What's new in group B streptococcus screening and guidelines?

OLD & NEW TOOLS

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INTRODUCTION & BURDEN

Group B streptococcal diseases in neonates
- Since the 1970s, leading cause of life-threatening infections in newborns
  - Neonatal illness/death
  - Long-term disabilities

Streptococcus agalactiae or GBS
- Gram positive cocci
- β-hemolytic
- Encapsulated
- 10 capsular serotypes (Ia, Ib, II-IX)

Group B streptococcal diseases in neonates
- Since the 1970s, leading cause of life-threatening infections in newborns
  - Neonatal illness/death
  - Long-term disabilities

80 % EOD & VLOD

A. Schuchat, Clin Microb Rev 1991;14:497-513

CONTENT
- Introduction & burden
  - History and historical context of perinatal GBS disease
  - Early and contemporary epidemiology
  - Pathogenesis and risk factors
- Prevention strategies
  - Maternal intrapartum chemoprophylaxis
  - Evolution of policies, effectiveness and concerns
  - Towards a European consensus and revised Belgian guidelines
  - Maternal immunization
- Screening: old and new tools
- Take home messages
**Group B streptococcal diseases in neonates**

- Since the 1970s, leading cause of life-threatening infections in newborns
- Neonatal illness/death
- Long-term disabilities

**Maternal morbidity**
- Along pregnancy
- Peripartum

- Serious diseases among elderly and adults with underlying diseases
- Significant mortality

**GBS colonized mothers**
- Non-colonized newborns: 40 - 60%
- Colonized newborns: 60 - 40%

**GBS EOD vertical transmission**
- 60 - 40%
- 40 - 60%

**Additional Risk Factors for Early-Onset GBS Disease**

- Obstetric factors:
  - Prolonged rupture of membranes,
  - Preterm delivery,
  - Intrapartum fever
- GBS bacterium
- Previous infant with GBS disease
- Immunologic:
  - Low specific IgG to GBS capsular polysaccharide

*No difference in occurrence either in GBS Positive or Negative women, except intrapartum fever

**Stages in the pathogenesis of GBS neonatal EOD: Bacterial & individual factors**

- Colonization: adhesion to epithelial cells different virulence factors (pil, capsule, ...)
- Brain barrier
- Phagocytes, antibodies, complement
- Sepsis
- Pathogenesis
GUIDELINES FOR PREVENTION OF GBS PERINATAL DISEASE

- Universal antenatal screening-based strategy
- Risk-based strategy
- No guideline

Stages in the pathogenesis of GBS neonatal EOD: Bacterial & individual factors

Colonization: adhesion to epithelial cells of different virulence factors (pili, capsule, ...)

Preventing transmission

Intrapartum antibioprophylaxis

> 4 (2) hours before delivery

Highly effective in preventing GBS EOD (1st clinical trials in late 80s)

Impact of prevention practices Early- and Late-onset GBS Diseases in the 1990s, U.S.

Group B Strep Association formed
1st ACOG & AAP statements
CDC draft guidelines published
Consensus guidelines: Screening >50%, more effective than RF

European strategies for prevention of GBS EOD

- Intrapartum antibioprophylaxis recommended
  - Screening-based strategy
    - France, 2001
    - Belgium, 2003, revision ongoing 2013
    - Germany, 1996, revised 2008
    - Switzerland, 2007
  - Risk-based strategy
    - UK, the Netherlands, Denmark
  - No guidelines
    - Bulgaria, ...

Impact of prevention practices Early- and Late-onset GBS Diseases, U.S.

Early-onset GBS

Late-onset GBS

Before national prevention policy

Incidence of early- and late-onset invasive group B streptococcal disease in selected Active Bacterial Core surveillance areas, 1989-2008 (CDC 2010)

- Risk-based strategy
- Universal strategy
- Antenatal strategy

 Which prevention strategy for GBS perinatal diseases?

