GBS Prévention

Nouveaux outils & stratégies attendues

Pierrette Melin
Centre National de Référence de *Streptococcus agalactiae*
Microbiologie clinique, CHU de Liège, Université de Liège

CONTENT

- Introduction & burden
- Prevention strategies
- Maternal intrapartum prophylaxis (IAP)
  - Screening : old and new tool
- Maternal immunization (Vaccine)
- Take home messages

INTRODUCTION & BURDEN

Streptococcus agalactiae or GBS

Rebecca Lancefield 1895-1981

Gram positive cocci
β-hemolytic
Encapsulated

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

1887, Noccard-Mollereau, bovine mastitis
1933, Group B Antigen
1964, severe neonatal sepsis, *Eickhoff et al N Eng J med*
➢ 1970, N°1 in neonatal infections

Streptococcus agalactiae or GBS

Streptococcus agalactiae clones infecting humans were selected and fixed through the extensive use of tetracycline

- Genome-based phylogeny reveals the expansion of a few clones
- Human GBS belong mainly to a small number of TcR clones

V.Dacunha, MR.Davies, …, C.Poyart and P.Glaser
In *Nat Commun.* 2014 Aug 4;5:4544. doi: 10.1038/ncomms5544.

1887, Noccard-Mollereau, bovine mastiti
1933, Group B Antigen
1964, severe neonatal sepsis, *Eickhoff et al 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

Group B streptococcal diseases in neonates

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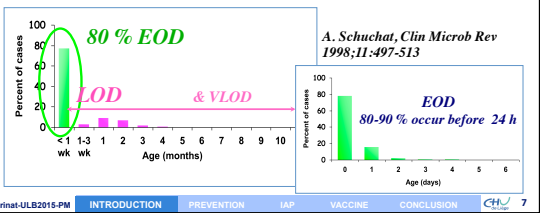


Group B streptococcal diseases in neonates

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

EOD
0.3-3 per 1,000 live birth

LOD
0.4-0.5 per 1,000 live birth

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

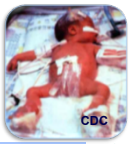
GBS EOD vertical transmission

GBS colonized mothers

60 - 40 % → Non-colonized newborns
40 - 60 % → Colonized newborns
Risk factors
2 - 4 % GBS EOD (+ 50% no RF)

96 - 98 %
Asymptomatic

sepsis
pneumonia
meningitis
long term sequelae



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

Meningitis

Brain barrier
Pili, III ST-17
β-hemolysin, …

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

GBS pathogenesis

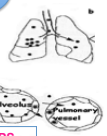
Ascendant transmission (amnionitis)

Sepsis

IL1, IL6, TNF α, PGE2, TxA_2 ,

Bacteria
Peptidoglycan
β-hemolysin, …

Resistance to phagocytose
- Capsule
- C5a peptidase
- …..



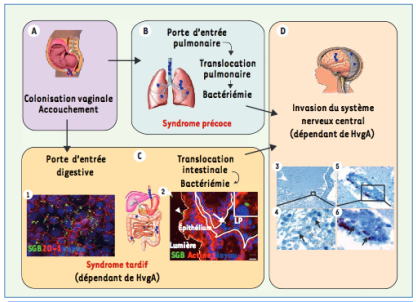
β-hemolysin, invasins (pneumonia)

Phagocytes cells, CPS Antibodies, Complement

Stages in the pathogenesis of GBS neonatal EOD

GBS surface proteins as ajor determinants for meningeal tropism

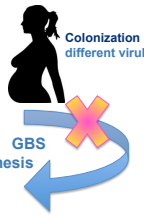
Tazi A et al. 2011 Curr Op Microbiology - http://dx.doi.org/10.1051/medsci/2011274010



- Intrapartum antibioprophylaxis (IAP)
- Immunoprophylaxis
  Key strategy

PREVENTION STRATEGIES FOR GBS PERINATAL DISEASE

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



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

GBS pathogenesis

Preventing transmission

Intrapartum antibioprophylaxis
> 4 (2) hours before delivery

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

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

GBS vaccine
« nearly within reach »

