Group B Streptococci: Chains & Changes

New Guidelines for the Prevention of Early-Onset GBS

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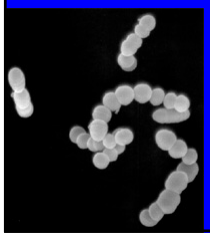


Disclaimer

The findings and conclusions in this presentation are those of the author and do not necessarily represent the official position of the CDC/ATSDR.

Case History

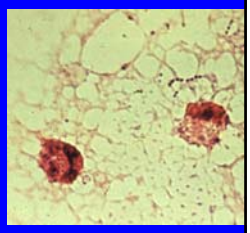
A 33 year old gravida 1, para 1, woman gave birth to a 3,500 gram male infant at term after an uneventful pregnancy. She had good prenatal care and appropriate GBS screening at 36 wk. Her vaginal/rectal swab was negative for GBS, she had no risk factors, and no antibiotics during her labor.

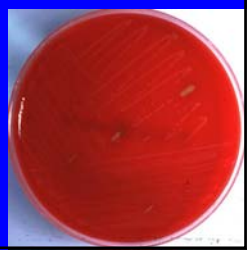
Case History (cont)

At birth and at 8 hr of age, exams were normal. At 18 hr the newborn began vomiting and refused to feed. The baby became lethargic, his anterior fontanelle was bulging, and a lumbar puncture was done.

Case History (cont)

- Lumber puncture revealed cloudy spinal fluid
  - 5,000 WBCs/mm^3 (98%Segs)
  - Glucose 25 mg/dl
  - Protein 170 mg/dl
- Gram stain had many WBCs and gram positive cocci in chains
- Blood and CSF cultures grew GBS
- Why does this occur?

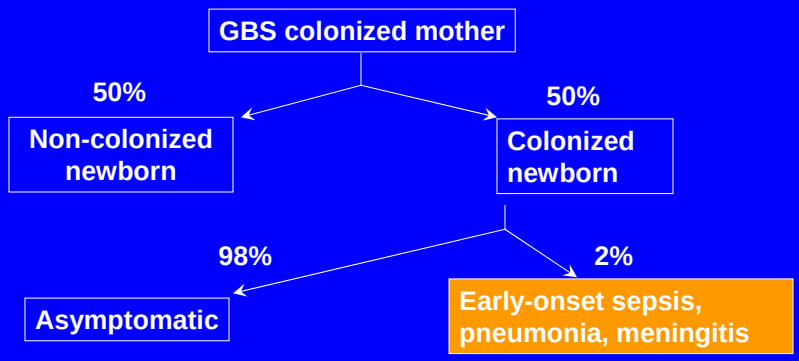




Background of GBS Disease

- GBS emerged as important pathogen in 1970s
- Over 7500 cases of GBS sepsis and meningitis in newborns annually in 1990
  - Early-onset disease < 7 days after birth
  - Late-onset disease ≥7 days after birth
- Early 1980's clinical trials showing intrapartum antibiotic prophylaxis (IAP) prevented early-onset disease (Boyer and Gotoff, NEJM 1986)

Mother to Infant Transmission



GBS Maternal Colonization

- GBS Carriers
  - 10% - 30% of women
  - higher in African Americans and nonsmokers
  - clinical signs not predictive
  - dynamic condition
- Risk factor for early-onset disease: GBS colonization at delivery
  - prenatal cultures late in pregnancy can predict delivery status

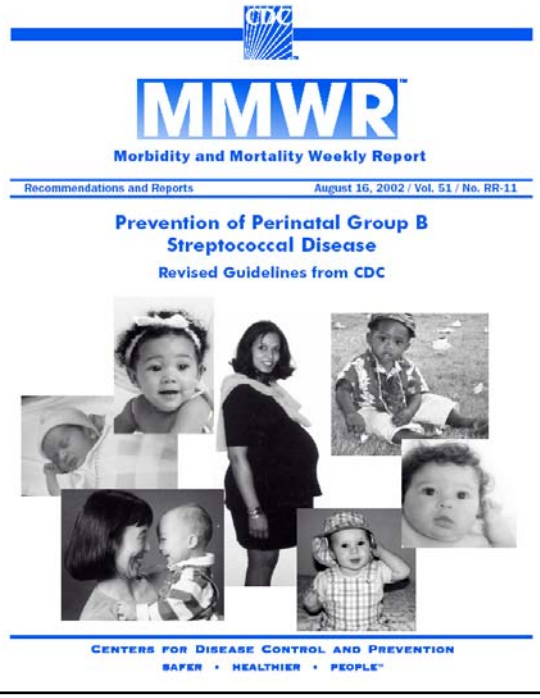
Additional Risk Factors for Early-Onset GBS Disease

