Prevention of Perinatal Group B Streptococcal Disease

POC test for GBS screening in delivery room

Pierrette Melin
National Reference Centre for group B streptococci
Clinical Microbiology, University Hospital of Liege, University of Liege, Belgium

Background
- Burden - Guidelines - Prevention strategies
- Antenatal culture Screening
- Intrapartum POC screening, Xpert® GBS

Advantages & drawbacks
- Objective
- Material and methods
- Results & discussion
- Conclusion

Group B streptococcal diseases in neonates
- Since the 1970s, leading cause of life-threatening infections in newborns
  - Neonatal illness/death
  - Early & Late Onset Disease
  - Long-term disabilities
- Early Onset Disease (EOD)
  - Incidence:
    - Before mid-1990s: 3/1000 live births
    - Today, prevention era: 0.3 - 1/1000 live births
  - Meningitis: 10 %
  - Mortality: 5 - 10 % (20-30 % if premature)

GBS EOD vertical transmission
- GBS colonized mothers
  - 60 - 40 %
- Non-colonized newborns
  - 40 - 60 %
- Colonized newborns

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Today, prevention era: 0.3 - 1/1000 live births
Intrapartum antibiotic prophylaxis
- Universal prenatal screening-based strategy
- Risk-based strategy
- No guideline
- Immunoprophylaxis

GUIDELINES FOR PREVENTION OF GBS PERINATAL DISEASE

Stages in the pathogenesis of GBS neonatal sepsis:
EOD: Bacterial & individual factors

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

GBS pathogenesis

GBS identification

Colonized newborns

Non-colonized newborns

60 - 40 %

40 - 60 %

2 - 4 % GBS EOD

60 - 40 %

40 - 60 %

GBS vertical transmission

Asymptomatic

96 - 98 %

pneumonia

Swabbed

PUMF

Critical factors influencing accuracy

Late-onset GBS

Sequelae

Risk-based strategy? Screening-based strategy?

Identification of woman at risk

GBS colonization at delivery

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

60 - 40 %

Non-colonized newborns

Colonized newborns

GBS EOD

Intrapartum antibiotic prophylaxis

> 4 hours before delivery

Highly effective in preventing GBS EOD (1st clinical trials in late 80s)

Impact of prevention practices Early- and Late-onset GBS Diseases, U.S.

Incidence of early- and late-onset invasive group B streptococcal disease in select American Bacterial Core surveillance areas, 1989-2000 (CDC 2010)

Antenatal GBS culture-based screening

Goal of GBS screening

To predict GBS vaginal colonization (rectal) colonization at the time of delivery

Before national prevention policy

Transition

Universal screening

Improved screening method

CDC’s 1st consensus guidelines

CDC’s 1st consensus guidelines

Universal screening

No effect on GBS LOD

Incidence of early- and late-onset invasive group B streptococcal disease in selected American Bacterial Core surveillance areas, 1989-2000 (CDC 2010)
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 (35-37 wks)
- Screening methods (antenatal vs intrapartum)
- Culture
- Procedure
- Media
- Non-culture
- Nucleic Acid Amplification Test (NAAT)

Antenatal GBS culture-based screening

Theranostic approach
Alternative to GBS prenatal screening: intrapartum screening

Turnaround time
Optimal management of patient

Results
- Sensitivity > 90%
- Specificity > 95%

30-45 minutes, 24 hrs/7 days

Xpert® GBS for intrapartum screening

- Real Time PCR on GeneXpert system
  - Amplification of a conserved region adjacent to the cfb gene of GBS
- On vaginal or vagino/rectal swab
- Fully automated
- Easy handling (2 min hands-on time)
- Result in 35-45 minutes

INTRAPARTUM SCREENING FOR GBS

A POCT in the delivery room
Xpert® GBS, Cepheid

Inclusion of women without prenatal screening/care
Identification of women with change of GBS status after 35-37 wks gestation
Increased accuracy of vaginal GBS colonization status at time of labor & delivery
No antimicrobial susceptibility results (in case of penicillin allergy)

