GBS AND THE NEONATE: PREVENTION STRATEGIES

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« Médecine préventive »
Épidémiologie et prévention des infections néonatales à streptocoques B

Disclosure
INTRODUCTION & BURDEN
**Streptococcus agalactiae or GBS**

Gram positive cocci
- Catalase -
- β-hemolytic
- CAMP test +
- Hippurate +
- Esculine -
- Orange pigment

10 capsular serotypes (Ia, Ib, II-IX)

1887, Nocard-Mollereau, bovine mastitis
1933, Group B Antigen
1964, severe neonatal sepsis

➢ 1970, Nº1 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

- Maternal morbidity
  - Along pregnancy
  - Peripartum

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

GLOBAL public health major concern!

Also in developing countries
GBS Neonatal Infections

A. Schuchat, Clin Microb Rev 1998;11:497-513
GBS Neonatal Infections
A. Schuchat, Clin Microb Rev 1998;11:497-513

80 % EOD

LOD

EOD : 80-90 % occur before 24 h
<table>
<thead>
<tr>
<th></th>
<th>EARLY Onset</th>
<th>LATE Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td>0.5 - 4.7 per 1000</td>
<td>0.3 - 1.8 per 1000</td>
</tr>
</tbody>
</table>
| **Onset**               | &lt; 6 days of live  
\(X : 1 - 10 \text{ h}\)  | &gt; 6 days of live  
\(X : 1 \text{ mois}\)                             |
| **Transmission**        | Vertical  
*Intrapartum*                                         | Horizontal  
*At delivery*  
   *Nosocomial*  
   *In the community*  |
| **Clinical signs**      | Respiratory distress  
   with pneumonia  
   Sepsis  
   \(\text{Meningitis} : 5\text{-}15 \%\)  | Fever  
   Bacteremia  
   \(\text{Meningitis} (35\%)\)  
   (Cellulitis, Osteomyelitis)  |
| **Mortality**           | 5 – 10\%                                             | 0-6\%                                               |
| **Sequelae**            | When meningitis : neurological sequelae  
   Pulmonary weakness |                                                      |
| **Serotypes**           | All  
   (III, Ia & V)                                        | III, mainly  
   (Meningitis & Clone ST-17)  |
### Burden of neonatal GBS early onset diseases in European countries

<table>
<thead>
<tr>
<th>Location</th>
<th>Incidence per 1,000 live-births</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>2</td>
<td>Melin, Indian J Med Res 2004</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>0.2 - 4</td>
<td>Trijbels-Smeulders, Pediatr Infect Dis J 2004</td>
</tr>
<tr>
<td>Western Europe</td>
<td>0.3 - 2</td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Scandinavia</td>
<td>0.76 - 2</td>
<td></td>
</tr>
<tr>
<td>Southern Europe</td>
<td>0.57 - 2</td>
<td></td>
</tr>
</tbody>
</table>

Data assessing more accurately the true burden are needed

- Carriage rate?
- Ethnicity?
- Sub-reporting?
- Systematic diagnostic approach?
- Virulence?
GBS EOD vertical transmission

