GBS Prévention
Nouveaux outils & stratégies attendues
Pierrette Melin
Centre National de Référence de Streptococcus agalactiae
Microbiologie clinique, CHU de Liège, Université de Liège

INTRODUCTION & BURDEN

Streptococcus agalactiae or GBS

Streptococcus agalactiae clones infecting humans were selected and fixed through the extensive use of tetracycline
- Genome-based phylogeny reveals the expansion of a few clones
- Human GBS belong mainly to a small number of TcR clones
V.Dacunha, MR.Davies, ... C.Pujet and P.Glaser

1887, Noccard-Mollereau, bovine mastitis
1933, Group B Antigen
1964, severe neonatal sepsis, Eickhoff et al N Eng J med
1970, N°1 in neonatal infections

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

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

EOD: 0.3-3 per 1,000 live birth
LOD: 0.4-0.5 per 1,000 live birth

GBS colonized mothers
(10-35% of pregnant women)

Non-colonized newborns: 60 - 40%
Colonized newborns: 40 - 60%

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

- COLONIZATION: adhesion to epithelial cells different virulence factors (pili, scpB, ...)
- Ascendant transmission (amnionitis)
- β-hemolysin
- Invasins (pneumonia)
- Resistance to phagocytosis
- Capsular
- C5a peptidase
- Bacteria
- Peptidoglycan
- Brain barrier
- Pili III ST-17
- Sepsis
- 2 - 4 % GBS EOD (> 50% no RF)
- Meningitis
- Pneumonia
- Long term sequelae
- Sepsis pneumonia meningitis long term sequelae
- IL1, IL6, TNF α, PGE2, TxA2
- Antibodies, Complement

GBS EOD vertical transmission

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

GBS EOD vertical transmission

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

GLOBAL health major challenge!
Also in developing countries

- EOD: 0.3-3 per 1,000 live birth
- LOD: 0.4-0.5 per 1,000 live birth
**INTRODUCTION**

**PREVENTION**

**IAP**

**VACCINE**

**GBS PERINATAL DISEASE**

**GBS vaccine**

« nearly within reach »

**Help for clearing bacteria and preventing development of EOD**

**GBS pathogenesis**

**Stages in the pathogenesis of GBS**

neonatal EOD : *Bacterial & individual factors*

**Stages in the pathogenesis of GBS**

neonatal EOD : *Bacterial & individual factors*

**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.**

**Impact of prevention practices**

**Early- and Late-onset GBS Diseases, U.S.**
**European strategies for prevention of GBS EOD**

- *Intrapartum antibioprophylaxis recommended*
  - Screening-based strategy
    - Spain, 1999, 2003, revised 2012
    - France, 2001
    - Belgium, 2003, revised 2015
    - Germany, 1996, revised 2008
    - Switzerland, 2007
  - Risk-based strategy
    - UK, the Netherlands, Denmark
- *No guidelines*
  - Bulgaria, ...

**Universal screening-based strategy for prevention of GBS perinatal disease** (Be SHC 2003)

<table>
<thead>
<tr>
<th>Vagino-rectal GBS screening culture</th>
<th>at 35-37 weeks of gestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>For ALL pregnant women</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unless patient had previous infant with GBS invasive disease or GBS bacteriuria during current pregnancy or delivery occurs &lt; 37 weeks' gestation</td>
</tr>
</tbody>
</table>

**Concerns: Clinically relevant antimicrobial resistance**

- Increase of resistance to erythromycin and clindamycin

**Resistance to macrolides/lincosamides**

- Wide geographical variation of rates

**Resistance to macrolides/lincosamides on the rise** (Invasive isolates of GBS Belgium 1999-2012)
Concerns: Clinically relevant antimicrobial resistance

- Increase of resistance to erythromycin and clindamycin
  - Revised guidelines for microbiological detection of clindamycin resistance (SHC 2015)
  - Antimicrobial susceptibility testing on all GBS
  - Dtest recommended

Concerns: Clinically relevant antimicrobial resistance

- Reduced susceptibility to penicillin
  - Very few « not S » isolates recently characterized in Japan
    - Mutation in pbp genes, especially pbp2x
    - MIC= 0.25 -1 mg/L (but higher MIC to Ceph)
    - No clinical impact?
  - Very few in the U.S., Canada
  - Possibly unrecognized by standard antimicrobial susceptibility methods

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

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 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

Not 100% as colonization is dynamic


**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)

- Melin, 13-16% GBS Pos
- PPV= 56%
- NPV= 95%
- or 5% False negative
- or 30% of GBS pos in labor not detected with antenatal screening!


