GBS colonization and screening in pregnancy: how does it work in Europe?

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INTRODUCTION
Introduction
Burden of GBS neonatal early onset diseases

<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 - 3</td>
<td>Melin, Indian J Med Res 2004</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>0.2 - 4</td>
<td>Trijbeals-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?
GUIDELINES IN EUROPEAN COUNTRIES

- Universal prenatal screening-based strategy
- Risk-based strategy
- No guideline
European strategies for prevention of GBS EOD

- **Intrapartumantibioprophylaxis recommended**
  - **Screening-based strategy**
    - Spain, 1998, revised 2003
    - France, 2001
    - Belgium, 2003, revision ongoing 2011
    - Germany, 1996, revised 2008
    - Switzerland, 2007
    - Italy
  - **Risk-based strategy**
    - UK, the Netherlands, Denmark
- **No guidelines**
  - Bulgaria
MISSED OPPORTUNITIES
Remaining burden of GBS EOD

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DEVANI project, unpublished data 2011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
Choice of the anatomic sites

Lower vagina + rectum

Vagina & rectum > vagina or rectum > cervix

Badri et al., J Infect Dis 1977;135:308-12

- Lower vaginal area
  - For collection: use of speculum out of question
- Rectum (through anal sphincter!)
  - GBS reservoir, source of vaginal colonization
  - Rectum GBS positive and vagina negative
    - 15 to 20% of GBS positive pregnant women
- A single combined specimen
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
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)

30% of GBS pos in labor not detected with prenatal screening!
Melin et al. ICAAC 2000

Not 100% as colonization is dynamic

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

<table>
<thead>
<tr>
<th>Nb women, medium</th>
<th>Direct culture 48hrs</th>
<th>Sub-culture from SEB %</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>200, Granada</td>
<td>88 %</td>
<td>100 %</td>
<td>Tazi A et al, 2008</td>
</tr>
<tr>
<td>500, Granada</td>
<td>72 %</td>
<td>99 %</td>
<td>Melin P et al, 2008</td>
</tr>
<tr>
<td>StrepB select</td>
<td>74 %</td>
<td>96 %</td>
<td></td>
</tr>
<tr>
<td>288, Blood /Lim</td>
<td>52 %</td>
<td>82 %</td>
<td>Shibuya R, 2009</td>
</tr>
<tr>
<td>New Granada</td>
<td>52 %</td>
<td>100 %</td>
<td></td>
</tr>
</tbody>
</table>
Evolution of culture methods

Blood agar +/- CNA

Revised guidelines from CDC (2002)

- Sub-culture < selective enrichment broth
  - Blood agar +/- colistin and nalidixic acid
    - Advantage
      - Growth of all GBS Isolates β-hemolytic or not
    - Disadvantages
      - Difficulty in seeing rare GBS colonies within mixed vaginal-rectal microbiota
      - Difficulty in recognizing non-hemolytic GBS in mixed microbiota

Sensitivity and specificity to be improved
Evolution of culture methods
Use of differential agar media

Recommended by some European guidelines (+ CDC 2010)


Pigment-based  Chromogenic media

GRANADA
(M.de la Rosa, JCM)

Strepto B
Select

Strepto B
ID
Granada medium agar
(Anaerobic incubation)

M de la Rosa Fraile, JCM 1983 & 1992

• Orange color: GBS pigment, Granadaene

• 100% specific for GBS

//β-hemolysis

• Granada original, bioMérieux
• Group B Streptococcus Differential Modified Granada Medium™ (BD)
• Carrot Medium (Hardy)

Does not show non-hemolytic strain!
(< 4% of invasive isolates ??)
Strepto B ID agar (BioMérieux)  
Strep B Select agar (BioRad)

High sensitivity for growth of GBS  
- pink to red colonies (bioM)  
- or pale to darkblue-turquoise colonies (BioR)

Chromogenic media  
Not 100 % specific for GBS: Id to confirm(latex)  
(GAS, GCS, Staphylococci, alpha-hemolytic colonies, etc.)
Which agar or which combination?
+/- Blood agar

Workload - costs - extra-testing - non $\beta$-hemolytic GBS detection to be considered
## 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 /condition</td>
</tr>
</tbody>
</table>

(non nutritive medium: Amies/Stuart or Granada like tube)(Length and T°)

- Request form: To specify prenatal « GBS » screening + expected address for delivery

- 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

Turnaround time
collect specimen at admission

Optimal management of patient

Specimen analysis

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

Benitz et al. 1999, Pediatrics, Vol 183 (6)
Time between admission and delivery

Optimal time for IAP efficiency $\geq$ 4 hour

Cumulative histogram (% of patients) of time elapsed between admission to labor room and delivery for 532 women (sites CHR & CHBA)

P. Melin, 2004 ICAAC #G499
Real Time PCR for intrapartumscreening

- Advance in PCR techniques & development of platforms
  - BD GeneOhm™ Strep B Assay (+/- 1 hr) (in laboratory)
  - Xpert GBS, Cepheid (35-75 min) (can be performed as a POCT)
Rapid non-cultural GBS screening
Real-time PCR

- **IDI Strep B** (BD GeneOhm)
  - Sensitivity: 94%
  - Specificity: 96%
  - PPV: 84% and NPV: 98.6%

  *HD Davies et al., CID 2004*

- **Xpert™ GBS**
  - Sensitivity: 92%
  - Specificity: 95.6%
  - PPV: 86.7% and NPV: 97.4%

*Intrapartum RT-PCRs surpass sensitivity of antenatal cultures*
*Sensitivity // inoculum density = real time risk*
Real-time PCR, very promising, but ...

- Still an expensive technology
- 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!
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
  - IAP not widely recommended
  - Need better data assessing more accurately the true burden
- GBS vaccine eagerly expected