GBS colonized mothers

60 - 40 %

Non-colonized newborns

40 - 60 %

Colonized newborns

GBS colonized mothers

Non-colonized newborns

Colonized newborns

INTRODUCTION & BURDEN
GBS EOD vertical transmission

GBS colonized mothers

Non-colonized newborns

Colonized newborns

60 - 40 %

40 - 60 %

96 - 98 %

Asymptomatic

GBS colonized mothers

Non-colonized newborns

Colonized newborns

60 - 40 %

40 - 60 %

96 - 98 %

Asymptomatic
GBS EOD vertical transmission

GBS colonized mothers

60 - 40 %
Non-colonized newborns

40 - 60 %
Colonized newborns

2 - 4 %
GBS EOD

Risk factors

96 - 98 %
Asymptomatic

sepsis
pneumonia
meningitis
long term sequelae

GBS EOD Risk factors

GBS colonized mothers

CDC
Stages in the pathogenesis of GBS

neonatal EOD: *Bacterial & individual factors*

**Colonization**: adhesion to epithelial cells
different virulence factors (pili, scpB, ...)

**GBS pathogenesis**

**Meningitis**
- Brain barrier
- Pili,
- β-hemolysin, ...

**Sepsis**
- IL1, IL6, TNF α,
- PGE2, TxA₂,
- Bacteria
- Peptidoglycan
- β-hemolysin, ...

**Resistance to phagocytose**
- Capsule
- C5a peptidase
- ....

**Phagocytes cells, Antibodies, Complement**
- β-hemolysin, invasins (pneumonia)
- Ascendant transmission (amnionitis)
GBS maternal colonization

Risk factor for early-onset disease (EOD): vaginal GBS colonization at delivery

- GBS carriers
  - 10 - 35 % of women
  - Clinical signs not predictive
  - Dynamic condition
  - Intestinal reservoir
  - Prenatal cultures late in pregnancy can predict delivery status
Additional Risk Factors for Early-Onset GBS Disease

- Obstetric factors:
  - Prolonged rupture of membranes,
  - Preterm delivery,
  - Intrapartum fever
- GBS bacteriuria
- 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

Lorquet S., Melin P. & al.
J Gynecol Obstet Biol Reprod 2005
GBS EOD - Belgian data

- **Incidence**
  - 1985 -1990: 3/1000 live births
  - 1999, estimation: 2/1000 live births
  - 2010, estimation: < 1/1000 live births

- **Meningitis**: 10 %
- **Mortality**: 5 - 10 %

- **60 % EOD (130 cases)**: WITHOUT any maternal/obstetric risk factor except colonization

- **Prenatal screening**
  - Recto-vaginal cultures: 13-35 % GBS Positive

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*P. Melin - 2001, 2007 - Reference laboratory for GBS.*
Data from DEVANI Project (2008-2011)

Belgium – Bulgaria – Czech Republic – Denmark – Germany – Italy – Spain – United Kingdom

EUROPEAN DATA
Mothers of newborns with EOD  
(Devani, 2008-2010 Europe)

**PW Screened in prenatal care**

<table>
<thead>
<tr>
<th></th>
<th>Cases’ mothers</th>
<th>GBS positive Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vagino-rectal swab</td>
<td>24%</td>
<td>84%</td>
</tr>
<tr>
<td>IAP if GBS positive</td>
<td>41%</td>
<td></td>
</tr>
</tbody>
</table>

**Notified risk factors for EOD**

<table>
<thead>
<tr>
<th></th>
<th>Cases’ mothers</th>
<th>GBS positive Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROM &gt;18h</td>
<td>24.8%</td>
<td>5%</td>
</tr>
<tr>
<td>T° &gt;= 38°C</td>
<td>14.3%</td>
<td>1%</td>
</tr>
<tr>
<td>GBS Bacteriuria</td>
<td>8.5%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Previous GBS sibling</td>
<td>0.9%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>
Distribution of CPS serotypes among GBS from neonatal infections
(Devani, 2008-2010 Europe)

Type III:
- 82% LOD
- 43% EOD

The graph shows the distribution of CPS serotypes among GBS with Type III being the most prevalent, accounting for 82% LOD and 43% EOD.
- Universal prenatal screening-based strategy
- Risk-based strategy
- No guideline
Which prevention strategy for GBS perinatal diseases?

- Intrapartum antibioprophylaxis
- Immunoprophylaxis
Prevention of perinatal GBS EOD

- Intrapartum antibiotics
  - Highly effective at preventing EOD in women at risk of transmitting GBS to their newborns (> 4 h)
    (clinical trials in late 80s)

Risk-based strategy or Screening-based strategy

Who is the women at risk?
Prevention of perinatal GBS EOD

- Screening-based strategy

**INTRAPARTUM ANTIMICROBIAL PROPHYLAXIS**

Main goal:
- To prevent 70 to 80% of GBS EO cases

Secondary:
- To reduce peripartum maternal morbidity
Impact of prevention practices
Early- and Late-onset GBS Diseases in
the 1990s, U.S.

