INTRODUCTION & BURDEN

Perinatal Group B Streptococcal Disease

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Content

- History and historical context of perinatal GBS disease
- Early and contemporary epidemiology
- Pathogenesis and risk factors
- Prevention strategies through
  - Maternal intrapartum chemoprophylaxis
  - Evolution of policies, effectiveness and concerns
  - Towards European consensus
- Maternal immunization

Streptococcus agalactiae or GBS

Gram positive cocci
- Encapsulated
- Catalase +
- β-hemolytic
- CAMP test +
- Hippurate +
- Esclunie-
- Orange pigment

Rebecca Lancefield
1895-1981

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

1887, Noccard-Mollereau, bovine mastitis
1933, Group B Antigen
1964, severe neonatal sepsis, Eschloff et al N Eng J Med
> 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

- EOD: 80-90 % occur before 24 h

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

- Incidence per 1,000 live births
  - EOD: 0.3 – 3
  - LOD: 0.5

- Onset
  - 0 – 6 days (or 0-72 hrs)
  - 1 week – 3 months (up to 1 y)

- Mean age at onset
  - 12 hrs
  - 1 month

- Transmission
  - Vertical
  - Intrapartum
  - Horizontal (vertical?)
  - At delivery
  - Nosocomial
  - In the community

- Portal of entry
  - Inhalation ➔ pneumonia ➔ translocation into bloodstream ➔ Likely intestinal

- Clinical presentation
  - Respiratory distress with fulminant pneumonia
  - Septicemia
    - Meningitis (25-70%)
    - Cellulitis, osteomyelitis

- Mortality
  - < 10 %
  - 0 - 6%

- Capsular serotypes
  - All (Ia, III, V)
  - III, mainly
  - Hypervirulent clone ST17 /meningitis
**INTRODUCTION & BURDEN**

- **GBS colonized mothers**
  - 60 - 40 %
  - 40 - 60 %

- **Non-colonized newborns**
  - 96 - 98 %

- **Colonized newborns**
  - 96 - 98 %

**GBS EOD vertical transmission**

- **Asymptomatic**
  - 96 - 98 %

**GBS EOD colonized mothers**

- 60 - 40 %
- 40 - 60 %

**GBS EOD non-colonized newborns**

- 2 - 4 %

**GBS EOD long term sequelae**

- Sepsis
- Pneumonia
- Meningitis
- Long term sequelae

**GBS EOD horizontal transmission**

- CDC

Risk factors

Airborne spread

- GBS EOD

**GBS EOD screening**

- 96 - 98 %

**GBS EOD vaccine**

- 96 - 98 %

**GBS EOD conclusion**

- 96 - 98 %

**Distribution (%) of capsular types of GBS isolated in Belgium from different groups of patients (1998-2007)**

- Type III Hypervirulent clone ST17
- EOD → meningitis

- 236 neonatal EOD; 64 neonatal LOD; 721 adults
**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

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**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

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**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

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

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

- **Blood Brain barrier**
  - Pili, III ST-17
  - β-hemolysin,

- **Bacteria**
  - Peptidoglycan
  - β-hemolysin, ...

- **Sepsis**
  - IL1, IL6, TNF α,
PGE2, TxA2,

- **Resistance to phagocytosis**
  - Capsule
  - CSa peptide

- **Phagocytes cells, CPS**
  - Antibodies
  - Complement

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**GBS pathogenesis**

- Ascendant transmission (amnionitis)

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*Carriage not restricted to women!

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Loquet S., Melin P. & al. J Gynecol Obstet Biol Reprod 2005
GUIDELINES FOR PREVENTION OF GBS PERINATAL DISEASE

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

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

- Colonization: adhesion to epithelial cells different virulence factors (pili, scpB, ...)
- GBS pathogenesis
- Intrapartum antibioprophylaxis > 4 (2) hours before delivery

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

- GBS vaccine « still expected » Nearly within reach

Which prevention strategy for GBS perinatal diseases?

- Intrapartum antibioprophylaxis (IAP)
- Immunoprophylaxis

GBS pathogenesis

- Ascendant transmission (amnionitis)
- Resistance to phagocytose
- Capsule - C5a peptidase
- Antibodies, Complement

GBS vaccine

- Phagocytes cells, CPS (& pili)

β-hemolysin, invasins

GBS vaccine « still expected » Nearly within reach
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.

- Group B Strep Association formed
- 1st ACOG & AAP statements
- CDC draft guidelines published
- Consensus guidelines: Screening -Risk-based
- Screening >50% more effective than RF

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

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
INTRODUCTION & BURDEN

VACCINE

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

European strategies for prevention of GBS EOD

Intrapartum antibioprophylaxis recommended

Screening-based strategy
- Spain, 1996, 2003, revised 2012
- France, 2001
- Belgium, 2003, revision ongoing 2013
- Germany, 1996, revised 2008
- Switzerland, 2007

Risk-based strategy
- UK, the Netherlands, Denmark

No guidelines
- Bulgaria, …

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

SHC, Belgium July 2003
Revision ongoing

Universal screening-based strategy for prevention of GBS perinatal disease

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

For ALL pregnant woman

GBS Neg
- Not done, incomplete or unknown GBS result

GBS POS
- Facultative Intrapartum rapid GBS test**

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

Intrapartum prophylaxis NOT indicated

GBS Neg
- Intrapartum prophylaxis NOT indicated

GBS POS
- Intrapartum antibioprophylaxis indicated
**INTRODUCTION & BURDEN**

Adhesion to a common protocol is a key of success
Multidisciplinary collaboration is mandatory

