GBS SCREENING
Belgium: current and future guidelines

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INTRODUCTION & BURDEN
**Streptococcus agalactiae or GBS**

**Gram positive cocci**
- Catalase -
- β-hemolytic
- CAMP test +
- Hippurate +
- Esculine-
- Orange pigment

**10 capsular serotypes (Ia, Ib, II-IX)**

- 1887, Nocard-Mollereau, bovine mastitis
- 1933, Group B Antigen
- 1964, severe neonatal sepsis
- ➢ 1970, N°1 in neonatal infections
Group B streptococcal diseases in neonates

- Since the 1970s, leading cause of life-threatening infections in newborns
  - Neonatal illness/death
  - Long-term disabilities
- Maternal morbidity
  - Along pregnancy
  - Peripartum
- Serious diseases among elderly and adults with underlying diseases
  - Significant mortality

GLOBAL public health major concern!
Also in developing countries
GBS Neonatal Infections

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

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

INTRODUCTION & BURDEN

80 % EOD

LOD

EOD : 80-90 % occur before 24 h
Burden of neonatal GBS early onset diseases in European countries

<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</td>
<td>Melin, Indian J Med Res 2004</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>0.2 - 4</td>
<td>Trijbels-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?
GBS EOD vertical transmission

GBS colonized mothers

Non-colonized newborns 60 - 40 %

Colonized newborns 40 - 60 %
INTRODUCTION & BURDEN

GBS EOD vertical transmission

GBS colonized mothers

60 - 40 %
Non-colonized newborns

40 - 60 %
Colonized newborns

96 - 98 %
Asymptomatic

GBS colonized mothers

GBS
EOD vertical
transmission

Non-colonized newborns

Colonized newborns

GBS
colonized mothers

96 - 98 %
Asymptomatic
GBS EOD vertical transmission

GBS colonized mothers

60 - 40 %

Non-colonized newborns

40 - 60 %

Colonized newborns

2 - 4 %

GBS EOD

Risk factors

96 - 98 %

Asymptomatic

96 - 98 %

Asymptomatic

sepsis
pneumonia
meningitis
long term sequelae

CDC

INTRODUCTION & BURDEN

GBS colonized mothers

60 - 40 %

Non-colonized newborns

40 - 60 %

Colonized newborns

2 - 4 %

GBS EOD

Risk factors

96 - 98 %

Asymptomatic

96 - 98 %

Asymptomatic

sepsis
pneumonia
meningitis
long term sequelae

CDC
GBS maternal colonization

Risk factor for early-onset disease (EOD): vaginal GBS colonization at delivery

- GBS carriers
  - 10 - 35 % of women
  - Clinical signs not predictive
  - Dynamic condition
  - Intestinal reservoir
  - 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
  - 1985-1990: 3/1000 live births
  - 1999, estimation: 2/1000 live births
  - 2010, estimation: < 1/1000 live births

- Meningitis: 10%

- Mortality: 5-10%

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

- Prenatal screening
  - Recto-vaginal cultures: 13-35% GBS Positive

- Universal prenatal screening-based strategy
- Risk-based strategy
- No guideline

GUIDELINES FOR PREVENTION OF GBS PERINATAL DISEASE
Stages in the pathogenesis of GBS

neonatal EOD : \textit{Bacterial \& individual factors}

\begin{itemize}
  \item Colonization: adhesion to epithelial cells different virulence factors (pili, scpB, \ldots)
  \item Ascendant transmission (amnionitis)
  \item \textit{β}-hemolysin, invasins (pneumonia)
  \item Bacteria Peptidoglycan \textit{β}-hemolysin, \ldots
  \item IL1, IL6, TNF \textit{α}, PGE2, TxA\textsubscript{2}, \ldots
  \item Resistance to phagocytose
    - Capsule
    - C5a peptidase
    - \ldots
  \item Phagocytes cells, Antibodies, Complement
  \item Brain barrier Pili, \textit{β}-hemolysin, \ldots
  \item Sepsis
  \item Meningitis
\end{itemize}
Which prevention strategy for GBS perinatal diseases?

- Intrapartum antibioprophylaxis
- Immunoprophylaxis
Stages in the pathogenesis of GBS

neonatal EOD: *Bacterial & individual factors*

Colonization: adhesion to epithelial cells
different virulence factors (pili, scpB, ...)

---

*Intrapartum antibioprophylaxis > 4 (2) hours before delivery*
Stages in the pathogenesis of GBS

neonatal EOD: *Bacterial & individual factors*

**GBS vaccine**
« still expected »

Colonization: adhesion to epithelial cells
different virulence factors (pili, scpB, ...)

