Prevention of perinatal group B streptococcal diseases

Update & Guidelines

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Medical microbiology, University hospital of Liege
Belgian reference laboratory for GBS
TRANSMISSION « Mother-Baby »

GBS colonized mothers

60 - 40 %
Non-colonized newborns

40 - 60 %
Colonized newborns

2 - 4 %
GBS EOD

96 - 98 %
Asymptomatic

sepsis
pneumonia
meningitis
long term sequelae

pm-chu Ig ISP Nov. 2005
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
Prevention of perinatal GBS disease

- **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**

35-37 wks Screening-based strategy

Or

Risk factors-based strategy
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.*
Screening for GBS

Useful or not?
Effectiveness of both CDC 1996 approaches


"RF" easier and cheaper than "screening" BUT

- Population-based surveillance study, U.S.
  - > 600,000 live births
    - "Screening" > 50% more effective than "RF"
    - AUDIT: « IAP given when mandatory »
      - Given more often if « GBS Positive screening » than if presence of >= 1 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
“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

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Secr.: Dubois JJ, CSH

pm-chu lg ISP Nov. 2005
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

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

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

Not done, incomplete or unknown GBS result

! Facultative! Intrapartum rapid GBS Ag test**

GBS Neg

GBS POS

if NO

Intrapartum prophylaxis NOT indicated

if YES

Intrapartum ANTIBIOPROPHYLAXIS INDICATED

if YES

if NO
Prenatal GBS screening: Laboratory procedure (Belgian CH, 2003)

Minimum:

1. **V+R or V&R**
2. LIM broth
   - Overnight, 35-37°C
3. Sub-culture onto “Granada” agar
   - Overnight, 35-37°C anaerobically

- **Presence of orange colonies = GBS**
- **Absence of orange colonies**

**Positive screening**

**Negative screening**
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.
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)
Percentage of women who could not benefit from a full IAP

Cumulative histogram (% of patients): time elapsed between admission to labor room and delivery for 532 women (CHR & CHBA, Liege - 2003)

- GBS Positive
- GBS negative

Melin et al. 2004, ICAAC, Abstract G-499
## Strep B OIA test

**Belgian multicentric study, 2000**

<table>
<thead>
<tr>
<th>Detection method</th>
<th>Sensibility</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal cultures</td>
<td>Percentage</td>
<td>56.3</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Strep B OIA</td>
<td>62</td>
<td>99.3</td>
<td>93.6</td>
<td>94.4</td>
</tr>
</tbody>
</table>

*(47-93)*

*2003, sensibility B OIA: 65%, Specificity when warm atmosphere*

*Melin et al. 2003, ICAAC, Abstract # ....*
# PCR IDI Strep B

## GBS Positive culture

<table>
<thead>
<tr>
<th>IDI-Strep B</th>
<th>From primary culture on Granada I</th>
<th>CDC protocol &amp; Granada II</th>
<th>TOTAL</th>
<th>GBS neg culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>Density</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4+</td>
<td>3+</td>
<td>2+</td>
<td>1+</td>
</tr>
<tr>
<td>(N=154)</td>
<td>(54)</td>
<td>(28)</td>
<td>(18)</td>
<td>(30)</td>
</tr>
</tbody>
</table>

| GBS Positive | 133 | 54 | 27 | 16 | 23 | 13 | 26 | 159 | 6* |
| SENSITIVITY %| 86.4 | 100 | 96.4 | 88.9 | 76.7 | 54.1 | 43.3 | 74.3 |

| SPECIFICITY :| 99.1 % |
| Positive Predictive Value :| 96.4 % |
| Negative Predictive Value :| 92.7 % |

23.6% (16.8 + 6.8%) Vaginal culture GBS +
*: 3/6 positive by an Ag method

P.Melin et al, ICAAC 2004
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 everye 4 h until delivery.
  - Acceptable alternative, but broader spectrum, potential selection of R bacteria
Intrapartum Antibio-Prophylaxis if penicillin allergy (Belgian HC 2003)

- **Patients at low risk for anaphylaxis**
  - Céfazolin
    - 2 g IV initial dose, then 1 g 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 clindamycine: ask for infectiologist opinion
Management of neonates at risk for GBS EOD

Rem.: 95% of GBS EOD are symptomatic < 24 h of live

Neonates born to women who received IAP

Symptomatic NN / asymptomatic NN

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

(Ampicilline + aminoside)

<table>
<thead>
<tr>
<th>*:</th>
<th>Full blood cell count (FBC) + differential</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRP</td>
</tr>
<tr>
<td></td>
<td>Bloodculture</td>
</tr>
<tr>
<td></td>
<td>(Lumbar P.)</td>
</tr>
<tr>
<td></td>
<td>Chest Xray</td>
</tr>
<tr>
<td></td>
<td>Endotracheal culture (if intubated or if resp. distress. or Rx infiltrate)</td>
</tr>
</tbody>
</table>