- Intrapartum antibioprophylaxis
- Immunoprophylaxis

Key strategy « nearly within reach »

Continuing Education Examination available at

www.cdc.gov/mmw

November 19, 2010

http://www.cdc.gov/mmwr/ContEd_2010/vol59/rr10057.htm

CDC draft guidelines published

Consensus guidelines: Screening >50%, more effective than RF

S. Schrag, New Engl J Med 2000


Revised Guidelines from CDC, 2010

Prevention of Perinatal Group B Streptococcal Disease

Morbidity and Mortality Weekly Report

CDC – NRC for group B streptococci

- Intrapartum antibioprophylaxis
- Immunoprophylaxis

Key strategy « nearly within reach »

- Risk-based strategy
- Universal strategy
- Antenatal strategy

Which prevention strategy for GBS perinatal diseases?

- Intrapartum antibioprophylaxis
- Immunoprophylaxis

Key strategy « nearly within reach »
Universal screening-based strategy for prevention of GBS perinatal disease (Be SHC 2003)

Vagino-rectal GBS screening culture at 35-37 weeks of gestation

For all pregnant women

**GBS Neg**
- Not done, incomplete or unknown GBS result

**GBS POS**
- Facultative use of intrapartum rapid GBS test

- 1. Vagino-rectal sampling (6/ml)
- Incubation at 37°C
- Not done if < 18 hrs

If NO
- Intrapartum prophylaxis NOT indicated

If YES
- INTRAPARTUM ANTIBIOPROPHYLAXIS
  - Unless patient had a previous infant with GBS invasive disease
  - or GBS bacteriuria during current pregnancy
  - or delivery occurs < 37 weeks’ gestation

GBS Pos
- Repeat culture
  - GBS Neg if YES
  - GBS Pos if YES
  - Resistance tests (MIC)

Concerns: Clinically relevant antimicrobial resistance

Increase of resistance to erythromycin and clindamycin

Erythromycin and clindamycin resistance among clinical isolates of GBS (Belgian data)

<table>
<thead>
<tr>
<th>Year</th>
<th>Erythromycin Resistant (%)</th>
<th>Clindamycin Resistant (%)</th>
</tr>
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<tbody>
<tr>
<td>1990</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1995</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>2000</td>
<td>10</td>
<td>30</td>
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<tr>
<td>2005</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>2010</td>
<td>30</td>
<td>70</td>
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</tbody>
</table>

Resistance to erythromycin:
- Constitutive + Inducible R (∼ 75% CR & 25% IR)
  - D-Test recommended

Concerns: Clinically relevant antimicrobial resistance

Increase of resistance to erythromycin and clindamycin

Reduced susceptibility to penicillin
- Very few non-S isolates recently characterized in Japan
  - Mutation in pbp genes, especially pbp2x
  - MIC > 0.25 mg/L
  - No clinical impact?
- Very few in the U.S., Canada
- All labs should send to reference lab
  - Any non-S isolate for confirmation
  - All invasive isolates for resistance surveillance

Adhesion to a common protocol is a key of success
Multidisciplinary collaboration is mandatory
Other concerns
Potential adverse / unintended consequences of prophylaxis
- Allergies
  - Anaphylaxis occurs but extremely rare
- Changes in incidence or resistance of other pathogens causing EOD
  - Data are complex ...
  - But most studies: stable rates of "other" sepsis
- Changes in GBS antimicrobial resistance
- Impact on newborn gut microbiota

Remaining burden of GBS EOD
Missed opportunities
In spite of universal screening prevention strategy
In spite the great progress
Cases still occur
- Among remaining cases of EOD
  - Some may be preventable cases
  - Missed opportunities for (appropriate) IAP
  - False negative screening

Background
- Correlate between maternal low level off CPS type Ab at time of delivery and risk for development of GBS EOD
  - Baker C et al., Kasper D, 1976, NEJM

