Prevention of perinatal GBS disease in Europe

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GBS EOD in Europe

- No European epidemiology
- 0.3 to 2% live births
  - Different types of networks for declaration
DEVANI

Vaccine Against Neonatal Infections

Design of a vaccine to immunize neonates against GBS infections through a durable maternal immune response

Countries within the DEVANI consortium
Guidelines for prevention of GBS perinatal disease

Universal prenatal screening

- Spain since the end of 1990s
  - Vagino-rectal screening
  - 2008, break-through in an area
    - Cases x 10 times during that period

- Belgium
  - Since the end of the 1990s in the French speaking Community
  - Since 2003, national official guidelines (Superior Council of Health)
    - Vagino-rectal screening

- France
  - +/- 2003 national official guidelines (ANAES)
    - Vaginal screening
Guidelines for prevention of GBS perinatal disease

Universal prenatal screening

- Vagino-rectal or vaginal screening recommended by professional associations
  - Italy
  - Germany
  - The Netherlands
No Universal Screening Guidelines for prevention of GBS perinatal disease

- Bulgaria
- Czech Republic

Risk-based strategy, but …

- Denmark
- Switzerland
- United Kingdom
Belgian recommendations
Why Universal Screening?

- Prospective investigation of 120 consecutive GBS EOD
  - French Community of Belgium
  - 1999-2000
  - > 40% had no “risk factor”
Belgian recommendations
Main differences vs CDCs guidelines

In 2003

- SOP for laboratory
  - Selective enrichment broth + subculture on selective differential media like Granada agar
  - Facultative use of rapid intrapartum testing
    - Under analytical restrictive conditions
    - If positive: IAP
    - If negative: as if no additional result
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)

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

Melin et al. ICAAC 2000
Evolution of culture methods

Revised guidelines from CDC (2002)

- Sub-culture < selective enrichment broth
  - Blood agar
    - Advantage
      - Growth of all GBS Isolates beta-hemolytic or not
    - Disadvantage
      - Difficulty in seeing GBS colonies within mixed flora (enterococci)
      - Difficulty in recognizing non-hemolytic GBS in mixed flora (enterococci)
Evolution of culture methods
Use of differential agar media

Recommended by some European guidelines

GRANADA
(M.de la Rosa, JCM)

1983, 1992

Pigment-based

Strepto B Select

Strepto B ID

2005  2007

Chromogenic media

pm-chulg – GBS CDC June 2009
Granada medium agar

M de la Rosa Fraile, JCM 1983 & 1992

• Orange color: GBS pigment, Granadaene

• 100% specific for GBS // β-hemolysis

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

Does not show non-hemolytic strain!
(<5 % of invasive isolates)
Strepto B ID agar (BioMérieux)

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

Chromogenic media
Not 100 % specific for GBS: Id to confirm (latex)
Strep B Select agar (BioRad)

GBS = pale to dark blue-turquoise colonies

Chromogenic media

Not 100 % specific for GBS: Id to confirm (latex)
Granada (BD) - Streptob ID - StrepB Select versus Blood agar +/- CNA
500 genital swabs (29.4 % GBS Positive)

<table>
<thead>
<tr>
<th></th>
<th>Direct culture</th>
<th>Lim sub-culture</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strep B Select</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(BioRad)</td>
<td>103 (70.1)</td>
<td>134 (91.1)</td>
<td>139 (94.6)*</td>
</tr>
<tr>
<td><strong>« Granada »</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(BD)</td>
<td>90 (61.2)</td>
<td>123 (83.7)</td>
<td>124 (84.4)</td>
</tr>
<tr>
<td><strong>Strep B ID</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(bioMérieux)</td>
<td>93 (63.2)</td>
<td>124 (84.3)</td>
<td>128 (87.1)</td>
</tr>
<tr>
<td><strong>BA + CNA</strong></td>
<td>76 (51.7)</td>
<td>113 (76.9)</td>
<td>120 (80.6)</td>
</tr>
<tr>
<td><strong>&gt;=1 Medium</strong></td>
<td></td>
<td></td>
<td>147 (100)</td>
</tr>
</tbody>
</table>