- Obstetric
  - prolonged rupture of membranes
  - preterm delivery
  - intrapartum fever
- GBS bacteriuria
- Previous infant with GBS disease
- Demographic
  - African American race
  - Young age
- Immunologic
  - Low antibody to GBS capsular polysaccharide

Establishment of Guidelines To Identify Women At Risk

- Recommendation for IAP issued in 1996 by ACOG and CDC and in 1997 by AAP
  - Risk-based approach
  - Culture-screening approach
- Later studies showed screening 50% more effective

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION



The Recommendations

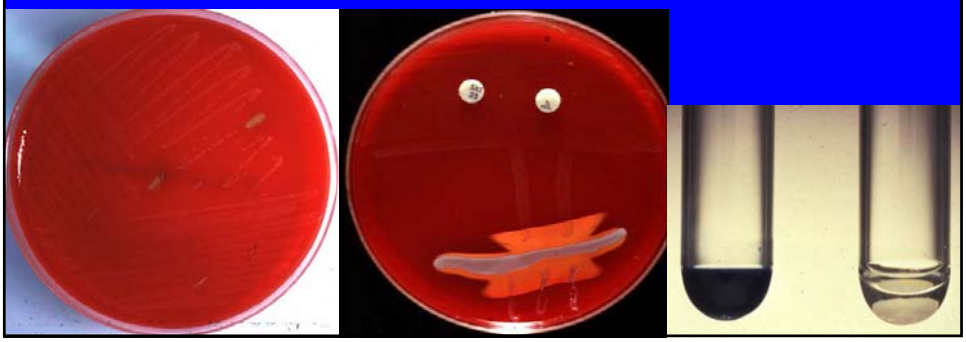
MMWR, Vol 51 (RR-11)

2002 Revised CDC Guidelines

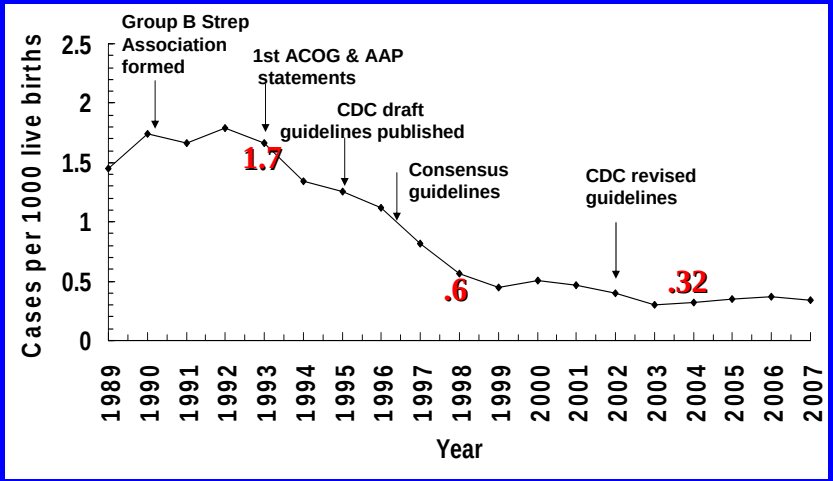
- Nov 2001 CDC consulted with multiple partners to revise 1996 guidelines using evidence-based approach where possible and scientific opinion when sufficient data were lacking
- New recommendations:
  - Universal prenatal culture-based screening for vaginal-rectal GBS colonization at 35-37 weeks gestation
  - Updated prophylaxis regimen for women with penicillin allergy
  - Detailed instructions on prenatal specimen collection, and expanded methods of GBS culture processing, including instructions on susceptibility testing
  - A number of additional issues related to management of threatened preterm delivery, planned cesarean section deliveries in group B strep colonized women, group B strep bacteriuria, management of newborns exposed to intrapartum chemoprophylaxis

