Prévenir les infections périnatales à streptocoques du groupe B

Stratégie & nouveautés

Pierrette Melin

Microbiologie médicale CHU de Liège
Laboratoire de référence belge des GBS
Background

- Important pathogen since the 1970s

- Perinatal GBS disease burden
  - Neonatal illness/death, long-term disability
    - Belgium: > 300 sepsis + meningitis/year
    - 34.8% of EOD through 1991-2005
      - (No.2 = E.coli: 12.5%)
  - Maternal morbidity

- Neonatal direct costs
GBS Neonatal Infections

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

80% EOD

LOD

EOD: 80% occur before 24 h
“Evidence-based”
Prevention of perinatal Group B streptococcal infections

Guidelines from Belgian Council of Hygiene - July 2003

http://www.health.fgov.be/CSH_HGR

General Recommendations & Specific suggestions

WORKING GROUP:
- Gynecologists-obstetricians
- Pediatrician-neonatologists
- Microbiologists
- French/Flemish
- University/non-university


Secr.: Dubois JJ, CSH
PRO SCREENING
Intrapartum antimicrobial prophylaxis (IAP)
Universal prenatal screening at 35-37 weeks gestation

Risk-based approach reserved for women with unknown GBS status at time of labor.

- Gyneco-Obstetricians
- Pediatricians
- Laboratory microbiologist
- Labor/delivery Ward
Adhesion to a common protocol is a key of success
Multidisciplinary collaboration is mandatory
Why IAP?

Why a Screening-based approach?

- Risks for GBS EOD
- Goals of IAP
- Effectiveness
- Belgian choice
- Concerns about use of prophylaxis
- Belgian results
GBS VERTICAL TRANSMISSION

GBS colonized mothers

Non-colonized newborns

Colonized newborns

Risk factors

2 - 4 %
GBS EOD

96 - 98 %
Asymptomatic

60 - 40 %

40 - 60 %

GBS EOD

sepsis
pneumonia
meningitis
long term
disability

CDC

CDC
GBS maternal colonization

Risk factor for early-onset disease (EOD):

vaginal GBS colonization at delivery

- GBS carriers
  - 10 - 30 % of women
  - Clinical signs not predictive
  - Dynamic condition
  - 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: 3/1000 live births
  - 1990: 3 cases + 4 likely cases/1000 live births
  - 1999, estimation: 2/1000 live births

- **Meningitis**: 10%

- **Mortality**: > 14%

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

- **Prenatal screening**
  - Recto-vaginal cultures: 13-25% GBS Positive

*P. Melin, 2001 - Reference laboratory for GBS.*
Prevention of perinatal GBS EOD

- Intrapartum antibiotics
  - Highly effective at preventing EOD in women at risk of transmitting GBS to their newborns (≥ 4 h)

**INTRAPARTUM ANTIMICROBIAL PROPHYLAXIS (IAP)**

- **Main goal:**
  - To prevent 70 to 80% of GBS EO cases
- **Secondary:**
  - To reduce peripartum maternal morbidity
How best to identify women at risk?

CDC 1996 recommendations

« IAP »

35-37 wks Screening-based strategy

Or

Risk factors-based strategy
Impact of prevention practices
Rate of Early- and Late-onset GBS Disease in the 1990s, U.S.

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

S. Schrag, New Engl J Med 2000
Screening for GBS or risk-factors?

P. Melin, 40th ICAAC, 2000
L. Mahieu, 2000, J Obst Gyn;5:460-4
Effectiveness of both CDC 1996 approaches

“RF” easier and cheaper than “screening” BUT

- Population-based surveillance study, U.S.
  - 312 GBS EOD; ± 600,000 live births
    - AUDIT (5144 files): “IAP given when mandatory”
      - 52% of all deliveries had screening
      - IAP given more often if “GBS Positive screening” than if presence of >= 1 RF

“Screening” > 50% more effective than “RF”
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
CDC