**GUIDELINES**

**SCREENING**

**VACCINE**

**CONCLUSION**

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**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**
  - 3 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

**Duration of antibiotherapy**

**Threatened preterm delivery**

**Planned caesarean delivery for GBS colonized women**
Concerns about potential adverse / unintended consequences of prophylaxis

- 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 profile

Concerns: Clinically relevant antimicrobial resistance

- Increase of resistance to erythromycin and clindamycin
- Susceptibility to penicillin
  - Very few « not S » isolates recently characterized in Japan
    - Mutation in pbp genes, especially pbp2x
    - MIC= 0.25 -1 mg/L
    - No clinical impact?
  - Very few in the U.S.
  - All labs should send to reference lab
  - Any « non-S » isolate for confirmation
  - All invasive isolates for resistance surveillance

Erythromycin and clindamycin resistance among clinical isolates of GBS (Belgian data)

- Resistance to erythromycin: Constitutive + Inducible R (≥ 75% CR / 25% IR)
  - D-Test recommended

Concerns about potential adverse / unintended consequences of prophylaxis

- Management of neonates
  - Increase of unnecessary evaluation
  - Increase of unnecessary antimicrobial treatments

  ➔ Algorithm for secondary prevention of EOD among newborns
  - Symptoms; maternal chorioamnionitis; prophylaxis; gestational age; time of rupture of membrane

Rem.: 80-90 % of GBS EOD are symptomatic < 24 h of life
**Secondary prevention of GBS EOD among newborns**

Improved management according to clinical signs and risks

- **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*

**Remainning burden of GBS EOD Missed opportunities**

In spite of universal screening prevention strategy
In spite the great progress
Cases still occur

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**SCREENING FOR GBS COLONIZATION**

WHEN?

HOW?

IMPACT?
Antenatal GBS culture-based screening

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

- Critical factors influencing accuracy
  - Anatomic sites
  - Timing of sampling
  - Screening methods
    - Culture
    - Procedure
    - Media
    - Non-culture

Crucial conditions to optimize SCREENING

- **WHEN** 35-37 weeks
- **WHO** ALL the pregnant women
- **Specimen** Vaginal + rectal swab(s)
- **Collection** WITHOUT speculum
- **Transport** Transport/collection device/condition (non nutritive medium: Amies/Stuart or Granada like tube) (type of swab)(Length and T°)
- **Request form** To specify prenatal « GBS » screening
- **Laboratory procedure**

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,CM)
- **Strepto B Select**
- **Strepto B ID**

Which agar or which combination?

+ Blood agar

Workload - costs - extra-testing - non β-hemolytic GBS detection to be considered
**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
    - Positive prenatal screening /negative at time of delivery
    - Unnecessary IAP

Need for more accurate predictor of intrapartum GBS vaginal colonization

**Alternative to GBS prenatal screening: intrapartum screening**

- Theranostic approach
  - Turnaround time
    - Optimal management of patient
    - Collect specimen at admission
  - 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) (can be performed as a POCT)

**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: for women with premature delivery or no prenatal care
- No antimicrobial result
  - In the future detection of R genes, but mixed microbiota!

**Background**

- Correlate between maternal low level off CPS type Ab at time of delivery and risk for development of GBS EOD
  
  *Baker C et Kasper D, 1976, NEJM*

**Prevention of GBS EOD and LOD**

*Prevention of maternal diseases*

**VACCINE**

*Likely the most effective, sustainable and cost effective approach*
INTRODUCTION & BURDEN

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, III, V
  - Clinical studies
    - Immunogenicity
    - Safety
    - Efficacy: scheduled/ongoing (Phase 3 studies)

GBS Protein-based Vaccine

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

VACCINE

Protein-based Vaccines

<table>
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<th>Protein</th>
<th>Protective Ab</th>
<th>associated serotypes (in mouse)</th>
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<tr>
<td>Alpha-like proteins</td>
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<td>C5a peptidase</td>
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<td>Sip (1999)</td>
<td>Yes</td>
<td>All</td>
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<tr>
<td>BPS</td>
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<td>All</td>
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</tbody>
</table>

Sip = Surface Immunogenic Protein (Brodeur, Martin, Québec)
BPS = Groupe B Protective surface Protein

Protein-based Vaccines

Reverse vaccinology approach
Knowledge of complete GBS genome

- Comparison of genomes from 8 different GBS serotypes
  - 312 surface proteins were cloned
  - 4 Provide a high protective humoral response in mouse
    - Sip and 3 others
    - The 3 other proteins = « pilus like structures »
**GBS « pilus like structure »**
- Highly immunogenic proteins
- Elicit protective and functional antibodies
- Virulence factor
  - Adhesion
  - Transcytose through cells

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**CONCLUSION**

Take home messages

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**Summary**

“Screening” Prevention strategies
- Culture-based GBS prenatal screening
  - To optimize critical factors
  - Improved by selective differential agars
  - False + / False - !
  - Expected improvement from transport system
- Rapid intrapartum screening
  - Real time PCR
  - Yes but costs, logistic, ...
  - Need for more clinical and cost effectiveness trials

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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
  - Appears to be within reach