Group B streptococci, a European perspective with results of the DEVANI project

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Group B streptococci (GBS)
The global picture of neonatal disease

- **Worldwide mortality 0-4 years old** (WHO, Cause of death 2008)
  - 8.3 millions
    - 30-40% within first week of life
- **Neonatal bacterial sepsis**
  - +/- 1 million annually
    - GBS is the leading cause

- **Maternal immunization**
  - Cornerstone of prevention
    - Neonatal tetanos and influenza
  - Potential to protect young infants
Group B streptococci (GBS)
The global picture of neonatal disease

- In industrialized countries, since 1970’s
  - Leading cause of pneumonia, sepsis, meningitis
    - 0.5 to 4 /1000 live births
  - EOD, mortality 5-10%
  - LOD, mortality 3-5%
  - Meningitis
    - 50% permanent sequelae
      - From mild learning or motor disabilities to global cognitive impairment
  - Maternal colonization: 15-40%

- In resource-limited countries
  - Many common characteristics with industrialized countries

Global public health major concern!
Group B streptococci (GBS)
The global picture of neonatal disease

CDC, USA, MMWR, Vol 59 (RR-10) Nov.2010
Endorsed by ACOG, AAP, ACNM, AAFP and ASM

CSS, Belgium July 2003 (Revision ongoing)
Group B streptococci (GBS)
The global picture of neonatal disease

- Prevention through IAP
  - In industrialized countries
    - Substantial declines of EOD
      - Remaining burden
    - No effect on LOD
    - Several concerns
  - In resource limited countries
    - Not an option
    - Intrapartum vaginal and newborn chlorhexidine washes proven ineffective

Incidence of GBS EOD and LOD, 1990 to 2008, ABC surveillance areas, USA
European strategies for prevention of GBS EOD

- Prevention through IAP
  - Screening-based strategy
    - Spain, 1998, revised 2003
    - France, 2001
    - Belgium, 2003, revision ongoing 2011
    - Germany, 1996, revised 2008
    - Switzerland, 2007
  - Risk-based strategy
    - UK, the Netherlands
- No guidelines
  - Bulgaria, ...
GBS neonatal disease

- Mainly CPS type III followed by Ia, V, Ib, II
- Substantial perinatal morbidity and mortality
  - Especially in the first 48 hrs of life
- Concern about IAP
- Higher levels of maternal specific CPS Ab // reduction of risk of neonatal disease

GBS Vaccines

- Uniquely suited for maternal immunization
- To prevent GBS disease in young infants
Since the 1980’s:
GBS Vaccines, Challenges

Capsular polysaccharide (CPS) vaccines

- 10 serotypes Ia, Ib – IX
  - Variability of CPS distribution
    - Type of infections: EOD, LOD, in adults
    - Geographically and along time

- Conjugated vaccines

- Multivalent vaccines Ia, Ib, II, III, V

- Clinical studies (Phase I and II)
  - Immunogenicity; Safety; Efficacy (scheduled / ongoing)
  - Ia, Ib, III conjugated to CRM197 (Novartis) clinical trials in Belgium

Well tolerated and immunogenic
Functional Abs (opsonization, phagocytosis, killing, protecting)
Since the 1980’s: GBS Vaccines, Challenges

GBS Protein-based vaccines

- **Antigen = common surface protein**
  - Cross protection against different CPS
  - Better immunogenicity
    - Humoral response T-cell dependant → Long lasting immunity

- **Among several candidates**
  - +/- ubiquitous among all GBS
    - BPS (Group B protective surface protein), C5a peptidase
    - **Sip** (Surface immunogenic protein)
      Brodeur B et al, Infect Imm 2000
    - **Pili proteins** *(PI-1, PI-2a, PI-2b)*
      Maione D et al, Science 2006
GBS 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
    - Three 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
Vaccine Against Neonatal Infections

Design of a vaccine to immunize neonates against GBS infections through a durable maternal immune response
PROJECT  (01.2008 - 06.2011)

- Development of a vaccine against pili proteins & major CPS serotypes
- Development of a mouse model of GBS meningitis
- European epidemiology
  - Genito-rectal colonizing strains
  - Invasive neonatal strains and diseases
- Identification of protective levels of specific antibodies