The Recommendations

MMWR, Vol 51
(RR-11) August 2002

Universal prenatal screening
& RF reserved for unknown GBS culture results

Endorsed by AAP and by ACOG in 2002
Screening-based strategy for prevention of GBS perinatal disease (Belgian CH, 2003)

Recto-vaginal GBS screening culture at 35-37 weeks of gestation

For ALL pregnant women

- Intrapartum fever > 38°C***
- ROM > 18 hrs

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

! Facultative! Intrapartum rapid GBS Ag test**

≥ 1 Risk factor:
- Intrapartum fever ≥ 38°C***
- ROM ≥ 18 hrs

if NO

Intrapartum prophylaxis NOT indicated

if YES

INTRAPARTUM ANTIBIOPROPHYLAXIS INDICATED

if NO

if YES

Neg

Pos
GBS Screening: Predictive Value of Antenatal Cultures by Interval to Delivery

N=826; 26.5% GBS carriers
Yancey et al., OB GYN 1996;88:811-5.
Crucial conditions to optimize SCREENING

<table>
<thead>
<tr>
<th>WHEN</th>
<th>35-37 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td>ALL the pregnant women</td>
</tr>
<tr>
<td>Specimen</td>
<td>Vaginal + rectal swab(s)</td>
</tr>
<tr>
<td>Collection</td>
<td>WITHOUT speculum</td>
</tr>
<tr>
<td>Transport</td>
<td>Transport/collection device (non nutritive medium: Amies/Stuart)</td>
</tr>
<tr>
<td>Request form</td>
<td>To specify prenatal « GBS » screening + expected address for delivery</td>
</tr>
</tbody>
</table>

(CDC 2002 – Belgian HC 2003)
Prenatal GBS screening: Laboratory procedure (Belgian HC, 2003)

**Minimum:**

- 35-37 wks V+R

- Selective enrichment broth (eg. LIM)
  - Overnight, 35-37°C

- Sub-culture onto “Granada” agar
  - Overnight, 35-37°C anaerobically

**Presence of orange colonies = GBS**

**Absence of orange colonies**

**POSITIVE screening**

**Negative screening**
Selective enrichment broth

Lim Broth =

Todd Hewitt broth + colistin (15 µg/ml) + nalidixic acid (10 µg/ml)

Overnight at 37°C and sub-cultured onto « Granada » (and/or BA ou BA+CNA)
Granada medium agar or BD™ Group B Streptococcus Differential Medium

Orange color: Specific for GBS // β-hemolysis
Strepto B ID agar - BioMérieux

High sensitivity for growth of GBS
GBS = pink to red colonies

Not 100 % specific for GBS: Id to confirm (latex)
What to do in case of Positive GBS screening?

- Send results to requesting doctor *and a copy to expected site for delivery*
- DO NOT treat during pregnancy if asymptomatic
  - *(! To treat if GBS bacteriuria!)*
- To schedule IAP
Intrapartum Antibio-Prophylaxis
(Belgian HC 2003)

- **Penicillin G**
  - 5 millions U, IV initial dose, then 2.5 millions U IV every 4 hours until delivery.

- **Ampicilline**
  - 2 g IV initial dose, then 1 g IV every 4 h until delivery.
**Intrapartum Antibio-Prophylaxis**

*If penicillin allergy* (Belgian HC 2003)

- **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**
  - **Clindamycin**
    - 900 mg IV every 8 hours until delivery.
    - *If GBS resistant to clindamycin: ask for infectiologist opinion*
Feasibility in Belgium

- **Screening**
  - Follow-up visit already scheduled around 35-37 wks gestation
  - Accessability to laboratories

- **IAP** (*intra-venous*)
  - Most of deliveries occur at hospital
Concerns about potential adverse / unintended consequences of prophylaxis

- **Allergies**
  - Anaphylaxis occurs but rarely

- **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**
Susceptibility pattern of GBS

Melin et al. 2002, ICAAC, Abstract...
## Interpretation criterion (MH with blood) (CLSI 2006)