Laboratory Practices Did Not Change

- Isolation and identification methods same for 1996 and 2002
- 2002 guidelines recommended AST for women at high risk for penicillin allergies; GBS in urine pregnant women be reported

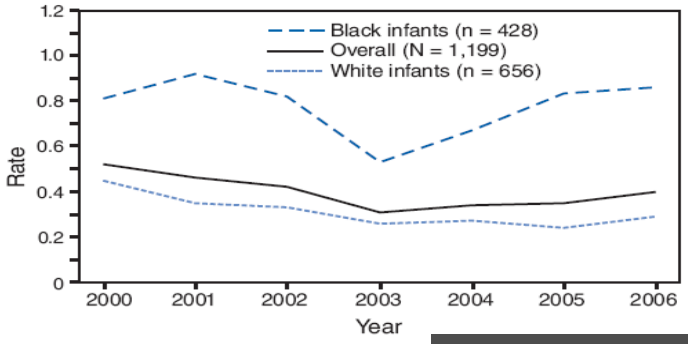


Incidence of Early-Onset Invasive GBS Disease, Selected Active Bacterial Core Surveillance Areas, 1989-2007



Trends in Early-Onset GBS Disease

FIGURE 1. Rate* of early-onset† invasive group B streptococcal disease, by race and year — Active Bacterial Core surveillance system, United States,§ 2000–2006¶

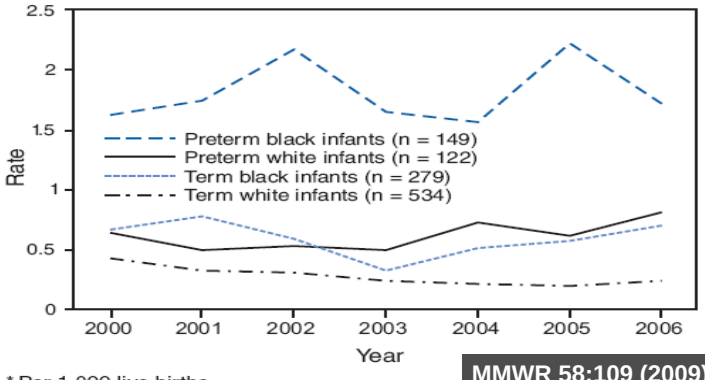


MMWR 58:109 (2009)

* Per 1,000 live births.
† Occurring in infants aged <7 days.
§ Includes selected counties in California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee. Additional information available at http://www.cdc.gov/ncidod/dbmd/abcs.
¶ Rates for 2000–2006 include surveillance areas participating since 2000, with the addition of Colorado in 2001. New Mexico, where surveillance began in 2004, is not included in comparison of incidence over time.

Trends in Early-Onset GBS Disease

FIGURE 2. Rate* of early-onset† invasive group B streptococcal disease, by race, prematurity status, and year — Active Bacterial Core surveillance system, United States,§ 2000–2006¶



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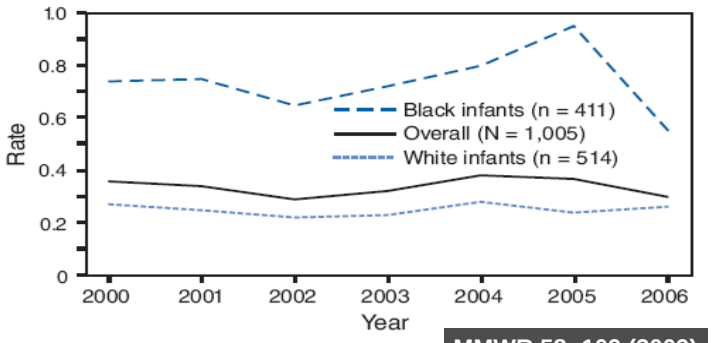
Trends in Late-Onset GBS Disease