Consortium of 8 European countries
### Material and methods (Targets)

- **200 GBS neonatal diseases (EOD & LOD)**
  - Strain isolated from blood, CSF or another normal sterile site and perinatal mother’s serum
    - 25 per country

- **400 GBS negative mothers of healthy babies**
  - Serum
    - 50 per country

- **800 GBS positive mothers of healthy babies**
  - Strain and perinatal mother’s serum
    - 100 per country

For each patient included in the study (2009-2010)

**Case Report Form** (eplatform web.database)

**Signed consent form**
Epidemiology

Material and methods

- **Determination of capsular type**
  - Serotyping by latex microagglutination (SSI, Dk)
  - Set up of an international EQA (Afshar et al, JCM 2011)

- **Assessment of presence of pili genes**
  - PCR PI-1, PI-2a and PI-2b (Baldassari L et al, submitted)

- **MLST** (Jones N. et al., JCM 2003)

- **FACS analysis**
  - *Pili expression*

- **GBS serology**
  - *Abs Ia, Ib, III and V*
  - *Abs PI-1, PI-2a and PI-2b*
Descriptive and statistical analysis

- Description and comparison of populations
  - Demographic - anamnestic – clinical – biological data – CPS - Pili - MLST
    - Europe and countries
    - Pregnant women of healthy babies vs mothers of EOD/LOD
    - Neonatal cases: EOD and LOD

- CPS – Pili – MLST relations

- Serological relations
  - Protective thresholds
159 GBS neonatal infections
EOD / LOD = 1.12

1525 healthy infant’s mothers
1122 GBS Pos
7 controls / NI case

pm-isp-24.11.2011
PROVISIONAL ANALYSIS
### “Pregnant women”

<table>
<thead>
<tr>
<th></th>
<th>Healthy babies’mothers (1525: 1122 pos)</th>
<th>GBS EOD’s mothers (78)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GBS prenatal screening</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%, Number (Pos)</td>
<td>89.5%, 1365 (954)</td>
<td>47.4% (48.6%)</td>
<td></td>
</tr>
<tr>
<td>Vagino-rectal swab</td>
<td>80%</td>
<td>33.3%</td>
<td></td>
</tr>
<tr>
<td>IAP if GBS pos</td>
<td>60%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td><strong>GBS intrapartum screening</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% (Pos)</td>
<td>16.7% (58%)</td>
<td>16.5% (92.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Maternal age at delivery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (years)</td>
<td>30.8 (15-48)</td>
<td>35.9 (26-40)</td>
<td></td>
</tr>
<tr>
<td><strong>Notified Risk Factor for neonatal GBS EOD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROM &gt; 18h</td>
<td>5%</td>
<td>17.9 %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T° &gt;= 38°C</td>
<td>1%</td>
<td>11.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GBS bacteriuria</td>
<td>3.9%</td>
<td>11.4%</td>
<td>0.02</td>
</tr>
<tr>
<td>Previous GBS sibling</td>
<td>0.3%</td>
<td>1.3%</td>
<td></td>
</tr>
<tr>
<td>No RF</td>
<td>88.7%</td>
<td>51.3%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
“Pregnant women”
Type of delivery

<table>
<thead>
<tr>
<th></th>
<th>Healthy babies’mothers</th>
<th>GBS EOD’s mothers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal</td>
<td>51.9%</td>
<td>68.1%</td>
</tr>
<tr>
<td>Planned C-section</td>
<td>12.9%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Non-elective C-section</td>
<td>11.0%</td>
<td><strong>27.8%</strong> (P&lt;0.01)</td>
</tr>
<tr>
<td>Unknown</td>
<td>24.3%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>
## Mothers of newborns with GBS disease