S. Schrag, New Engl J Med 2000
Why is Screening more protective than the risk-based approach?


Broader coverage of « at-risk » population

- Captures colonized women without obstetric RF
- High level of compliance with recommendations
- Enhanced compliance with risk-based approach cannot prevent as many cases as universal screening
Impact of prevention practices
Early- and Late-onset GBS Diseases, U.S.

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

GUIDELINES
INTRODUCTION & BURDEN

GUIDELINES

SCREENING

VACCINE

CONCLUSION
European strategies for prevention of GBS EOD

- **Intrapartum anti-bioprophylaxis recommended**
  - Screening-based strategy
    - France, 2001
    - Belgium, 2003, revision ongoing 2012
    - 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

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

For ALL pregnant women

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

GBS Neg

Not done, incomplete or unknown GBS result

GBS POS

> 1 Risk factor:
- Intrapartum fever $\geq$ 38°C
- ROM $\geq$ 18 hrs

if NO

Intrapartum prophylaxis NOT indicated

if YES

INTRAPARTUM ANTIBIOPROPHYLAXIS INDICATED

if YES

Not done, incomplete or unknown GBS result

! Facultative! Intrapartum rapid GBS test**
Adhesion to a common protocol is a key of success
Multidisciplinary collaboration is mandatory
INTRODUCTION & BURDEN

GUIDELINES

SCREENING

VACCINE

CONCLUSION
Intrapartum IV Antibio-Prophylaxis

(CDC 2010, Belgian SHC 2003)

- **Penicillin G**
  - 5 millions U, IV initial dose, then 2,5 to 3 millions U IV every 4 hours until delivery.

- **Ampicilline**
  - 2 g IV initial dose, then 1 g IV every 4 h until delivery.
  - Acceptable alternative, but broader spectrum, potential selection of R bacteria

- **If penicillin allergy**
  - **Patients at low risk for anaphylaxis**
    - Cefazolin, 2 g IV initial dose, then 1g IV every 8 h until delivery.
  - **Patients at high risk for anaphylaxis**
    - Clindamycine, 900 mg IV every 8 hours until delivery.
    - If GBS resistant to clindamycin: use vancomycin
Concerns about 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 profile**
Concerns: Clinically relevant antimicrobial resistance

- **Increase of resistance to erythromycin and clindamycin**
- **Susceptibility to penicillin**
  - Very few « not S » isolates recently characterized in Japan
    - Mutation in pbp genes, especially pbp2x
    - MIC = 0.25 -1 mg/L
    - No clinical impact?
  - Very few in the U.S.
  - All labs should send to reference lab
    - Any « non-S » isolate for confirmation
    - All invasive isolates for resistance surveillance

*Noriyuki Nagano et al, AAC 2008*
Erythromycin and clindamycin resistance

Erythromycin R
- USA, 15-35%
- Ireland, 15-20%
- Europe, 10-30%
- Belgium, 32%

GBS isolated in Belgium, from invasive diseases
Concerns about potential adverse / unintended consequences of prophylaxis

- **Management of neonates**
  - Increase of unnecessary evaluation
  - Increase of unnecessary antimicrobial treatments

→ **Algorithm for secondary prevention of EOD among newborns**
  - Symptoms; maternal chorioamnionitis; prophylaxis; gestational age; time of rupture of membrane

**Rem.:**
80-90 % of GBS EOD are symptomatic < 24 h of live
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

CDC revised guidelines 2010
DEVANI project, unpublished data 2011
SCREENING FOR GBS COLONIZATION
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
  - Timing of sampling
  - Screening methods
    - Culture
      - Procedure
      - Media
    - Non-culture
From direct plating on blood agar
Evolution of culture methods

Use of selective enrichment broth
- 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
(M.de la Rosa,JCM)

1983, 1992
Pigment-based

Strepto B Select

StreptoB ID

2005  2007
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)*
Prenatal culture-based screening: Limiting factors