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

GBS pathogenesis

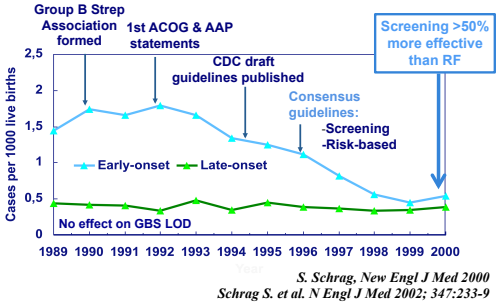
Help for clearing bacteria and preventing development of EOD

Ascendant transmission (amnionitis)

β-hemolysin, invasins (pneumonia)

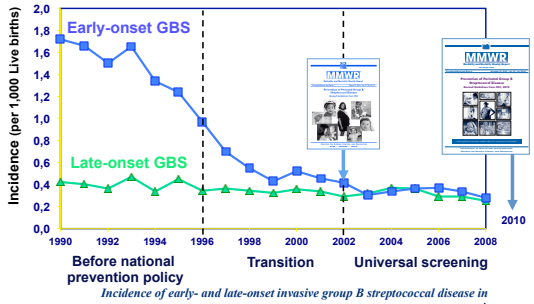
Phagocytes cells, Antibodies, Complement

Impact of prevention practices Early- and Late-onset GBS Diseases in the 1990s, U.S.



S. Schrag, New Engl J Med 2000
Schrag S. et al. N Engl J Med 2002; 347:233-9

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)

European strategies for prevention of GBS EOD

- **Intrapartum antibioprophylaxis recommended**
  - Screening-based strategy
    - Spain, 1998, 2003, revised 2012
    - France, 2001
    - Belgium, 2003, revised 2015
    - Germany, 1996, revised 2008
    - Switzerland, 2007
  - Risk-based strategy
    - UK, the Netherlands, Denmark
- **No guidelines**
  - Bulgaria, …

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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

*Unless patient had a previous infant with GBS invasive disease or GBS bacteriuria during current pregnacy or delivery occurs < 37 weeks' gestation **

GBS Neg

Not done, incomplete or unknown GBS result

GBS POS

if YES

INTRAPARTUM ANTIBIOPROPHYLAXIS INDICATED

! Facultative ! Intrapartum rapid GBS test**

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

if NO

if YES

Intrapartum prophylaxis NOT indicated

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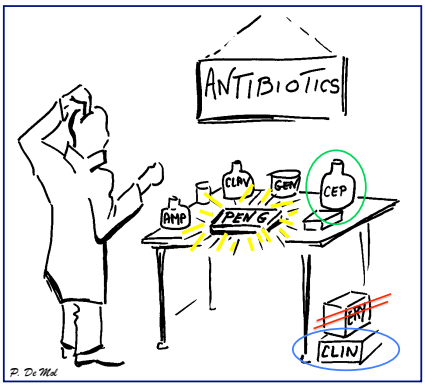

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Concerns : Clinically relevant antimicrobial resistance

- **Increase of** resistance to erythromycin and clindamycin

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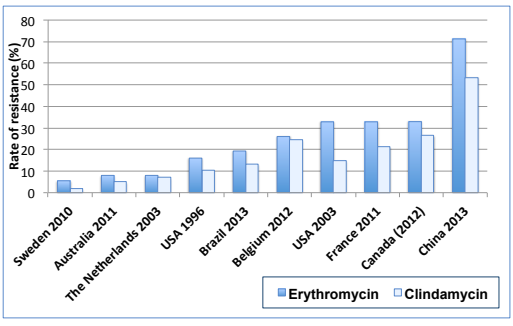
Resistance to macrolides/lincosamides Wide geographical variation of rates



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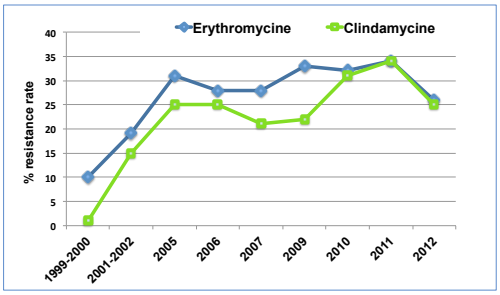
Resistance to macrolides/lincosamides on the rise (Invasive isolates of GBS Belgium 1999-2012)



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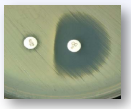
Concerns : Clinically relevant antimicrobial resistance

- Increase of resistance to erythromycin and clindamycin
  - Revised guidelines for microbiological detection of clindamycin resistance (SHC 2015)
    - Antimicrobial susceptibility testing on all GBS
    - Dtest recommended



Concerns : Clinically relevant antimicrobial resistance

- Reduced susceptibility to penicillin
  - Very few « not S » isolates recently characterized in Japan
    - Mutation in pbp genes, especially pbp2x
    - MIC= 0.25 -1 mg/L *(but higher MIC to Ceph. !)*
    - No clinical impact ?