**Antenatal culture-based screening: Limiting factors**

- Positive and negative predictive values
  - False-negative results
    - Failure of GBS culture (reduced viability during transport, oral ATB, feminine hygiene) or 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)


**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°C)
- Request form To specify prenatal “GBS” screening
- Laboratory procedure

[CDC 2010 - Belgian SCH 2002]
Crucial conditions to optimize SCREENING

**Transport-collection system & transport-storage condition**

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

**Use of a selective enrichment Lim broth as transport media**

**Results:**

Recovery of GBS in Lim BD at 4°C, RT and 35°C

- **4°C**
- **RT**
- **35°C**

**Important amplification**

**Continuous decrease**

Transport conditions to be recommended for optimizing GBS antenatal screening

**Belgian Health Superior Council, 2015**

- **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)

Antenatal culture-based screening combined with amplification molecular methods

- **Broth enrichment followed by amplification molecular assay**
  - The Xpert GBS LB assay
  - The LAMP Illumigene GBS Assay
Alternative to GBS antenatal screening: intrapartum screening

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

- 968 Pregnant women
- Intrapartum Xpert GBS, Cepheid (performed in lab)
  - vs intrapartum culture
    - antenatal culture (French recom.)
    - vaginal swab/CNA-BA
      - Sensitivity 98.5%
      - Specificity 99.6%
      - PPV 97.8%
      - NPV 99.7%

Cost and effectiveness of intrapartum group B streptococcus screening for term deliveries.

2009 Antenatal screening
- 11.7% GBS POS

2010 Xpert GBS intrapartum screening
- Performed by midwives as a POCT!!
- 16.7% GBS POS
- Less GBS EOD & less severe

Cost neutral per delivery

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 ?
  - CDC 2010: for women with premature delivery or no prenatal care
  - In combination with prenatal screening strategy ?
  - Drawbacks: no antimicrobial result
  - In the future detection of R genes, but mixed microbiota!
Revised Belgian guidelines
(Superior Health Council, 2015)
(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 (IgE mediated penicillin allergy)
- Universal screening at time of delivery could be used
  - IF POCT with high PPV and NPV
  - Real time PCR or other methods
  - TAT < 1 hour
- In case of known IgE 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)

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

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

Prevention of GBS EOD and LOD
Prevention of maternal diseases

Di Renzo GC, Melin P, Berardi A, et al
Intrapartum GBS screening and antibiotic prophylaxis. a European consensus conference.
J Matern Fetal Neonatal Med. 2014 Aug 27;1-17
Background

- Correlate between maternal low level off CPS type Ab at time of delivery and risk for development of GBS EOD

*Baker C et Kasper D, 1976, NEJM*

Vaccine for pregnant women:
Likely the most effective, sustainable and cost effective approach

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

VACCINE

GBS Vaccines

**GBS Protein-based Vaccine**

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

VACCINE

Protein-based Vaccines

<table>
<thead>
<tr>
<th>Protein</th>
<th>Protective Ab</th>
<th>associated serotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha</td>
<td>Yes</td>
<td>Ia, Ib et II</td>
</tr>
<tr>
<td>Alp1</td>
<td>Yes</td>
<td>Ia</td>
</tr>
<tr>
<td>Rib</td>
<td>Yes</td>
<td>III</td>
</tr>
<tr>
<td>Alp2</td>
<td>Yes</td>
<td>V, VIII</td>
</tr>
<tr>
<td>Alp3</td>
<td>Yes</td>
<td>V, VIII</td>
</tr>
<tr>
<td>Beta C protein</td>
<td>Yes</td>
<td>Ib</td>
</tr>
<tr>
<td>C3a peptidase</td>
<td>Yes</td>
<td>All</td>
</tr>
<tr>
<td>Sip (1999)</td>
<td>Yes</td>
<td>All</td>
</tr>
<tr>
<td>BPS</td>
<td>Yes</td>
<td>All</td>
</tr>
</tbody>
</table>

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

GBS « pilus like structure »

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

VACCINE

VACCINE

Protein-based Vaccines

Reverse vaccinology approach
Knowledge of complete GBS genome

- Comparaison of genomes from 8 different GBS serotypes
  - 312 surface proteins were cloned
  - 4 Provide a high protective humoral response in mouse
    - Sip and 3 others
    - The 3 other proteins = « pilus like structures »
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

Summary

“Screening” Prevention strategies

- Culture-based GBS antenatal screening
  - False ±/False ±
  - To optimize critical factors
  - Improved by selective differential agars
  - Expected improvement from transport system
- Rapid intrapartum screening
  - Real time PCR
    - Yes but costs, logistic, ...
    - Need for more clinical and cost effectiveness trials
    - No result for clindamycin susceptibility

Thank you!