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

Improvement of prevention
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 (vaginal swab/CNA-BA)
    - Sensitivity 98.5%
    - Specificity 99.6%
    - PPV 97.8%
    - NPV 99.7%

Xpert® GBS POC test in the delivery room study

Objectives
Study in CHU Liège / UZ Antwerp, Belgium (900 patients)

1. To assess the practical aspects and analytical performances
   - Tests performed by midwives
   - Evolving team of +/- 50 midwives
   - For screening all women at onset of labor

2. To evaluate the cost-effectiveness of the intrapartum screening strategy
   ⇒ To consolidate the proposal of the European Expert Group

Specimen collection & processing

Initial protocol
Antenatal screening
- Vagino/rectal specimen
  - Collected at 35-37 weeks’ gestation

Intrapartum screening
- Vaginal specimen using a double swab
  - Collected at onset of labor

Culture
- Direct & from Lim broth

Xpert® GBS: Procedure
- Procedure performed by midwives
- GeneXpert system installed at the Obstetrics facility

Xpert® GBS test Expression of results
- Presence of GBS
  - Indeterminate status for GBS

Use of results
- Criteria for giving intrapartum antibiotic prophylaxis
  - Presence of defined risk factors
  - Positive GBS result of the antenatal screening at 35-37 weeks’ gestation
  - Positive result of intrapartum screening provided by Xpert® GBS test

Xpert® GBS test

- Positive GBS result of the antenatal screening at 35-37 weeks’ gestation
- Positive result of intrapartum screening provided by Xpert® GBS test
Results

Global overview

<table>
<thead>
<tr>
<th>Study period</th>
<th>Liege</th>
<th>Antwerp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of deliveries</td>
<td>608</td>
<td>7</td>
</tr>
<tr>
<td>GBS antenatal colonization rate</td>
<td>19.4%</td>
<td>14.7%</td>
</tr>
<tr>
<td>Number tested intrapartum with Xpert® GBS test</td>
<td>486</td>
<td>78</td>
</tr>
<tr>
<td>Xpert® GBS test</td>
<td>[74% of deliveries]*</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>13%</td>
<td>5%</td>
</tr>
<tr>
<td>Negative</td>
<td>83%</td>
<td>91%</td>
</tr>
<tr>
<td>Error</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Invalid</td>
<td>0%</td>
<td>1%</td>
</tr>
</tbody>
</table>

*Lower inclusion rate among antenatally GBS positive screened women

Culture results (Liege)

- Colonization rate (35-37 wks)
  - 19.4% GBS positive
- Performances of the antenatal culture screening
  - Intrapartum culture as gold standard

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>67.3%</td>
<td>94.2%</td>
<td>68.8%</td>
<td>93.8%</td>
</tr>
</tbody>
</table>

Xpert® GBS results (Liege, 2014)

Intrapartum (IP) culture as gold standard

Pre-study

- Bias: low inclusion rate of known GBS positive women
- Wrong handling

**Reminder of protocol and procedure**

<table>
<thead>
<tr>
<th>Pre-study</th>
<th>Study</th>
</tr>
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<tbody>
<tr>
<td>112 / 16</td>
<td>225 / 32</td>
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Post-study

<table>
<thead>
<tr>
<th>Pre-study</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>112 / 16</td>
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<td>NPV</td>
<td>96.7%</td>
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**Checking of swabs dropped in the bottom of the cartridge**

In the lab, Liege GBS colonies from discrepant results tested POSITIVE with Xpert® GBS
Xpert® GBS results (Lieve, 2014)
Intrapartum (IP) culture as gold standard