<table>
<thead>
<tr>
<th></th>
<th>GBS EOD’s mothers (78)</th>
<th>GBS LOD’s mothers (72)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GBS prenatal screening</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% (Pos)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vagino-rectal swab</td>
<td>47.4% (48.6%)</td>
<td>61.1% (45.5%)</td>
</tr>
<tr>
<td>IAP if GBS pos</td>
<td>33.3%</td>
<td>56.8%</td>
</tr>
<tr>
<td></td>
<td>27%</td>
<td>26%</td>
</tr>
<tr>
<td><strong>GBS intrapartum screening</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% (Pos)</td>
<td>16.5% (92.3%)</td>
<td>14.1% (60%)</td>
</tr>
<tr>
<td><strong>Maternal age at delivery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (years)</td>
<td>35.9 (26-40)</td>
<td>31.2 (20-44)</td>
</tr>
<tr>
<td><strong>Notified Risk Factor for neonatal GBS EOD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROM &gt; 18h</td>
<td>17.9%</td>
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<td>11.5%</td>
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<td>GBS bacteriuria</td>
<td>11.4%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Previous GBS sibling</td>
<td>1.3%</td>
<td>0%</td>
</tr>
<tr>
<td>No RF</td>
<td>51.3%</td>
<td>52.1%</td>
</tr>
</tbody>
</table>
# Neonatal Invasive GBS Diseases

<table>
<thead>
<tr>
<th></th>
<th>GBS EOD (5.1% death)</th>
<th>GBS LOD (1.5% death)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>78 (52)</td>
<td>72 (48)</td>
<td></td>
</tr>
<tr>
<td>Age at onset</td>
<td>&lt; 1 day (88%)</td>
<td>38 d (6-109)</td>
<td></td>
</tr>
<tr>
<td>Birth weight</td>
<td>2.9 kg (1-4.9!)</td>
<td>2.7 kg (0.7-4.1)</td>
<td></td>
</tr>
<tr>
<td>Gestational age &lt; 37 weeks</td>
<td>37.7 wks (26-42)</td>
<td>36.2 wks (24-43)</td>
<td>0.05</td>
</tr>
<tr>
<td>Sex M/F</td>
<td>1.16</td>
<td>0.89</td>
<td>0.42</td>
</tr>
<tr>
<td>Predominant manifestation at onset</td>
<td>isory漱</td>
<td>Respiratory distress (38% of cases)</td>
<td>Fever (63% of cases)</td>
</tr>
<tr>
<td>Type of infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Bacteremia without focus</td>
<td>26.8%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>- Sepsis/Shock</td>
<td>70.7%</td>
<td>75.3%</td>
<td></td>
</tr>
<tr>
<td>- Meningitis</td>
<td>8.5%</td>
<td>30.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Pneumonia</td>
<td>13.4%</td>
<td>2.7%</td>
<td>0.017</td>
</tr>
<tr>
<td>- Others</td>
<td>2.4%</td>
<td>9.6%</td>
<td></td>
</tr>
<tr>
<td>- Birth in Twins</td>
<td>5.1%</td>
<td>15.7%</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Distribution of CPS serotypes among GBS from neonatal infections and among healthy babies’ mothers
Distribution of Pili genes among GBS from neonatal infections and among healthy babies’ mothers

NI: 100% with pili gene(s), most common pattern is PI-1+b2
PW: 0.6% without pili genes, most common is PI-1+2a
Relation pili / CPS among GBS from PW

Association between certain serotypes and pili gene pattern
Relation pili / CPS among GBS from newborns

![Graph showing the relation between pili and CPS among GBS from newborns.](image-url)
MLST – Clonal analysis of GBS
646 GBS from PW and 121 from NI

In PW: 66 Sequence types (ST) for 9 clonal complexes (CC)
Five CC include 92% of isolates tested

In NI: 6 CC; the most frequent is CC17, the hypervirulent clone
DEVANI Project
Preliminary conclusions

- Set up of a mouse meningitis model
- In European countries
  - Difference of prevention strategies
  - Difference of resource for routine diagnostic of severe neonatal infection
- In Belgium, difficult to include cases even if they occurred
- Standardization of typing methods
- Among neonatal infections:
  - Higher prevalence of GBS CPS III, pili pattern PI-1+2b and CC17
- Assessment of presence of pili genes
  - 100% in NI et 99% in PW
- MLST et CPS more heterogenous among GBS from PW
- No significant difference in CC distribution /country
- Serological analysis ongoing
Consortium and Team

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