Rem. ! NOT recommended :

1- Urinary GBS Ag
2- « Monitoring » cultures
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
  - If sepsis suspected**
    - Full evaluation
    - Empiric therapy

- **< 35 wks.**
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
Duration of antibiotherapy

Threatened preterm delivery

Planned caesarean delivery for GBS colonized women
Strains isolated from neonatal EOD or LOD and sent to the Belgian ref. Lab. for GBS

Surveys & feed-back

CDC

CSH

EOD

LOD

No strains

1999 2000 2001 2002 2003 2004
Summary

**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**
Conclusions & perspectives

- Not the ideal strategy:
  - Temporary, waiting for vaccines
- Other approaches are investigated
  - Vaginal douching with antiseptic solution
  - Real time PCR for intrapartum screening

- To implement in the daily practice
- Screening method
  - V+R culture
    - Necessary
- !! Transmission of results !!
### Rough cost-effective «analysis» for 1.000 women

<table>
<thead>
<tr>
<th>Criteria for IAP</th>
<th>Screening option</th>
<th>RF options</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRM &gt;= 18 h, T°C &gt;= 38°C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GBS +</td>
<td>+/- 250</td>
<td>+/- 250</td>
</tr>
<tr>
<td>+/- 250</td>
<td>+/- 250</td>
<td>+/- 250</td>
</tr>
<tr>
<td>75 %</td>
<td>&lt;&lt; 50 %</td>
<td>&lt;&lt; 50 %</td>
</tr>
<tr>
<td>111</td>
<td>166</td>
<td></td>
</tr>
<tr>
<td>2,200 €</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N € x 111</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+/- 3,300 €</td>
<td></td>
<td></td>
</tr>
<tr>
<td>not estimated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>not estimated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hypothesis**: GBS prevalence in women: 20%; Natural incidence of GBS EOD: 3/1000; prevalence of RF as in our study in Liege in 2002
### Duration of antibiotherapy

<table>
<thead>
<tr>
<th>Focus of infection</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Suspected sepsis but not confirmed by clinical,</td>
<td>48 hours</td>
</tr>
<tr>
<td>biological or bactériological</td>
<td></td>
</tr>
<tr>
<td>- Proven sepsis</td>
<td>10 days</td>
</tr>
<tr>
<td>- Meningitis</td>
<td>minimum 14 days</td>
</tr>
<tr>
<td>- Ventriculitis/osteomyelitis</td>
<td>28 days</td>
</tr>
</tbody>
</table>

*If GBS confirmed:* switch to penicillin, aminoside 3-5 d
Threatened preterm delivery

Onset of labor or rupture of membranes at < 37 weeks of gestation with significant risk for imminent preterm delivery

No GBS culture

Obtain V+R for culture & initiate Pen IV

If GBS Neg at 48 h

Stop Pénicilline*

Prenatal culture

GBS POSITIVE

Pen IV, >= 48 h** (during tocolysis)

IAP at delivery

Prenatal culture

GBS Négative

No GBS prophylaxis

*Pénicilline
Planned caesarean delivery for GBS colonized women

C-section performed before

- Rupture of amniotic membrane
- Onset of labor

= very low risk for GBS EOD

↓

NO specific IAP

(if indicated, regular caesarean-prophylaxis after clamping the umbilical cord.)
Concerns about the number of women who is given IAP

Prevalence of factors inducing the decision of IAP
(CHR Liege, 2002, 1350 consecutive deliveries)

<table>
<thead>
<tr>
<th>FACTORS</th>
<th>« SCREENING » OPTION</th>
<th>« RISK FACTORS » OPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity</td>
<td></td>
<td>17 %</td>
</tr>
<tr>
<td>GBS bacteriuria</td>
<td></td>
<td>1.2 %</td>
</tr>
<tr>
<td>GBS Positive ROM &gt;= 18 h</td>
<td>15-25 %</td>
<td>/</td>
</tr>
<tr>
<td>T° &gt;= 38°C</td>
<td>/</td>
<td>19 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.6 %</td>
</tr>
</tbody>
</table>

Lorquet, Melin, Foidart, J Gynecol Obstet Biol Reprod 2005
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)**
Vaccination pour la prévention des infections à GBS

- Vaccins polysaccharidiques (Ag de type) :
  - Non conjugué
    - Peu immunogénique
    - Immunité à court terme
  - Conjugué
    - Différentes protéines porteuses
    - Bien toléré
    - Immunité à plus long terme
    - Améliore opsono-phagocytose

- Vaccins protéiques
  - Le plus efficace de tous: protéine de surface Sip de GBS