Towards a European Consensus for prevention of Perinatal Group B Streptococcal Disease

OLD & NEW TOOLS

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Streptococcus agalactiae
or group B streptococcus (GBS)
Group B streptococcal diseases in neonates

- Since the 1970s, leading cause of life-threatening infections in newborns
  - Neonatal illness/death
  - Long-term disabilities
Group B streptococcal diseases in neonates

- Since the 1970s, leading cause of life-threatening infections in newborns
  - Neonatal illness/death
  - Long-term disabilities

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

80% EOD

EOD 80-90% occur before 24 h

LOD & VLOD
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 health major challenge!
Also in developing countries
GBS EOD vertical transmission

GBS colonized mothers
(10-35% of pregnant women)

60 - 40 %
Non-colonized newborns

40 - 60 %
Colonized newborns
GBS EOD vertical transmission

GBS colonized mothers

60 - 40 %

Non-colonized newborns

40 - 60 %

Colonized newborns

96 - 98 %

Asymptomatic
GBS EOD vertical transmission

GBS colonized mothers

60 - 40 %

Non-colonized newborns

40 - 60 %

Colonized newborns

Risk factors

2 - 4 %

GBS EOD (± 50% no RF)

CDC

sepsis pneumonia meningitis long term sequelae

96 - 98 %

Asymptomatic
STRATEGIES FOR PREVENTION OF GBS PERINATAL DISEASE

- Through maternal intrapartum chemoprophylaxis
  - Universal antenatal screening-based strategy
  - Risk-based strategy
- Through maternal immunization
Point of intervention in the pathogenesis of GBS neonatal EOD

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

Intrapartum antibioprophylaxis > 4 (2) 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 in the 1990s, U.S.

Group B Strep Association formed
1st ACOG & AAP statements
CDC draft guidelines published
Consensus guidelines:
- Screening
- Risk-based

Screening >50% more effective than RF

S. Schrag, New Engl J Med 2000
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)

Before national prevention policy Transition Universal screening

Early-onset GBS

Late-onset GBS

Incidence (per 1,000 Live births)
Universal screening-based strategy for prevention of GBS perinatal disease *(Be SHC 2003)*

**Vagino-rectal GBS screening culture at 35-37 weeks of gestation**

For ALL pregnant women

- **GBS Neg**: Not done, incomplete or unknown GBS result
- **GBS POS**: ! Facultative! Intrapartum rapid GBS test**

**If NO**

- **Intrapartum prophylaxis NOT indicated**

**If YES**

- **> 1 Risk factor:**
  - Intrapartum fever $> 38^\circ C$***
  - ROM $> 18$ hrs

**Intrapartum antibioprophylaxis INDICATED**

Unless patient had a previous infant with GBS invasive disease or GBS bacteriuria during current pregnancy or delivery occurs $< 37$ weeks’ gestation *
Antibiotics and GBS in 2014

- **Penicillins**
  - GBS still fully susceptible to P and most β-lactams
  - Very rare non S GBS (Japan, USA, Canada, ... ?)
  - Under surveillance in Belgium (NRC)

- **Macrolides and lincosamides** (MLS, M & L phenotypes)
  - R on the rise
    - 5 – 35 % R, even more to erythromycin and clindamycin
    - Geographical differences

- **Gentamicin**
  - High level resistance reported (up to 13% in Argentina)

- **Fluoroquinolones**
  - Increasing for a decade, mainly in Japan, Korea, China (up to 37%)
Resistance to macrolides/lincosamides on the rise (Invasive isolates of GBS Belgium 1999-2012)
Immunoprophylaxis: Background

- Correlate between maternal low level of CPS type Ab at time of delivery and risk for development of GBS EOD

_Baker C et Kasper D, 1976, NEJM_

Vaccine for pregnant women: Likely the most effective, sustainable and cost effective approach
Immunoprophylaxis

GBS vaccine « within reach »

Help for clearing bacteria and preventing development of EOD

GBS pathogenesis

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

Ascendant transmission (amnionitis)

β-hemolysin, invasins (pneumonia)

Resilience of bacteria:
- Capsule
- β-hemolysin
- Pili
- scpB

Phagocytes cells, Antibodies, Complement

Phagocytes help for clearing bacteria and preventing development of EOD.
GBS Vaccines, since the 1980s

Challenges

Capsular polysaccharide vaccines

- 10 serotypes
  - Different distributions
    - EOD, LOD, invasives infections in adults
    - Geographically and along time