Pre-study Study Revision Following period
08.04 26.05 11.08 10.09

Number tested/
Number GBS Positive IP Culture
112 / 16 225 / 32 89 / 15 60 / 14

Sensitivity Including enrichment
78.6% 66.7% 46.7% 50%

Specificity
98.9% 100% 98.5% 97.6%

PPV
91.7% 100% 93.3% 87.5%

NPV
96.7% 91.7% 98.3% 87.2%

Xpert® GBS results (Antwerp, 2014)
Intrapartum (IP) culture as gold standard

Number tested
78

Sensitivity
50%

Specificity
100%

PPV
100%

NPV
54.7%

Authors Year/journal Nb patients Site S Sp % PPV % NPV %
Mueller et al. 2014 Eur J Obstet Gynecol Reprod Biol. 150 150 Lab Obst. 85.71 95.9 95.66 82.76 95.65
Abdelazim IA 2013 Aust N Z Obstet Gynaecol 100 100 Lab 98.3 99 97.4 99.4
Park JS et al. 2013 Ann Lab Med 175 175 Lab 86.6 95.6 65 98.7
Church DL et al. 2011 Diag Microbiol Infect Dis 231 231 Lab 100 100 100 100
Young BC et al. 2011 Am J Obstet Gynecol 559 559 Lab 90.8 97.6 92.2 97.1
El Helali N et al. 2009 Clin Infect Dis 968 968 Lab 98.6 99.6 97.8 99.7

Xpert® GBS for intrapartum testing
In Obstetric ward or in the lab !!
(main papers)

Pre-study Study Revision
08.04 26.05 11.08

Number tested
78

Sensitivity
50%

Specificity
100%

PPV
100%

NPV
54.7%
**Specimen collection & processing**

**Modified protocol restricted to Liege site (2015)**

Selected limited number of full-time midwives

<table>
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| • Vagino/rectal specimen
  • Collected at 35-37 weeks’ gestation | • Vaginal specimen using a double swab
  • Collected at onset of labor |

**Culture**

- (direct & from Lim broth)

**Xpert**

- **GBS**

**In labor room**

**Non-nutritive media, 38°C**

**Xpert® GBS results** *(Liege, July-sept. 2015)*

**Intrapartum (IP) culture as gold standard** *(61 deliveries; 11 GBS positive in IP culture, 18%)*

<table>
<thead>
<tr>
<th>PCR in delivery room</th>
<th>PCR in the lab 2-30 hours later</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number GBS Positive IP Culture</td>
<td>11 (18%)</td>
</tr>
<tr>
<td>Number of tests performed/number of positive results</td>
<td>41/8+1</td>
</tr>
<tr>
<td>Number of error/invalid</td>
<td>4 errors/3 invalid (11.5%)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>72.7%</td>
</tr>
<tr>
<td>Specificity</td>
<td>100%</td>
</tr>
<tr>
<td>Delta Ct values Delivery/Lab</td>
<td>+ 6.5 Ct (2.2 – 12.8)</td>
</tr>
</tbody>
</table>

- Difference of operator ??
- Difference of mucus behaviour and interference with PCR, from time of collection to a few hours later ??

**Number of tests performed/number of positive results**

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<tr>
<td>61/8+1</td>
<td>8+1</td>
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**Number of error/invalid**

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| Sensitivity | 72.7% |
| Specificity | 100%  |

**Summary**

- Xpert® GBS POCT in the delivery room
  - Theoretical superior clinical value
    - versus antenatal screening
  - Looks like easy to perform, BUT ...
    - Careful training of midwives
    - High turn-over in midwives team
    - Performances to be verified on EACH site!
    - To be supervised closely by the lab
    - Need for an internal specimen control
    - Role of excess of mucus ?

**CONCLUSION**

**Take home messages**

- Xpert® GBS POCT in the delivery room
  - Not ready as a standalone screening
  - High specificity but varying sensitivities !
  - Could be combined with risk factor strategy ??
  - Some expected improvements to secure the result AND the patient management
  - Commutability from lab to POC
  - Not always an unconditional success story

**Acknowledgements**

In Liege
- C. Meex
- J. Descy
- R. Sacheli
- Team of midwives

In Antwerp
- G. Ieven
- K. Denis
- Team of midwives

Cepheid Belgium team