GBS Vaccine
"still expected"
- GBS pathogenesis
- Ascendant transmission (amnionitis)
- Phagocytes, antibodies, complement
- Help for clearing bacteria and preventing development of EOD

Stages in the pathogenesis of GBS neonatal EOD: Bacterial & individual factors
- Colonization: adhesion to epithelial cells
- Different virulence factors (pili, scpB, ...)
- β-hemolysin, invasins (pneumonia)

Background
- Correlate between maternal low level off CPS type Ab at time of delivery and risk for development of GBS EOD
  - Baker C et al., Kasper D, 1976, NEJM

GBS Vaccines, since the 1980s
Challenges
Capsular polysaccharide vaccines
- 10 serotypes
  - Different distributions
    - EOD, LOD, invasive infections in adults
    - Geographically and along time
- Conjugated vaccines
- Multivalent vaccines Ia, Ib, (II), III and V
- Clinical studies (phases 1, 2 and 3)
  - Immunogenicity
  - Safety
  - Efficacy: scheduled/ongoing

Within reach!

GBS Vaccines
GBS Protein-based vaccine
- Ag = Surface proteins
  - Cross protection against different serotypes
  - Better immunogenicity
    - Humoral response T-cell dependent
    - Long lasting immunity

CDC revised guidelines 2010
DEVANI project, unpublished data 2011

GBS vaccine "still expected"

GBS Protein-based Vaccine
- Ag = Surface proteins
  - Cross protection against different serotypes
  - Better immunogenicity
    - Humoral response T-cell dependent
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CDC revised guidelines 2010
DEVANI project, unpublished data 2011
Protein-based Vaccines

<table>
<thead>
<tr>
<th>Protein</th>
<th>Protective Ab associated serotypes (in mouse)</th>
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<tr>
<td>Alpha-like proteins</td>
<td></td>
</tr>
<tr>
<td>Alpha</td>
<td>Yes</td>
</tr>
<tr>
<td>Alp1</td>
<td>la</td>
</tr>
<tr>
<td>Rib</td>
<td>Yes</td>
</tr>
<tr>
<td>Alp2</td>
<td>Yes</td>
</tr>
<tr>
<td>Alp3</td>
<td>Yes</td>
</tr>
<tr>
<td>Beta C protein</td>
<td>Yes</td>
</tr>
<tr>
<td>C5a peptidase</td>
<td>Yes</td>
</tr>
<tr>
<td>Sip (1999)</td>
<td>Yes</td>
</tr>
<tr>
<td>BPS</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Sip = Surface Immunogenic Protein (Brodatz, Martin, Quebec)
BPS= Groupe B Protective surface Protein

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GBS « pilus like structure »

- Highly immunogenic proteins
- Elicit protective and functional antibodies
- Virulence factor
  - Adhesion
  - Transcytose through cells

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Crucial conditions to optimize SCREENING

- **WHEN**
  - 35-37 weeks
- **WHO**
  - ALL the pregnant women
- **Specimen**
  - Vaginal + rectal swab(s)
- **Collection**
  - WITHOUT speculum
- **Transport**
  - Transport/collection device/condition
  - (non nutritive medium: Anaer/Stan or Granada like tube) (type of swab) (= length and T°C)
- **Request form**
  - To specify prenatal « GBS » screening
- **Laboratory procedure**

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Reverse vaccinology approach

Knowledge of complete GBS genome

- Comparison of genomes from 8 different GBS serotypes

D.Malone et al, Science 2006

- 312 surface proteins were cloned
- Provided a high protective humoral response in mouse
  - Sip and 3 others
  - The 3 other proteins = « pilus like structures »

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Introduction: Addressing the challenge of group B streptococcal disease

- Introduction, Rappuoli & Black
- GBS Review, Carol Baker
- Overview GBS epidemiology, Paul Hoash
- GBS epidemiology and vaccine needs, Melin & Efstratiou
- GBS epidemiology in developing countries
- IAP in USA et Vaccine Implications, S.Schrag & Venner
- GBS maternal vaccines Past Present and Future, Chen & Kasper
- GBS Public awareness etc
- Prevention through Vaccination, M. Edwards
- GBS Vaccination in pregnancy, P. Ferretti
- GBS vaccine Phase III trials
Antenatal GBS culture-based screening