FIGURE 3. Rate* of late-onset† invasive group B streptococcal disease, by race and year — Active Bacterial Core surveillance system, United States,§ 2000–2006¶



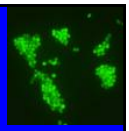
MMWR 58: 109 (2009)

* Per 1,000 live births.
† Occurring in infants aged 7–89 days.
§ Includes selected counties in California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee. Additional information available at http://www.cdc.gov/ncidod/dbmd/abcs.
¶ Rates for 2000–2006 include surveillance areas participating since 2000, with the addition of Colorado in 2001. New Mexico, where surveillance began in 2004, is not included in comparison of incidence over time.

Good News, Bad News from the Latest Data

- Screening for GBS increased 48% to 85% from ‘98-99 to ’03-04
- Infants exposed to antibiotics increased 27% to 32 %
- IAP given to 87% of GBS+ women
- IAP given to only 63% of GBS unknown women
- 74% of GBS cases occurs in term births
- 61% of term infants with GBS born to women who tested GBS -

Van Dyke et al. NEJM 360:2626 (2009)



Old Truths, New Findings Laboratory practice

- Vaginal /rectal swabs best recovery of GBS
- Broth enrichment superior to plating
- Overgrowth of enterococci from broth problem
- Direct antigen detection from broth very sensitive
- Newer chromogenic media expand options
- Molecular assays offer new opportunities

Chromogenic Media

- 25 publications from 2002-2008 evaluated chromogenic agars or broths
- Majority incorporate Granada medium which is selective and differential medium for GBS (uses Granadaene, a polyenic red pigment to differentiate GBS)
- Chromogenic media have been evaluated and positives do not require confirmation by antigen/latex detection
- Studies show majority agars and broths equivalent or better than SBA/CNA and Lim broth for GBS recovery – added advantage of detection after 24hrs

impedir la transmisión vertical de *S.agalactiae* y prevenir la infección neonatal (1, 2, 5, 8, 16). Así

transmission of GBS from colonized pregnant women to their neonates (1, 2, 5, 8, 16).

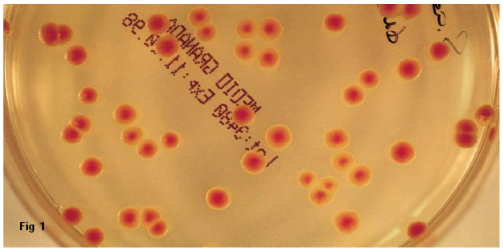


Fig 1

Granada Medium for the Recovery of GBS

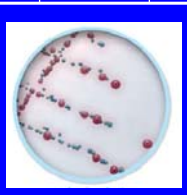
Fig 3

Commercially Available Chromogenic Media

Media	Agar/Broth	Color detection	Non-Hemo GBS	Incubation	Sensitivity
chromID™StreptoB	Agar	Pale pink-red	Yes	18-24hrs (aerobic)	Good
Granada Agar	Agar	Orange/red colonies	No	24hrs (anaerobic)	Good
Granada™Biphasic broth	Broth	Orange/red color	No	18-24hrs (aerobic)	Good
NEL-GBS	Agar/broth	Orange	No	16-24hrs (aerobic)	Poor
StrepB Carrot Broth™	Broth	Orange/red color	No	18-24hrs (aerobic)	Good

Streptococcus B (red to orange characteristic colonies)

Granada Biphasic broth



chromID™StreptoB

StrepB Carrot Broth™

PCR Assays Available

Assay	GeneOhm™	Smart GBS	GeneXpert®
Hands on Time	18 min	25 min	2-3 min
Total Test Time	70 min	75 min	≤ 80 min
Complexity	High	High	Moderate
Ext Controls	Yes	Yes	No
Cost	$18-26	$18-26	$40-45

PCR Tests Performance Based on Mfg Package Insert

Test	% Sensitivity	%Specificity
BD GeneOhm Strep B	94%	96%
Cepheid Smart GBS	85%	97%
Cepheid Xpert GBS	92%	90%