* StrepB Select > BA (p<0.5)

P. Melin, 2008 ECCMID P1388
Granada (BD) - StreptoB ID - StrepB Select versus Blood agar +/- CNA

« False-Positive »
= Characteristic colonies not confirmed as GBS

<table>
<thead>
<tr>
<th>Identified as</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strep B Select</strong></td>
</tr>
<tr>
<td>GAS, GCS, GDS-enterococci, Staphylococci, <em>S.bovis</em>, α-hemolytic colonies,</td>
</tr>
<tr>
<td>(yeasts, Gram negative bacilli)</td>
</tr>
<tr>
<td><strong>Granada</strong></td>
</tr>
<tr>
<td>/</td>
</tr>
<tr>
<td><strong>Strep B ID</strong></td>
</tr>
<tr>
<td>GCS, Staphylococci, α-hemolytic colonies, (Gram negative bacilli)</td>
</tr>
<tr>
<td><strong>BA +/- CNA</strong></td>
</tr>
<tr>
<td>GAS, GCS, GFS, Staphylococci, GDS-enterococci, (Gram negative bacilli)</td>
</tr>
</tbody>
</table>
### Positive predictive value

**Granada (BD) - StreptoB ID - StrepB Select versus Blood agar +/- CNA**

<table>
<thead>
<tr>
<th></th>
<th>PPV Primoculture</th>
<th>PPV Lim sub-culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strep B Select</td>
<td>71.5 %</td>
<td>77.9 %</td>
</tr>
<tr>
<td>Granada</td>
<td>100 %</td>
<td>100 %</td>
</tr>
<tr>
<td>Strep B ID</td>
<td>80.9 %</td>
<td>87.9 %</td>
</tr>
<tr>
<td>BA +/- CNA</td>
<td>62.8 %</td>
<td>65.7 %</td>
</tr>
</tbody>
</table>

**Sensitivity**

Strep B Select > Granada - Strep B ID > CNA

**Specificity**

Granada > Strep B ID > Strep B Select > CNA

*pm-chulg – GBS CDC June 2009  
P. Melin, 2008 ECCMID P1388*
Which agar or which combination?
+/- Blood agar

Workload – costs – extra-testing to be considered
Vagino-rectal swab or Vaginal & rectal swabs

Inoculate swab(s) in 1 LIM broth

Overnight
And subculture following
at 35-37°C
to one of the media

Granada agar
Anaero

StrepB Select
Ambient air
48 h at 35-37°C

ID StreptoB
Ambient air

POSITIVE GBS Screening if
Orange colonies = GBS
Blue-turquoise colonies = suggestive GBS Id. to confirm
Pink colonies = suggestive GBS Id. to confirm

Negative GBS Screening if
No orange colonies
No blue-turquoise colonies
No pink colonies
Limiting factors

- Positive and negative predictive values
  - False-negative results
    - Up to 1/3 of GBS 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 prenatal GBS screening: intrapartum screening

Collect specimen at admission

Optimal management of patient

Specimen analysis

Results

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

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

Optimal time for IAP efficiency $\geq 4$ hours

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

- GBS Positive
- GBS negative

28.7%
26.9%
Available antigenic tests
- Variety of Immuno-assays
- Lack of sensitivity
  - Announced $5 \times 10^5$ CFU, but not confirmed

Hybridization tests
- Not enough rapid
- Lack of sensitivity if no enrichment step
Real Time PCR for intrapartum screening

- BD GeneOhm™ Strep B Assay (+/- 1 hr)
- Xpert GBS, Cepheid (+/- 75 min)
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%
Real-time PCR, very promising, but ...

- Still an expensive technology
- Logistic
  - 24/24 hours and 7/7 days
  - In the lab?
  - In the obstetrical department?
- In combination with prenatal screening strategy?
- No antimicrobial result
  - In the future detection of R genes, but mixed flora!
SUMMARY

- Culture-based GBS prenatal screening
  - To optimize critical factors
  - Use of selective differential agars
  - False +/- False - !
- Rapid intrapartum screening
  - Real time PCR
    - Yes but costs, logistic, …