- Conjugated vaccines

- Multivalent vaccines Ia, Ib, (II), III and V

- Clinical studies (phases 1, 2 and 3)
  - Immunogenicity
  - Safety
  - Efficacy: scheduled/ongoing

Within reach!
GBS Protein-based Vaccines

- **Ag = Surface proteins**
  - Cross protection against different serotypes
  - Better immunogenicity
    - Humoral response T-cell dependent
      - long lasting immunity

**GBS « pilus like structure »**

- Highly immunogenic proteins
- Elicit protective and functional antibodies
- Virulence factor
  - Adhesion
  - Transcytose through cells
Editorial

Introduction: Addressing the challenge of group B streptococcal disease

- **Introduction**, Rappuoli & Black
- **GBS Review**, Carol Baker
- **Overview GBS epidemiology**, Paul Heath
- **GBS epidemio and vaccine needs**, Melin & Efstratiou
- **GBS epidemiology in developing countries**
- **IAP in USA et Vaccine implications**, S. Schrag & Verani
- **GBS maternal vaccines Past Present and Future**, Chen & Kasper
- **GBS Public awareness** etc
- **Prevention through Vaccination**, M. Edwards
- **GBS Vaccination in pregnancy**, P. Ferrieri
- **GBS vaccine Phase III trial**
Prevention strategy for GBS EOD

TOWARDS A EUROPEAN CONSENSUS?

Conference held 6-8 June 2013, Florence, Italy

A European working party: Neonatologists, obstetricians, microbiologists

Representing countries
• with screening-based IAP,
• with risk-based IAP strategies
• or no guidelines at all
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
Other concerns
Potential adverse / unintended consequences of prophylaxis

- Costs, logistics, medicalization of pregnancy
- 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
- Changes in GBS antimicrobial resistance
- Impact on newborn gut microbiota
Screening for GBS Colonization

**WHY?**

**WHEN?**

**HOW?**

**IMPACT?**

Specimen collection

Processing

Culture or non culture approach?

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 (distal vagina + rectum)
  - Timing of sampling (35-37 wks gestation; “poor” PPV & NPV)
  - Screening methods
    - Culture
      - Procedure
    - Media
    - Non-culture
Antenatal culture-based screening: Limiting factors

- Positive and negative predictive values
  - False-negative results
    - Failure of GBS culture (reduced viability during transport, oral ATB, feminine hygiene) or new acquisition
    - Up to 1/3 of GBS positive women at time of delivery

Need for more accurate predictor of intrapartum GBS vaginal colonization
From direct plating on blood agar
Evolution of culture methods

Use of selective enrichment broth (Lim broth, e.g.)
- To maximize the isolation of GBS
- To avoid overgrowth of other organisms

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

- 1983, 1992 (Pigment-based)
- 2005, 2007, 2012 (Chromogenic media)

GRANADA (M.de la Rosa, JCM)
Strepto B Select
StreptoB ID
Brilliance StrepB
Crucial conditions to optimize SCREENING

Transport-collection system & transport-storage condition

- **Type of swab:** Nylon flocked >> regular fiber swab

- **Non nutritive media:** Amies or Stuart without charcoal
  - **Storage at 4°C or RT 1-4 days** (CDC, USA 2010) or Granada tube
  - **Storage maximum 48h at 4°C** (SHC, Be 2003)
IMPROVEMENT OF TRANSPORT CONDITION OF SWABS FOR GROUP B STREPTOCOCCAL (GBS) SCREENING

P. Melin, M. Dodémont, G. Sarlet, R. Sacheli, J. Descy, C. Meex, P. Huynen, MP. Hayette
National Reference Centre for GBS, University Hospital of Liège, Liège, Belgium

To sustain viability
Whatever is storage $T^\circ$ for a few days
Results: Recovery of GBS in Lim BD at 4°C, RT and 35°C (similar results for Lim from bioMérieux and Copan)

Rem., in Granada tube: amplification followed at 48-72hrs by abrupt decrease to no growth
Antenatal culture-based screening combined with *illumigene*® Group B Streptococcus assay

A loop mediated isothermal amplification (LAMP) assay by Meridian Bioscience, Inc

- Broth enrichment followed by *illumigene*® GBS
  - Speed and “accuracy”
  - Good comparison to reference culture method
  - “Easy” to perform BUT not as easy as claimed and training very important
  - Overall cost and logistic to be considered
Alternative to GBS antenatal 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