GBS pathogenesis

Resistance to phagocytosis
- Capsule
- C5a peptidase
- ...

Ascendant transmission (amnionitis)
β-hemolysin, invasins (pneumonia)

Phagocytes cells, Antibodies, Complement
Prevention of perinatal GBS EOD

- Intrapartum antibiotics
  - Highly effective at preventing EOD in women at risk of transmitting GBS to their newborns (> 4 h)
    (clinical trials in late 80s)

Who is the women at risk?

Risk-based strategy or Screening-based strategy
Impact of prevention practices 
Early- and Late-onset GBS Diseases in 
the 1990s, U.S.

- Screening >50% more effective than RF

S. Schrag, New Engl J Med 2000
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
Impact of prevention practices
Early- and Late-onset GBS Diseases, U.S.

Incidence of early- and late-onset invasive group B streptococcal disease in selective Active Bacterial Core surveillance areas, 1989-2008 (CDC 2010)
Prevention of Perinatal Group B Streptococcal Disease
Revised Guidelines from CDC, 2010

Continuing Education Examination available at http://www.cdc.gov/mmwr/cme/cnted.html

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention

CDC, USA, MMWR, Vol 59 (RR-10) August 2010
Endorsed by
- AAP
- ACOG

SHC, Belgium July 2003
Revision ongoing

PREVENTION DES INFECTIONS PÉRINATALES À STREPTOCOQUES DU GROUPE B

.be
European strategies for prevention of GBS EOD

- Intrapartum antibioprophylaxis recommended
  - Screening-based strategy
    - France, 2001
    - Belgium, 2003, revision ongoing 2012
    - Germany, 1996, revised 2008
    - Switzerland, 2007
  - Risk-based strategy
    - UK, the Netherlands, Denmark
- No guidelines
  - Bulgaria, ...
Universal screening-based strategy for prevention of GBS perinatal disease

Vagino-rectal 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

GBS Neg

Not done, incomplete or unknown GBS result

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

if NO

Intrapartum prophylaxis NOT indicated

GBS POS

! Facultative! Intrapartum rapid GBS test**

if YES

INTRAPARTUM ANTIBIOPROPHYLAXIS INDICATED

if YES

Intrapartum prophylaxis NOT indicated
Remaining burden of GBS EOD
Missed opportunities

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
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

Use of differential agar media
Recommended by some European guidelines (+ CDC 2010)

- GRANADA (M.de la Rosa,JCM)
- Strepto B Select
- StreptoB ID

1983, 1992
1983, 1992
Pigment-based
Chromogenic media

2005
2007

From direct plating on blood agar
Evolution of culture methods

Use of selective enrichment broth
- To maximize the isolation of GBS
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1983, 1992
1983, 1992
Pigment-based
Chromogenic media

2005
2007
Which agar or which combination?

+/- Blood agar

Workload - costs - extra-testing - non β-hemolytic

GBS detection to be considered
<table>
<thead>
<tr>
<th><strong>WHEN</strong></th>
<th>35-37 weeks</th>
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<tbody>
<tr>
<td><strong>WHO</strong></td>
<td>ALL the pregnant women</td>
</tr>
<tr>
<td><strong>Specimen</strong></td>
<td>Vaginal + rectal swab(s)</td>
</tr>
<tr>
<td><strong>Collection</strong></td>
<td>WITHOUT speculum</td>
</tr>
<tr>
<td><strong>Transport</strong></td>
<td>Transport/collection device/condition</td>
</tr>
<tr>
<td>(non nutritive medium: Amies/Stuart or Granada like tube) (type of swab) (Length and T°)</td>
<td></td>
</tr>
<tr>
<td><strong>Request form</strong></td>
<td>To specify prenatal « GBS » screening</td>
</tr>
<tr>
<td><strong>Laboratory procedure</strong></td>
<td></td>
</tr>
</tbody>
</table>

*(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
Prenatal culture-based screening: Limiting factors

- **Unknown GBS status at presentation for delivery**
  - Screening performed but result not available
  - Women with no prenatal care

**Risk based strategy**
- 60% at GBS risk not identified
- > 10% of unnecessary IAP

**Need for rapid accurate predictor of intrapartum GBS vaginal colonization**
Alternative to GBS prenatal screening: intrapartum screening
Theranostic approach

Turnaround time
collect specimen at admission

Optimal management of patient

Specimen Analysis “POCT”? 

