Point of care testing of GBS, isn’t it obvious?

**BACKGROUND**

- **Burden**
  - Transmission - Prevention strategies

- **POCT for GBS, isn’t it clinically obvious?**
  - Risk-based or antenatal screening-based
  - Intra-partum antibiotic prophylaxis
  - Reduction of incidence of EOD, advantages & drawbacks
  - Room for improvement

- **POCT for GBS, is it technically obvious?**
  - Advantages & drawbacks
  - Expected characteristics
  - Available or coming POCTs

- **Take home message**

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**Group B streptococcus or GBS (Streptococcus agalactiae)**

- Since the 1970s, leading cause of life-threatening infections in newborns
  - Neonatal illness/death
    - Early & Late Onset Disease (EOD, LOD)
  - Long-term disabilities
  - **GBS EOD**
    - Before mid-1990s: 2-3/1000 live births
      - Today, prevention era: 0.2 – 1/1,000 live births
        - Meningitis: 10%
        - Mortality: 4 - 10% (20-30% if premature)
  - **GBS LOD**
    - 0.3 – 0.5/1,000 live births

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Neonatal GBS EOD

Vertical transmission

- Leading cause of life-threatening infections in newborns
  - Neonatal illness/death
  - Long-term disabilities
  - Vertical transmission during labor & birthing

GBS colonized mothers

Colonized newborns

Non-colonized newborns

50 - 40 %

40 - 60 %

(\(^*\)) : carriage 10-35% of pregnant women (transient, intermittent or chronic)

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


Primary risk factor for GBS EOD: vaginal GBS colonization at delivery

- Leading cause of life-threatening infections in newborns
  - Neonatal illness/death
  - Long-term disabilities
  - Vertical transmission during labor & birthing

GBS colonized mothers

Colonized newborns

Non-colonized newborns

50 - 40 %

40 - 60 %

Risk factors

2 - 4 %

Early onset disease (> 50% no RF)

96 - 98 %

Asymptomatic

Sepsis

Pneumonia

Meningitis

Long term sequelae

Strategies for prevention of neonatal GBS EOD

Antibiotic prophylaxis

Preventing transmission

Colonyed newborns

40 - 60 %
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**Strategies for prevention of neonatal GBS EOD**

- **Intrapartum antibioprophylaxis**
  - > 4 hours before delivery
  - Highly effective in preventing GBS EOD (1st clinical trials in late 80s)
  - To mitigate transmission and reduce chance of invasive infection.

**Challenge:**

- Identification of woman at risk
- Risk-based strategy?
- Screening-based strategy?

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

- *Early-onset GBS*
  - CDC’s 1st consensus guidelines:
    - Screening
    - Risk-based
  - Universal screening
  - Improved screening method

- *Late-onset GBS*
  - No effect on GBS LOD

**European strategies for prevention of GBS EOD**

- **Intrapartum antibioprophylaxis recommended**
- **Screening-based strategy**
  - (issued by prof.societies; by public health authorities)
  - France, 2001, 2017
  - Belgium, 2003, revised 2015
  - Germany, 1996, revised 2008
  - Switzerland, 2007

- **Risk-based strategy**
  - UK, the Netherlands, Denmark

- **No guidelines**
  - Bulgaria, …

**Guidelines for prevention**

- Efficacy, concerns & drawbacks
- Room for improvement

POCT FOR GBS, ISN’T IT CLINICALLY OBVIOUS?
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About analytically reliable diagnostic devices/systems for Real-time NAAT GBS LB assays

Impact on diagnostics?
Impact on patient management, care?
Impact on Turn-around-time?

Clinical significance of results?
Cost-benefits?

When to use which techniques?
For selected patients?
Alone or combined with conventional methods?
Will results be able to change behaviour?

Antenatal GBS culture-based screening

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

§ Crucial factors influencing accuracy
§ Swabbed anatomic sites
§ Timing of sampling (35-37 wks)
§ Screening methods
§ Culture
§ Procedure
§ Media
§ Non-culture
§ Nucleic Acid Amplification Test (NAAT)

Remainng burden of streptococcal early onset disease
Missed opportunities / False negative screening (antenatal culture based screening)
Negative and positive predictive values to be improved

Intra-venous IAP

Cost-benefits?
For lab/global?
Country, reimbursement, availability of human resources, quality of culture procedures, etc.