- Positive and negative predictive values
  - False-negative results
    - Failure of GBS culture (oral ATB, feminine hygiene) or new acquisition
    - Up to 1/3 of GBS positive women at time of delivery
    - Continuing occurrence of EO GBS cases
  - False-positive
    - Unnecessary IAP

Need for more accurate predictor of intrapartum GBS vaginal colonization
Alternative to GBS prenatal screening: intrapartum screening
Theranostic approach

**Turnaround time**
collect specimen at admission

**Optimal management of patient**

**Results**
30-45 minutes, 24 hrs/7 d, robust

*Benitz et al. 1999, Pediatrics, Vol 183 (6)*
Real Time PCR for intrapartum screening

- Advance in PCR techniques & development of platforms
  - BD GeneOhm™ Strep B Assay (+/- 1 hr) (in laboratory)
  - Xpert GBS, Cepheid (35-50 min) (can be performed as a POCT)
Real-time PCR, very promising, but ...

- Still an expensive technology
  - Cost effective?
- Logistic
  - 24 hours 7 days
  - In the lab?
  - In the obstetrical department?
- In combination with prenatal screening strategy?
  - CDC 2010
- No antimicrobial result
  - In the future detection of R genes, but mixed microbiota!
Prevention of GBS EOD and LOD

VACCINE
Vaccines To Prevent GBS Disease

Improved use of intrapartum antimicrobial prophylaxis has resulted in a substantial reduction in early-onset GBS disease, but it is unlikely to prevent most late-onset neonatal infections, GBS-related stillbirths, or prematurity, and does not address GBS disease in nonpregnant adults. Immunization of women during or before pregnancy could prevent peripartum maternal disease and protect infants from perinatally acquired infection by transplacental transfer of protective IgG antibodies (125, 126). This would eliminate the need for prenatal GBS screening and intrapartum antimicrobial prophylaxis, along with associated costs and concerns regarding the potential adverse effects of intrapartum antibiotic use discussed previously.
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, invasives infections in adults
    - Geographically and along time

- Conjugated vaccines

- Multivalent vaccines Ia, Ib, III, V

- Clinical studies
  - Immunogenicity
  - Safety
  - Efficacy: scheduled/ongoing
GBS Vaccines

GBS Protein-based Vaccine

- **Ag** = Surface proteins
  - Cross protection against different serotypes
  - Better immunogenicity
    - Humoral response T-cell dependent
      = long lasting immunity
## Protein-based Vaccines

<table>
<thead>
<tr>
<th>Protein</th>
<th>Protective Ab</th>
<th>associated serotypes (in mouse)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha-like proteins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha</td>
<td>Yes</td>
<td>Ia, Ib et II</td>
</tr>
<tr>
<td>Alp1</td>
<td></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><strong>Beta C protein</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C5a peptidase</td>
<td>Yes</td>
<td>All</td>
</tr>
<tr>
<td><strong>Sip (1999)</strong></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, Québec)*  
*BPS= Groupe B Protective surface Protein*
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 »

D.Maione et al, Science 2006
GBS « pilus like structure »

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

- European epidemiology
  - Genito-rectal colonizing strains
  - Invasive neonatal strains
- Identification of protective levels of specific antibodies
- Consortium of 8 European countries
- Development of a vaccine against pili proteins & major CPS serotypes
Good data - Coordination - Interaction

CONCLUSION
Take home messages
In Europe, as globally

- Neonatal GBS diseases
  - EOD and LOD, a public 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
  - Need better data assessing more accurately the true burden
- GBS vaccine eagerly expected
SUMMARY

- Culture-based GBS prenatal screening
  - To optimize critical factors
  - Improved by selective differential agars
  - False +/False -!
- Rapid intrapartum screening
  - Real time PCR
    - Yes but costs, logistic, …
- Antimicrobial R
  - Surveillance of Penicillin by NRC
  - To perform AST for macrolides/clinda
Thanks !