Goal of GBS screening
To predict GBS vaginal (rectal) colonization at the time of delivery

- Critical factors influencing accuracy
  - Swabbed anatomic sites (distal vagina + rectum)
  - Timing of sampling
  - Screening methods
    - Culture
    - Procedure
    - Media
    - Non-culture

Optimal time for culture-based screening
35-37 weeks gestation

Culture-based screening done 1 to 5 or > 6 weeks before delivery (Yancey, 860 cases; Melin, 531 cases)

- Sensitivity
- Specificity


Optimal time for screening
35-37 weeks gestation

Culture-based screening done 1 to 5 or > 6 weeks before delivery (Yancey, 860 cases; Melin, 531 cases)

- Not 100% as colonization is dynamic


Antenatal culture-based screening: Limiting factors

- Positive and negative predictive values
- False-negative results
  - Reduced viability during transport
  - Oral ATB, feminine hygiene
  - New acquisition
- Failure of GBS culture
  - Oral ATB, feminine hygiene
  - New acquisition
- Up to 1/3 of GBS positive women at time of delivery

Need for more accurate predictor of intrapartum GBS vaginal colonization

From direct plating on blood agar
Evolution of culture methods

Use of selective enrichment broth (Lim broth, e.g.)
- To maximize the isolation of GBS
- To avoid overgrowth of other organisms

Use of differential agar media
Recommended by some European guidelines (+ CDC 2010)

- Granada
- Strep B Select
- Strept B ID
- Brilliance

1963, 1992

Pigment-based
Chromogenic media

Which agar or which combination?

- +/- Blood agar

Workload - costs - extra-testing - non β-hemolytic GBS detection to be considered
Crucial conditions to optimize SCREENING

- WHEN 35-37 weeks
- WHO ALL the pregnant women
- Specimen Vaginal + rectal swab(s)
- Collection WITHOUT speculum
- Transport Transport/collection device/condition
  (non nutritive medium: Amies/Stuart or Granada like tube) (type of swab) (Length and T°)
- Request form To specify prenatal GBS screening
- Laboratory procedure

(CDC 2010 - Belgian SCH 2003)

Crucial conditions to optimize SCREENING

Transport-collection system & transport-storage condition

- Type of swab: Nylon flocked >> regular fiber swab

Transport-collection system & storage condition

- Recommendations CDC, USA (2010)
  - Non nutritive media: Amies or Stuart without charcoal
  - Storage at 4°C or RT 1-4 days
  - Or Granada like tube ??
- Recommendations CSS, Belgium (2003)
  - Non nutritive media: Amies or Stuart without charcoal
  - Storage maximum 48h at 4°C

Viability of GBS NOT fully preserved by storage of vaginorectal swabs in Amies transport medium, mainly if not stored under refrigeration.
To sustain viability
Whatever is storage T° for a few days
Use of a selective enrichment Lim broth as transport media

Transport conditions to be recommended for optimizing GBS antenatal screening
Belgian Health Superior Council, 2013

- Transport system
  - Use of a selective enrichment Lim broth with a flocked swab
    (BD, Copan, bioMérieux, i.e.)
  - Transport and storage condition
    - At RT° (up to 35°C)
    - As soon as possible
    - Viability sustained at least 4 days

- Remark
  - If use of Amies or Stuart medium (non nutritive medium)
  - To be processed as soon as possible within 24 hours (max 48 h)

Intrapartum screening theranostic approach: expected advantages

- Inclusion of women without prenatal screening/care
- Identification of women with change of GBS status after 35-37 wks gestation
- Increased accuracy of vaginal GBS colonization status at time of labor & delivery