- 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

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) (could be performed as a POCT)
Xpert GBS for intrapartum screening

*(selected paper amongst many others)*

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%
    - NPV 99.7%
    - PPV 58.3%
    - NPV 92.1%
Xpert GBS for intrapartum screening

(selected paper amongst many others)

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></td>
<td><em>Performed by midwives as a POCT!!</em></td>
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11.7% GBS POS

16.7% GBS POS

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 (with Lim enrichment step)
    - 24.5% GBS pos
      - Sensitivity 91.7%
      - Specificity 99.3%
      - PPV 97.7%
      - NPV 97.3%
# Xpert GBS for GBS screening

*(selected paper amongst many others)*

<table>
<thead>
<tr>
<th>Performance of NAAT versus enriched GBS culture</th>
<th>NAAT TEST</th>
<th>Swab for NAAT and culture</th>
<th>NAAT Sens.</th>
<th>NAAT Spec.</th>
<th>NAAT PPV</th>
<th>NAAT NPV</th>
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</thead>
<tbody>
<tr>
<td>Abdelazim IA 2013 Aust N Z Obstet Gynaecol</td>
<td>IP V (Todd Hewitt)</td>
<td>98.3%</td>
<td>99%</td>
<td>97.4%</td>
<td>99.4%</td>
<td></td>
</tr>
<tr>
<td>Park JS et al 2013 Ann Lab Med</td>
<td>AP V/R (Todd Hewitt)</td>
<td>86.6%</td>
<td>95.6%</td>
<td>65%</td>
<td>98.7%</td>
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<tr>
<td>Church DL et al 2011 Diag Microbiol Infect Dis</td>
<td>AP V/R (StrepBcarrot)</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>De Tejada BM et al 2011 Clin Microbiol Infect</td>
<td>IP V/R (Todd Hewitt)</td>
<td>85.00%</td>
<td>96.6%</td>
<td>85.7%</td>
<td>96.3%</td>
<td></td>
</tr>
<tr>
<td>Young BC et al 2011 Am J Obstet Gynecol</td>
<td>IP V/R (Todd Hewitt)</td>
<td>90.8%</td>
<td>97.6%</td>
<td>92.2%</td>
<td>97.12</td>
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<tr>
<td>Money D et al 2008 Obstet Gynaecol Can</td>
<td>IP V/R (enrichment)</td>
<td>90.5%</td>
<td>96.1%</td>
<td>86.7%</td>
<td>97.4%</td>
<td></td>
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<tr>
<td>Smith D et al 2008 Diag Microbiol Infect Dis</td>
<td>BD GeneOhm strepB™</td>
<td>77.1%</td>
<td>84.6%</td>
<td>79.3%</td>
<td>Non specified</td>
<td></td>
</tr>
<tr>
<td>Davies HD et al 2004 Clin Inf Dis</td>
<td>IP V/R (Todd Hewitt/Lim broth)</td>
<td>94%</td>
<td>95.9%</td>
<td>83.8%</td>
<td>98.6%</td>
<td></td>
</tr>
</tbody>
</table>
Real-time PCR, very promising, BUT ...

- Rapid & accurate technology in laboratory
- Robustness to be improved to be used as a POCT
  
  (2014 NRC GBS : CHULg & UIA, preliminary results)
- Still an expensive technology (specific equipment)
  - Need for more cost-effectiveness clinical study
- Logistic
  - 24 hours 7 days
  - In the lab or as a POCT?
- In combination with prenatal screening strategy?
  - CDC 2010: for women with premature delivery or no prenatal care
- Drawback: 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 global 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
- New tools to improve GBS detection

GBS vaccine eagerly expected

- Appears to be within reach
Summary

“Screening” Prevention strategies

- Culture-based GBS antenatal screening
  - False +/False -
  - To optimize critical factors
  - Improved by selective differential agars
  - Expected improvement from transport system

- Rapid intrapartum screening
  - Real time PCR as a POCT
    - Yes but robustness, costs, logistic, ... !!!
    - Need for more clinical and cost effectiveness trials
    - No result for clindamycin susceptibility
Revised Belgian guidelines
(Superior Health Council, expected end 2014)
(Neonatologists, obstetricians, microbiologists, midwives)

Main recommendations

- Universal antenatal screening at 35-37 wks gestation
  - Lim broth as transport media
  - Selective differential culture media
  - Determination of clindamycin susceptibility (if GBS positive)