<table>
<thead>
<tr>
<th>Phenotypes of resistance to macrolide - lincosamide : Dtest</th>
</tr>
</thead>
<tbody>
<tr>
<td>cMLS Erythro R &amp; Clinda R</td>
</tr>
<tr>
<td>iMLS Erythro R &amp; Clinda S/I/R with Dtest +</td>
</tr>
<tr>
<td>M Erythro R &amp; Clinda S with Dtest -</td>
</tr>
</tbody>
</table>

### Zone Diameter (mm)

<table>
<thead>
<tr>
<th>Zone</th>
<th>MIC (mg/L)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>≥ 24</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>≥ 21</td>
<td>16-20</td>
<td>≤ 15</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>≥ 19</td>
<td>16-18</td>
<td>≤ 15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Zone</th>
<th>MIC (mg/L)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>≤ 0.12</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>I</td>
<td>&lt; 0.25</td>
<td>0.5</td>
<td>≥ 1</td>
</tr>
<tr>
<td>R</td>
<td></td>
<td>0.5</td>
<td>≥ 1</td>
</tr>
</tbody>
</table>
Concerns about potential adverse / unintended consequences of prophylaxis

- **Management of neonates**
  - Increase of unnecessary evaluation
  - Increase of unnecessary antimicrobial treatments
Management of neonates at risk for GBS EOD

Rem.: 90% of GBS EOD are symptomatic < 24 h of life

Neonates born to women who received IAP
Symptomatic NN / asymptomatic NN
At low/at high risk

To minimize unnecessary evaluation and antimicrobial treatment
Management of symptomatic newborns at risk for GBS EOD

Clinical signs of sepsis

1- Full diagnostic evaluation *
2- Empiric antibiotherapy
   (Ampicillin + aminoside)

*:- Full blood cell count (FBC) + differential
- CRP
- Bloodculture
- (Lumbar P.)
- Chest Xray
- Endotracheal culture (if intubated or if resp.distress. or Rx infiltrate)

Rem. ! NOT recommended :
1- Urinary GBS Ag
2- « Monitoring » cultures
Management of asymptomatic newborns « at high risk » for GBS

If antibiotherapy given to mother for
- Suspicion of chorioamnionitis or
- Premature AND prolonged rupture of membranes

Full evaluation
Empiric therapy
Management of asymptomatic newborns « at low risk » for GBS EOD

If IAP given to the mother, gestational age:

>= 35 wks.

Duration of IAP

> 4 h

No evaluation

< 4 h

Limited evaluation*

Observation

< 35 wks.

If sepsis suspected**

Full evaluation

Empiric therapy

If IAP given to the mother, gestational age:

>= 35 wks.

Duration of IAP

> 4 h

No evaluation

< 4 h

Limited evaluation*

Observation

< 35 wks.

If sepsis suspected**

Full evaluation

Empiric therapy
Duration of antibiotherapy

Threatened preterm delivery

Planned caesarean delivery for GBS colonized women
Preventive strategies
Current Belgian benefits

Conclusions & perspectives

Prevention of GBS perinatal Diseases
PRO-SCREENING

Currently the best choice but NOT the ideal strategy
Temporary, waiting for vaccines, other approach

- To implement in the daily practice
- V+R Screening method
- !! Transmission of results !!
- Epidemiological surveillance
Alternative to prenatal GBS screening: intrapartum screening

Collect specimen at admission

Optimal management of patient

Specimen analysis

Results

30 - 45 minutes

Benitz et al. 1999, Pediatrics, Vol 183 (6)
Perspectives

- Other investigated approaches
  - Real time PCR for intrapartum screening

(GenExpert - Cepheid)
Belgian Challenge =
To prevent annually > 200 cases of neonatal GBS EOD

GDLux Challenge =
To prevent annually > 10 cases of neonatal GBS EOD
Key GBS Resources

- **MMWR**: August 16, 2002 / 51(RR11); 1-22
- **ACOG Comm Opin** 2002, N°279
  - Obstet Gynecol, 2002;100:1405-12
- **CDC’s GBS Internet page**
  - http://www.cdc.gov/groupBstrep/
- **Conseil supérieur d’hygiène (brochure strep B)**