Real Time PCR for intrapartum screening

- Advance in PCR techniques & development of platforms
  - BD GeneOhm™ Strept B Assay (+/- 1 hr) (in laboratory)
  - Xpert GBS, Cepheid (35-45 min) (can be performed as a POCT)
Xpert GBS for intrapartum screening
(slected paper amongst many others)

Cost and effectiveness of intrapartum group B streptococcus polymerase chain reaction testing for term deliveries.
Obstet Gynecol 2012 Apr;119(4):822-9

2009
2010
Antenatal screening
11.7% GBS POS

Xpert GBS intrapartum screening
16.7% GBS POS
Less GBS EOD & less severe

Cost neutral per delivery

Xpert GBS for intrapartum screening (selected paper amongst many others)

Real-time PCR, very promising, BUT ...

• Rapid, robust & accurate technology
• Still an expensive technology (specific equipment)
• Cost effective?
• Need for more cost-effectiveness clinical study
  2014 NRC GBS - CHULg & USA
• Logistic
• 24 hours 7 days
• In the lab?
• In the obstetrical department as a POCT?
• In the lab?
• In the obstetrical department as a POCT?
• In combination with prenatal screening strategy?
• CDC 2010: for women with premature delivery or no prenatal care
• Drawback: no antimicrobial result
• In the future detection of R genes, but mixed microbiota!

Revised Belgian guidelines
(Superior Health Council, expected autumn 2014)
(Neonatologists, obstetricians, microbiologists, midwives)

Main recommendations
• Universal antenatal screening at 35-37 wks gestation
• Lim broth as transport media
• Selective differential culture media
• Determination of clindamycin susceptibility (if ßlactam mediated penicillin allergy)
• Universal screening at time of delivery can be used
  • If POCT with high PPV and NPV
  • Real time PCR or other methods
  • TAT < 1 hour
  • In case of known ßlactam mediated penicillin allergic women
  • Determination of clindamycin susceptibility for GBS positive screening
• IAP for all GBS positive pregnant women
  • documented by antenatal testing (or intrapartum testing if performed)
  • performed
  • in case of known ßlactam allergy)

Prevention strategy for GBS EOD
TOWARDS A EUROPEAN CONSENSUS?

Conference held in June 2013, Florence, Italy

A European working party:
Neonatologists, obstetricians, microbiologists
Representing countries
• with screening-based IAP,
• with risk-based IAP strategies
• or nothing

Xpert GBS in intrapartum screening
(Diagnostic Accuracy of a Rapid Real-Time Polymerase Chain Reaction Assay for Universal Intrapartum Group B Streptococcus Screening)
Najoua El Helali, Jean-Claude Nguyen, Aïcha Ly, Yves Giovangrandi and Ludovic Trinquart
Clinical Infectious Diseases 2009;49:417–23

• 968 Pregnant women
• Intrapartum Xpert GBS, Cepheid (performed in lab)
  • vs intrapartum culture
  • antenatal culture (French Department)
    • Sensitivity 98.5%
    • Specificity 99.6%
    • PPV 97.8%
    • NPV 99.7%

Real-time PCR, very promising, BUT ...
Towards « European Consensus »
Decision taken by the European working party

Main recommendations

- Universal screening at time of delivery
  - POCT with high PPV and NPV
  - Real time PCR or other methods
  - TAT < 1 hour
- IAP for all GBS positive pregnant women
  - Documented by intrapartum testing (or late pregnancy test if performed)
- Late pregnancy prenatal screening in known penicillin allergic women
  - Determination of clindamycin susceptibility if GBS positive screening

In Europe, as globally

Neonatal GBS diseases
- EOD and LOD, a global health concern
- IAP efficient for prevention of EOD
  - Best strategy still a matter of debate
  - Not 100% efficient
  - No effect on LOD
- IAP not widely recommended
- New tools to improve GBS detection
- Toward a European consensus
- GBS vaccine eagerly expected
  - Appears to be within reach

Thank you!