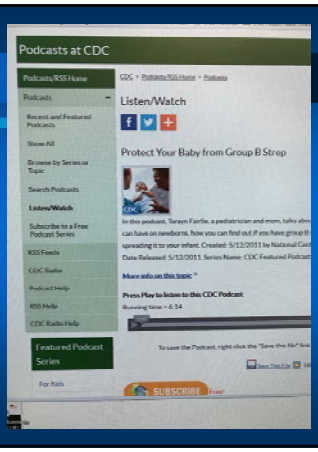
Labor & Delivery

Web Sites

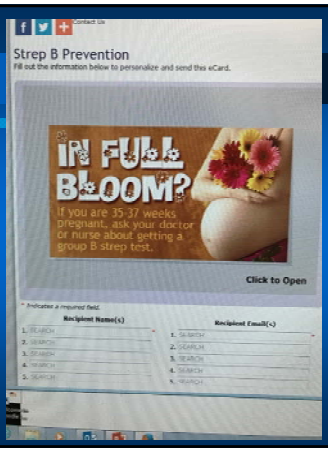
- CDC's GBS Internet page
  - http://www.cdc.gov/groupbstrep
- GBS Association home page
  - http://www.groupbstrep.org

Non-profit organization formed in June, 1990 by parents whose babies died from GBS

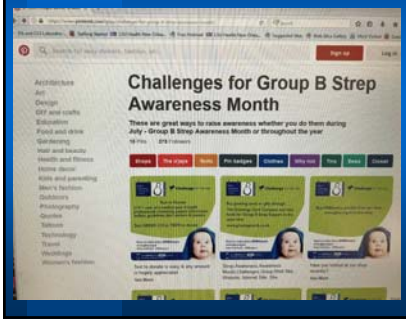
Podcasts



e-cards



July is GBS Awareness Month



Prevent Group B Strep App

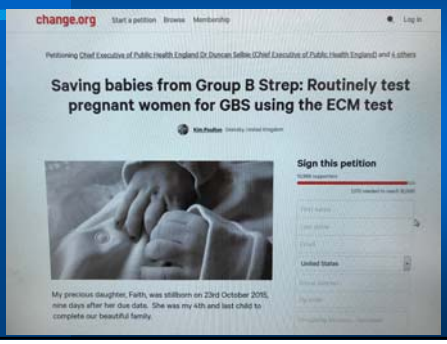
Strepelle Home to Lab Test Kit

- Only available in United Kingdom
- Two swabs collected by pregnant female (vaginal & rectal)
- Swabs mailed to lab in transport gel
- Results in 3 days
- Cost $39.99

United Kingdom

- Kim Poulton, a UK mum, is petitioning for GBS screening to be routine for all pregnant women in the UK.
- She asks for supporters to read, share, and sign her petition.
  - https://www.change.org/p/groupbstrep

Petition in United Kingdom



Key GBS Resources

- MMWR 2010;59 (No. RR-10):1-36
- CDC's GBS Internet page
  - http://www.cdc.gov/groupbstrep
- GBS Association home page
  - http://www.groupbstrep.org