Impact on Turn-around-time?
Up to 48h shorter, but not essential as antenatal. Elegant, streamlined solution.
Concerns about potential adverse / unintended events related to IAP

- Allergies
  - Anaphylaxis occurs but extremely rare
- Changes in incidence or resistance of other pathogens causing EOD
  - Data are complex …
  - BUT Most studies: stable rates of « other » sepsis
- Impact on development of the neonatal intestinal microbiome.

- Changes in GBS antimicrobial resistance profile
  - Increase of resistance to clindamycin (10 to 40% in Europe, USA; up to 70% in Asia)
  - Very very rare decrease of susceptibility to penicillin

Concerns about preventive strategies & IAP

Risk-based approach

- A lot of missed opportunities
  - Lack of adherence
  - Incomplete assessment of risks
- Up to 65% of cases not associated to RF

Antenatal screening-based approach

- Some missed opportunities
  - Change of GBS status
  - Colonization dynamics
- False Negative screening
  - Change of GBS status
  - Colonization dynamics

Unnecessary IAP

- Half up to 80% of women with RF are not GBS colonized (except intrapartum fever)
- False Positive screening
  - Change of GBS status
  - Colonization dynamics

Up to 30 % of antenatal positive
**Towards a « European Consensus »**

Decision taken by a European working party (Neonatologists, obstetricians, microbiologists)

including countries with screening-based IAP, with risk-based IAP strategies or no strategy at all (June 2013, Florence, Italy)

**Main recommendations**

- **Universal screening at time of delivery** (when appropriate POCT available)
  - POCT with high PPV and NPV
  - Real time PCR or other methods
  - TAT < 1 hour
- **IAP for all GBS positive pregnant women**
  - documented by intrapartum testing (or late pregnancy test if performed)
- **Late pregnancy antenatal screening in known penicillin allergic women**
  - Determination of clindamycin susceptibility if GBS positive screening

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**Intrapartum screening**

**Expected advantages & drawback**

- Inclusion of women without antenatal 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, antenatal screening

**IAP addressed to right target**

- Reduction of inappropriate / unnecessary IAP
- Broader coverage of « at GBS risk women »

**Improvement of prevention**

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**POCT FOR GBS, IS IT TECHNICALLY OBVIOUS ?**

Old or new tools to detect GBS?
Response to a 30 year “dream” but also an obvious need.

GBS POCT
performed on vaginal specimen
at admission for delivery

= Valuable alternative method for accurate identification of GBS colonized women at delivery

**Improvement of prevention**
XXI<sup>st</sup> century, Medical evolutionary background

Factors impacting on development and daily practice of microbiology

- Medical environment
  - Increasing emphasis on evidence-based medicine and adherence to guidelines
- Economic environment
  - Cost-effective use of available resources
  - Reimbursement system, regulation
- Evolution of technological background
  - Exponential progress: molecular biology and robots
  - New platforms from “sample-in / result-out”
  - Continuation of advance to accelerate in the near future
- Quality assurance, traceability, LIS
- Global increase of antimicrobial resistance

Theranostic approach
Alternative to GBS prenatal screening: intrapartum screening

- Turnaround time
  - Collect specimen at admission
  - Optimal management of patient
  - Results
    - Sensitivity > 90%
    - Specificity > 95%
  - Full automation
  - With internal QC
  - Easy to perform, to interpret
  - Training!

A POCT in the delivery room
INTRAPARTUM SCREENING FOR GBS

Fully automated and robust test & platform
- Sensitivity >90%, specificity>95%, negative and positive predictive values
- Turn Around Time (TAT) < 1 hour
- Internal QC / embedded process control / control for presence of specimen on board
- Workflow; very limited hands-on-time
- Easyness to perform and to interprete (clear-cut result)
  - Low rate of invalid / error results
  - Availability 24h/7d
  - Limited training (high turnover among nurses/midwives)
  - Cost-effective
  - Traceability, connectivity to electronic medical files
  - Small footprint, low noise level
  - Minimized waste