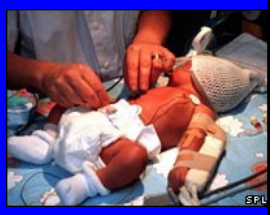
Direct PCR vs Enrichment Broth and Culture

Study	Test	N	Site	Sensitivity
Davies	IDI (BD)	803	Vag/Rec	94%
Edwards	IDI (BD)	784	Vag/Rec	79%
Aziz	IDI (BD)	315	Vag	62.5%
Atkins	IDI (BD)	233	Vag/Rec	87%
Smith	BD GeneOhm	200	Vag	77%
Money	BD GeneOhm	180	Vag/Rec	91%
Edwards	GeneXpert	784	Vag/Rec	91%
Gavino	GeneXpert	55	Vag/Rec	96%

Molecular vs Culture

- Many studies did not resolve discrepancies between culture + PCR- samples, and culture - PCR+ samples
- Direct testing of vag/rec specimens
  - Mean 89.8% (79-97%)
- Lim broth enrichment and PCR
  - Mean 96.3% (92.5-100%)
- Molecular test faster and highly specific
- Molecular test ⇩ sensitivity, ⇧ $$, and no organism for susceptibility testing

Can Molecular Tests Work? Pittsburgh Experience



- 9000 deliveries /yr
- Run test 24/7
  - Shift 1 and 2 in clinical micro
  - Shift 3 in general lab
- Previously used IDI, now GeneXpert (Cepheid) on all GBS unknowns (15%)
- Decreased GBS cases 50%

Culture Concerns ClinMicroNet Review

- Transport media
  - Charcoal media should be acceptable
  - Little data supporting viability GBS after 4 days at RT or 4°C (viability decreases rapidly after 24 hrs)
- Overgrowth with enterococci from broths
- Antibiotic susceptibility testing issues (test all GBS+ or hold culture for testing if antibiotic susceptibility testing not indicated)
- Screening urine cultures for GBS for pregnant women
  - Outcome data lacking
  - Pregnant status often not stated on forms
  - Impacts workload and cost

Task 1: Review collection and transport recommendations

- Type of swab acceptable for antenatal screening ie. vaginal/rectal swabs only; cervical swabs or perianal / perirectal not acceptable
- Recommend use of non-nutritive transport media - eg. Amies or Stuart (with or without charcoal)
- Retain "Transport media will maintain GBS viability for up to 4 days at RT or 4°C"
- Trans-Vag Broth (Todd Hewitt broth with 8 µg/ml gentamicin and 15 µg/ml nalidixic acid) requires the addition of 5% defibrinated sheep blood for increased recovery of GBS (Remel)
- Include that if "susceptibility testing is ordered for penicillin-allergic women, specimen requisitions should identify the patient as penicillin allergic and that this should authorize the laboratory to perform reflex antibiotic susceptibility testing"