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

Benitz et al. 1999, Pediatrics, Vol 183 (6)
Intrapartum screening theranostic approach: expected advantages

- Identification of women without prenatal screening/care
- Inclusion of women with change of GBS status after 35-37 wks gestation
- Increased accuracy of vaginal GBS colonization status at time of labor & delivery

IAP addressed to right target
- Reduction of inappropriate/unnecessary IAP
- Broader coverage of « at GBS risk women »

Improvement of prevention
Real Time PCR for intrapartum screening

- Advance in PCR techniques & development of platforms
  - BD GeneOhm™ Strep B Assay (+/- 1 hr) (in laboratory)
  - Xpert GBS, Cepheid (35-45 min) (can be performed as a POCT)
Xpert GBS for intrapartum screening

Diagnostic Accuracy of a Rapid Real-Time Polymerase Chain Reaction Assay for Universal Intrapartum Group B Streptococcus Screening

Najoua El Helali, Jean-Claude Nguyen, Aïcha Ly, Yves Giovangrandi and Ludovic Trinquart

*Clinical Infectious Diseases 2009;49:417–23*

- 968 Pregnant women
- Intrapartum Xpert GBS, Cepheid (performed in lab) vs intrapartum culture
  - Prenatal culture *(French recom.)*
  - *(vaginal swab/CNA-BA)*
  - Sensitivity 98.5%
  - Specificity 99.6%
  - PPV 97.8%
  - NPV 99.7%
  - PPV 58.3%
  - NPV 92.1%
Xpert GBS for intrapartum screening

Cost and effectiveness of intrapartum group B streptococcus polymerase chain reaction screening for term deliveries.
El Helali N, Giovangrandi Y, Guyot K, Chevet K, Gutmann L, Durand-Zaleski I

*Obstet Gynecol 2012 Apr;119 (4):822-9*

<table>
<thead>
<tr>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antenatal screening</td>
<td>Xpert GBS intrapartum screening</td>
</tr>
<tr>
<td>11.7% GBS POS</td>
<td>16.7% GBS POS</td>
</tr>
</tbody>
</table>

Performed by midwives as a POCT!!
Less GBS EOD & less severe

Cost neutral per delivery
Xpert GBS for intrapartum screening

Real-Time PCR Assay Provides Reliable Assessment of Intrapartum Carriage of Group B *Streptococcus*

Michelle J. Alfa, Shadi Sepehri, Pat De Gagne, Michael Helawa, Gunwat Sandhu, and Godfrey K. M. Harding

*JCM, Sept. 2010, p. 3095–3099*

- 205 Pregnant women
- Intrapartum Xpert GBS, Cepheid
  - vs intrapartum culture

  24.5% GBS pos (vagino-rectal swab/LIM)
  - Sensitivity 91.7%
  - Specificity 99.3%
  - PPV 97.7%
  - NPV 97.3%
Real-time PCR, very promising, but ...

- Rapid, robust & accurate technology
- Still an expensive technology (specific equipment)
  - Cost effective?
    - Need for more cost-effective clinical study
- Logistic
  - 24 hours 7 days
  - In the lab?
  - In the obstetrical department as a POCT?
- In combination with prenatal screening strategy?
  - CDC 2010
- No antimicrobial result
  - In the future detection of R genes, but mixed microbiota!
CONCLUSION
Take home messages
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
    - No effect on LOD
  - IAP not widely recommended
  - Need better data assessing more accurately the true burden
- GBS vaccine eagerly expected
Summary

“Screening” Prevention strategies

- Culture-based GBS prenatal screening
  - To optimize critical factors
  - Improved by selective differential agars
  - False +/- False - !

- Rapid intrapartum screening
  “From a dream to reality”
  - Real time PCR
    - Yes but costs, logistic, …
    - Need for more clinical trial and cost effectiveness evaluation

"From a dream to reality"
Thanks!
Prevention of perinatal GBS EOD

- Screening-based strategy

**INTRAPARTUM ANTIMICROBIAL PROPHYLAXIS**

**Main goal:**
- To prevent 70 to 80% of GBS EO cases

**Secondary:**
- To reduce peripartum maternal morbidity
Intrapartum IV Antibio-Prophylaxis
(CDC 2010, Belgian SHC 2003)

- **Penicillin G**
  - 5 millions U, IV initial dose, then 2,5 to 3 millions U IV every 4 hours until delivery.

- **Ampicilline**
  - 2 g IV initial dose, then 1 g IV every 4 h until delivery.
  - Acceptable alternative, but broader spectrum, potential selection of R bacteria

- **If penicillin allergy**
  - **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: use vancomycin