Benitz et al. 1999, Pediatrics, Vol 183 (6)
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
    - antenatal culture (French recom.) (vaginal swab/CNA-BA)
    - Sensitivity 98.5%
    - Specificity 99.6%
    - PPV 97.8% PPV 58.3%
    - NPV 99.7% NPV 92.1%

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

<table>
<thead>
<tr>
<th>Pre-study</th>
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<th>Revision</th>
<th>Following period</th>
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<tbody>
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<td>112 / 16</td>
<td>225 / 32</td>
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<tr>
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<td>3% - 11%</td>
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Xpert® GBS
POC test in the delivery room study

Objectives
Study in CHU Liège / UZ Antwerp, Belgium (900 patients), 2014-2015

1. To assess the practical aspects and analytical performances
   - Tests performed by midwives
   - Evolving team of +/- 50 midwives/hospital
   - 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

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

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Key message

Xpert® GBS POCT in the delivery room

- High specificity but varying sensitivities!
- Some invalid or error results
  - Time, cost to retest ???
  - Some expected improvements to secure the result AND the patient management (specimen control)
- Mucus interference
- Higher Ct when test perform immediately after collection: better results a few hours later

Commutability from lab to POC:
Not always an unconditional success story!
→ Clinical validation of GBS POCT:
crucial to be performed on site, by midwives and on fresh specimens

GenePOC™ GBS DS test for intrapartum screening

- Real Time PCR on revogene™ instrument
  - Detection of a cfb gene sequence specific of the GBS genome
- On vaginal or vagino/rectal swab
- Fully automated
- Easy to use: 3 steps in 1 min
- Result in 70 minutes
- Single-use microfluidic cartridges
  - Testing 1 up to 8 samples in one run
- Embedded process control to monitor sample processing conditions
  - Internal control to monitor PCR conditions and the absence of reaction inhibition

GenePOC™ GBS DS Assay, validation by the Belgian NRC GBS
- Currently tested in parallel with reference culture
- Results: so far so good, evaluation still ongoing

GenePOC™ GBS DS test for intrapartum screening

Clinical performances characteristics of the GBS DS Assay in comparison to reference method

<table>
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<th>Reference Method</th>
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<tr>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>GBS DS Assay</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>107</td>
</tr>
<tr>
<td>Negative</td>
<td>4^</td>
</tr>
<tr>
<td>Total</td>
<td>111</td>
</tr>
</tbody>
</table>

Sensitivity: 96.4%
Specificity: 93.5%
PPV: 89.9%
NPV: 98.5%

^: GBS DNA detected in ½ false negative specimens tested using a second NAAT method
^: GBS DNA detected in 13/15 false positive specimens tested using a second NAAT method

Limit of detection

- GBS Strain
  - L4 in simulated matrix
  - µg/mL
  - Serotype III (ATCC 12403): 700
  - Non-hemolytic (ATCC 13813): 275

Intrapartum group B Streptococcus (GBS) detection by point-of-care real-time PCR testing (POCT)
Luiz Von Müller*, Germany

GenePOC™ GBS DS test, CE-marked, 2017
& the revogene™ instrument, CE-marked & FDA cleared

INTRAPARTUM SCREENING FOR GBS

Point of care testing of GBS, isn’t it obvious? ECCMID 2018
CONCLUSION
Take home messages

Summary

Neonatal GBS diseases & prevention

- GBS still a perinatal threat
- EOD and LOD, a public health concern
- Immunoprophylaxis, highly desirable but not yet available
- IAP efficient for prevention of EOD
  - Up to 80% reduction of EOD
  - Best strategy still a matter of debate
  - Antenatal screening >> risk factors ??
- IAP not widely recommended
- Towards European consensus 2014
  - Universal screening, intrapartum when appropriate GBS POCT available

Summary

Intrapartum GBS POCT

- Clinically OBVIOUS to reduce
  - Missed opportunities of IAP
  - Unnecessary IAP
  - Inappropriate management of newborn
- Clinically OBVIOUS
  - To better address the right target for IAP
  - But no AST result for penicillin allergic woman
  - A lot of papers relating the superiority of intrapartum GBS POCT–based IAP (Xpert® GBS)
    - Which “reference method”? 
    - Testing in lab versus on delivery site ?
    - Room for technical improvement ?
- Hope in the new GenePOC™ GBS DS test & coming others still in the pipeline of development

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