Task 2: Review bacteriuria recommendations

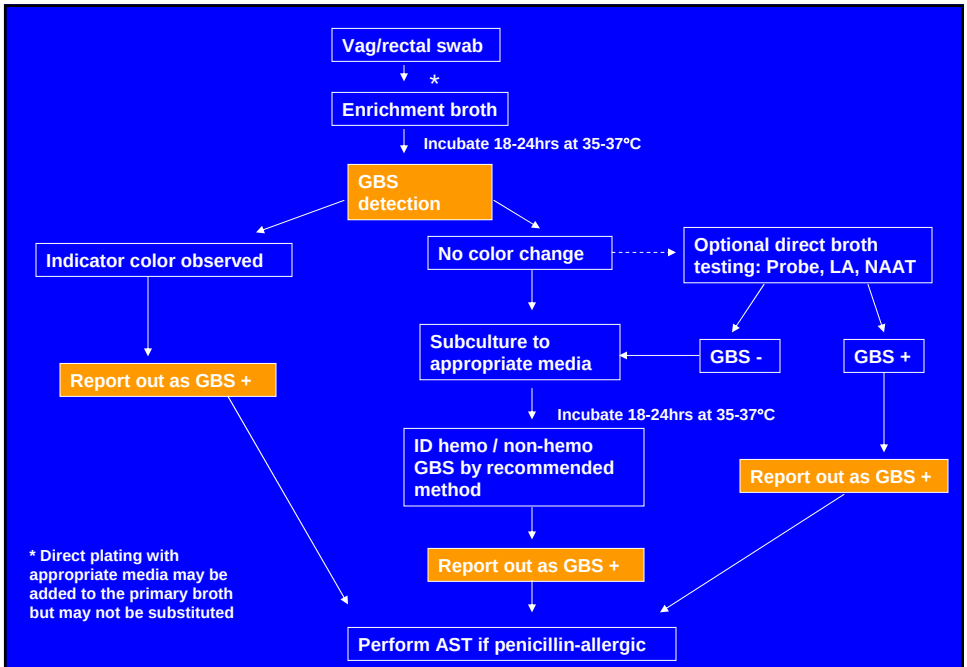
GBS Bacteriuria During Pregnancy

The presence of GBS bacteriuria in **any concentration** in a pregnant woman is a marker for heavy genital tract colonization. Therefore, women with **any quantity** of GBS bacteriuria during pregnancy should receive intrapartum chemoprophylaxis. Vaginal and rectal screening at 35-37 weeks is not necessary for these women. GBS can cause both symptomatic and asymptomatic urinary tract infections, which should be diagnosed and treated according to current standards of care for urinary tract infections in pregnancy. Women with GBS urinary tract infections during pregnancy should receive appropriate treatment at the time of diagnosis as well as intrapartum GBS prophylaxis. **Laboratory personnel should report any presence of GBS bacteriuria in specimens obtained from pregnant women. For this to occur, labeling of urine specimens to indicate that they were obtained from a pregnant woman is imperative**.

- GBS can cause symptomatic and asymptomatic UTI
- Laboratories should report significant concentrations of GBS bacteriuria in pregnant women as they do for other urinary tract pathogens such as E. coli ($\geq 10^4$ organisms/ml)
- GBS bacteriuria is a marker for heavy genital tract colonization and these women should receive IAP.
- Screening at 35-37 wk not necessary for these women

Task 3: Finalize culture recommendations

- Include additional culture options with pigmented broths and chromogenic agars
- Include option step for nucleic acid amplification testing (NAAT) from broth enrichment along with other tests using probes and latex agglutination
- Prepared revised and simplified algorithms / flowcharts

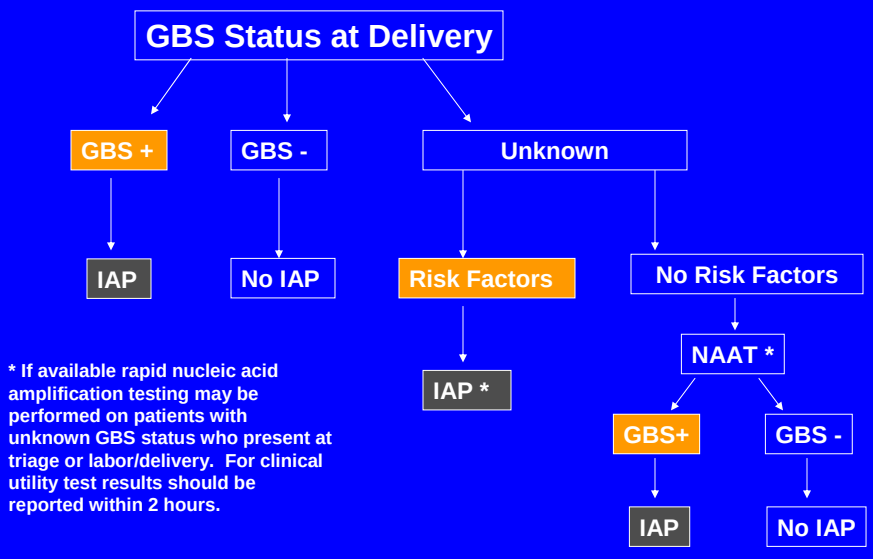


Algorithm for processing antepartum vaginal/rectal swabs

Task 4: Prepare a draft set of direct PCR testing recommendations

- Recommendation for use PCR for antepartum and intrapartum testing: included in algorithm / flowchart for processing of AP vag/rec swabs
  - Antepartum before labor begins
  - Intrapartum between onset of labor and delivery