- Universal screening at time of delivery could be used in the future
  - If availability of POCT with high PPV and NPV
    - Real time PCR or other methods
    - TAT max 1 hour
  - Late pregnancy prenatal screening in known pen-allergic women
    - Determination of clindamycin susceptibility if GBS positive screening

- IAP for all GBS positive pregnant women
  - documented by antenatal testing (or intrapartum testing if performed)
GUIDELINES

Intrapartum GBS screening and antibiotic prophylaxis: a European consensus conference

G. C. Di Renzo¹, P. Melin², A. Berardi³, M. Blennow⁴, X. Carbonell-Estrany⁵, G. P. Donzelli⁶, S. Hakansson⁷, M. Hod⁸, R. Hughes⁹, M. Kurtzer¹⁰, C. Poyart¹¹, E. Shinwell¹², B. Stray-Pedersen¹³, M. Wielgos¹⁴, and N. El Helali¹⁵
Prevention strategy for GBS EOD: TOWARDS A EUROPEAN CONSENSUS?

Agreement for

Screening-based intrapartum antimicrobial prophylaxis

Intrapartum screening-based

As soon as proven efficiency of a POCT and cost-effectiveness

Provisionally, where antenatal screening is already recommended

- Use of improved methods for antenatal screening
  (Collection & transport / selective enrichment broth / selective differential agars)
Thank you!
GBS and non-S to β-lactams

- Existence and molecular mechanisms of clinical isolates with reduced Penicillin susceptibility (PRGBS)
  - First report in Japan by Kimura K et al, AAC 2008
  - Following reports from Japan, USA, Canada

- Penicillin MIC 0.25-1 mg/L
- Ceftizoxime MIC 4-128 mg/L

Acquisition of amino-acid substitutions in PBP2X and in PBP1A
→ elevation of cephalosporins’ MICs
PR GBS detection

→ possibly unrecognized by standard antimicrobial susceptibility methods !!

- **Recommended methods for initial screening**
  - 3-Disk diffusion
    - Oxacillin, ceftizoxime,
    - Ceftibuten (no zone)
  - MICs to oxacillin and ceftizoxime
    - Usually high for PR GBS

*Kimura et al, J Clin Microbiol 2009*
MLS acquired Resistance Phenotypes and genotypes

- **Target modification** (*erm* family genes)
  - Constitutive MLS resistance
  - Inducible MLS resistance (D-zone test)
  - Serotype associated (higher rates: IV, V > III > others)

Cross resistance to macrolides, lincosamides and streptogramin B

- **Active efflux** (*mefA* gene) → M phenotype
  
  Resistance to 14- & 15- membered ring macrolides (as erythromycin and azithromycin)

- **Enzymatic inactivation or ?** (*lnu* genes, *lsa* genes)
  - Clindamycin resistance
Phenotypes L

- **L phenotype**
  - Inactivation by lincosamide nucleotidyltransférases (*Inu*(B) and *Inu*(C) genes)
    - New Zealand, Canada, USA, Asia, Argentina

- **LSₐ or LSₐP phenotype**
  - Cross resistance to lincosamides, streptogramin A and pleuromutilin
  - *Isa*(C) gene
    - New Zealand (*Malbruny et al.*, AAC, 2011)
    - Belgium (*J.Descy et al.*, LISSSD abstract 100)
      - 0.6% from 1329 isolates (2008-2013)
European strategies for prevention of GBS EOD

- **Intrapartum antibioprophylaxis recommended** (national, regional or professional societies)
  - **Screening-based strategy**
    - France, 2001
    - Belgium, 2003, **revision ongoing 2014**
    - Germany, 1996, revised 2008
    - Switzerland, 2007
  - **Risk-based strategy**
    - UK, the Netherlands, Denmark

- **No guidelines**
  - Bulgaria, …
Transport-collection system & storage condition

Specimen storage in transport medium and detection of group B streptococci by culture.


Recovery of group B streptococci (GBS) was assessed in 1,204 vaginorectal swabs stored in Amies transport medium at 4 or 21°C for 1 to 4 days either by direct inoculation onto Granada agar (GA) or by culture in blood

These data indicate that viability of GBS is not fully preserved by storage of vaginorectal swabs in Amies transport medium, mainly if they are not stored under refrigeration.

Viability of GBS NOT fully preserved by storage of vaginorectal swabs in Amies transport medium, mainly if not stored under refrigeration.