Noriyuki Nagano et al, AAC 2008

  - Very few in the U.S., Canada
  - Possibly unrecognized by standard antimicrobial susceptibility methods
    - All labs should send to reference lab
      - Any « non-S » isolate for confirmation
      - All invasive isolates for resistance surveillance

Other concerns
Potential adverse / unintended consequences of prophylaxis

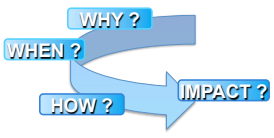
- Allergies
  - Anaphylaxis occurs but extremely rare
- Changes in incidence or resistance of other pathogens causing EOD
  - Data are complex …
  - But most studies: stable rates of « other » sepsis
- Changes in GBS antimicrobial resistance
- Impact on newborn gut microbiota

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

Van Dyke MK, Phares CR, Lynfield R et al. N Engl J Med 2009
CDC revised guidelines 2010
Poyart C, Reglier-Poupet H, Tazi et al. Emerg Infect Dis 2008
DEVANI project, unpublished data 2011



Specimen collection
Processing
Culture or non culture approach?

SCREENING FOR GBS COLONIZATION

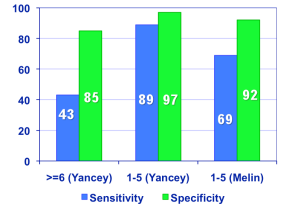
Antenatal GBS culture-based screening

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
  - Screening methods
    - Culture
      - *Procedure*
      - *Media*
    - Non-culture

Optimal time for screening
35-37 weeks gestation

Culture-based screening done 1 to 5 or ≥ 6 weeks before delivery *(Yancey, 860 cases; Melin, 531 cases)*

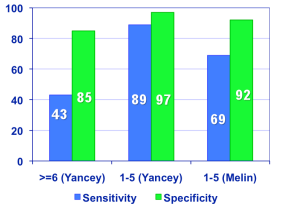


Not 100 % as colonization is dynamic

Yancey MK et al. Obstet Gynecol 1996;88:811-5

Optimal time for culture-based screening
35-37 weeks gestation

Culture-based screening done 1 to 5 or ≥ 6 weeks before delivery *(Yancey, 860 cases; Melin, 531 cases)*



Melin, 13-16% GBS Pos
PPV= 56%
NPV= 95%
or 5% False negative
or 30% of GBS pos in labor not detected with antenatal screening !

Yancey MK et al. Obstet Gynecol 1996;88:811-5

Antenatal culture-based screening: Limiting factors

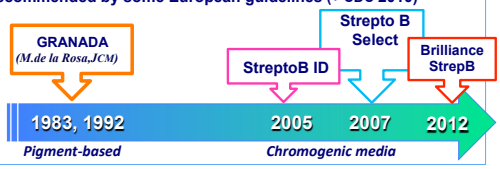
- **Positive and negative predictive values**
  - False-negative results
    - Failure of GBS culture *(reduced viability during transport, oral ATB, feminine hygiene)* or new acquisition
    - Up to 1/3 of GBS positive women at time of delivery

Need for more accurate predictor of intrapartum GBS vaginal colonization

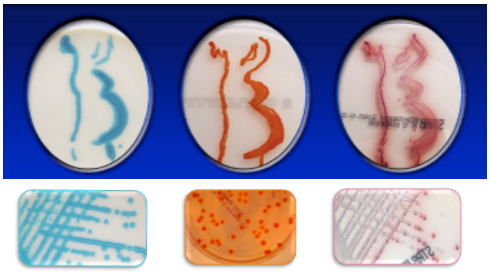
From direct plating on blood agar Evolution of culture methods

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)



Which agar or which combination?
+/- Blood agar



Workload - costs - extra-testing - non β-hemolytic GBS detection to be considered