- "If available rapid nucleic acid amplification testing may be performed on patients with unknown GBS status who present at triage or labor/delivery. For clinical utility test results should be reported within 2 hours"
  - PCR testing should be available 24/7



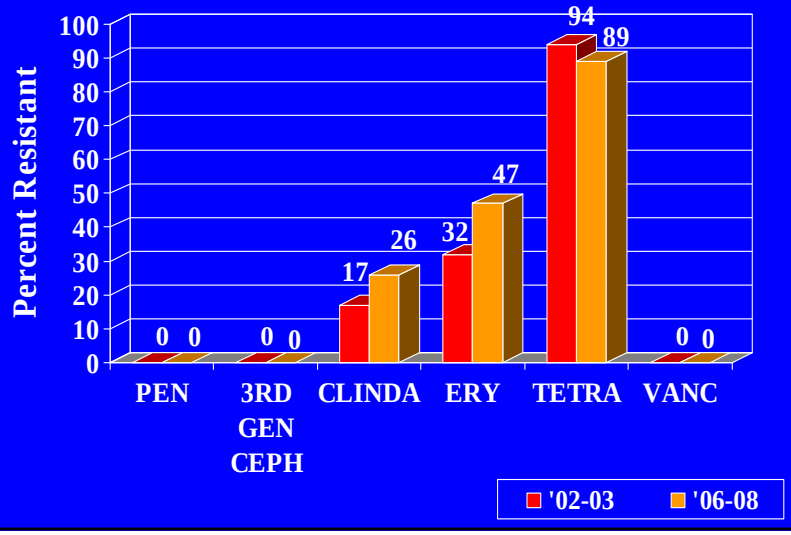
Algorithm for Intrapartum PCR testing

Task 5: List possible causes of false negatives GBS results from culture

- Improper collection sites
- Transport time
- Improper culture methods
- Antibiotic exposure
- Overgrowth with other organisms
- Failure to recognize non-hemo GBS
- Subjectivity in interpreting results

GBS from Prenatal Cultures

160 Loyola Isolates ’02-03
290 ABCs Isolates ’06-08



Considerations for GBS Susceptibility Testing

- >4 hr of beta lactam ~80% efficacious
- Other agents (clinda) not efficacious at 9 hr
- Potential to remove recommendations for macrolides
- Resulting in increase use of vancomycin
- Less confusing
- Susceptibility tests would not be required

What about Resistance to Penicillin?

- Isolates in Japan and U.S. have elevated MICs to beta lactams due to mutation in *pbp2x* gene
  - Pen 0.015 wild type
  - Pen 0.12 (bk pt ≤ .12)
  - Pen 0.25-1.0 (Japan)
  - Cefotax .12-25 (bk pt ≤.5)
  - Cefoxitin 16 (no bk pt)
- Single base change at residue 557 glutamine >>>glutamate (Q557E)
  - 1st step mutation similar to *S. pneumoniae*
- Accumulate additional mutations lead to full resistance

Dahesh et al. AAC 52: 2915, 2008

Summary of Proposed Changes

- Vaginal / Rectal Culture
  - Expand laboratories culture options
  - Retain recommendation for broth enrichment using Lim broth
  - Include option to use chromogenic broth procedures
  - Include optional antigen detection from broth
  - Retain the recommendation that direct plating can accompany broth inoculation
  - Include options for use of newer chromogenic agars
- Antibiotic Susceptibility
  - Changes for susceptibility testing based on any changes to IAP agents
  - Recommend detection of inducible clindamycin resistance using D-zone method for labs performing broth microdilution
- Urine Culture Screening
  - Revised guidelines needed to provide clear recommendations for GBS in pregnant women

http://www.cdc.gov/groupbstrep