Crucial conditions to optimize SCREENING

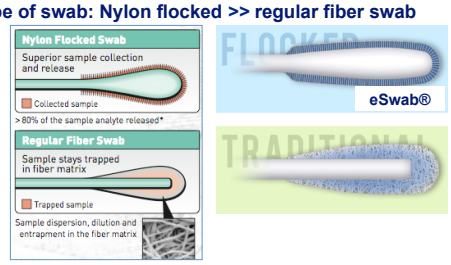
WHEN	35-37 weeks
WHO	ALL the pregnant women
Specimen	Vaginal + rectal swab(s)
Collection	WITHOUT speculum
Transport	**Transport/collection device/condition** (non nutritive medium: Amies/Stuart or Granada like tube) (type of swab)(Length and T°)
Request form	To specify prenatal « GBS » screening
Laboratory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

(CDC 2010 - Belgian SCH 2003)

Crucial conditions to optimize SCREENING

Transport-collection system & transport-storage condition

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



Crucial conditions to optimize SCREENING

Transport-collection system & storage condition

- Recommandations CDC, USA (2010)
  - Non nutritive media: Amies or Stuart without charcoal
  - Storage at 4°C or RT 1-4 days
    - Or Granada like tubes ??
- Recommandations CSS, Belgium (2003)
  - Non nutritive media: Amies or Stuart without charcoal
  - Storage maximum 48h at 4°C

ICAAC 2013
53rd ICAAC | SEPT 10-13 | Denver, CO

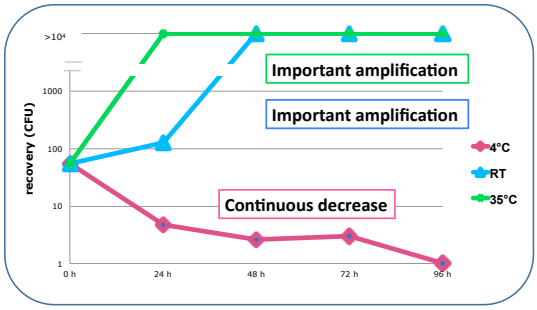
Improvement of Transport Condition of Swabs for Group B Streptococcal (GBS) Screening

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° for a few days

Use of a selective enrichment Lim broth as transport media

Results:
Recovery of GBS in Lim BD at 4°C, RT and 35°C



Transport conditions to be recommended for optimizing GBS antenatal screening
Belgian Health Superior Council, 2015

- Transport system
  - Use of a selective enrichment Lim broth with a flocked swab *(BD, Copan, bioMérieux, i.e.)*
- Transport and storage condition
  - At RT° (up to 35°C)
  - As soon as possible
    - Viability sustained at least 4 days
- Remark
  - If use of Amies or Stuart medium (non nutritive medium)
    - To be processed as soon as possible within 24 hours (max 48 h)

Antenatal culture-based screening combined with amplification molecular methods

Broth enrichment followed by amplification molecular assay

- ❑ The Xpert GBS LB assay
- ❑ The LAMP Illumigene GBS Assay

Alternative to GBS antenatal screening: intrapartum screening
Theranostic approach

Turnaround time
collect specimen at admission

Specimen Analysis "POCT" ?

Results

Optimal management of patient

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)

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%	PPV	58.3%
NPV	99.7%	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

2009	2010
Antenatal screening	Xpert GBS intrapartum screening *Performed by midwives as a POCT !!*
11.7% GBS POS	16.7% GBS POS
	Less GBS EOD & less severe

Cost neutral per delivery

Real-time PCR, very promising, BUT …

- Rapid, robust & accurate technology
- Still an expensive technology (specific equipment)
  - Cost effective ?
    - *Need for more cost-effectiveness clinical study*
      - ➔ *2014 NRC GBS - CHULg & UIA*
- 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
- Drawback: no antimicrobial result
  - In the future detection of R genes, but mixed microbiota !

Revised Belgian guidelines

(Superior Health Council, 2015)

(Neonatologists, obstetricians, microbiologists, midwives)

Main recommendentions

- Universal antenatal screening at 35-37 wks gestation
  - Lim broth as transport media
  - Selective differential culture media
  - Determination of clindamycin susceptibility *(IgE mediated penicillin allergy)*
- Universal screening at time of delivery could be used
  - IF POCT with high PPV and NPV
    - Real time PCR or other methods
    - TAT < 1 hour
  - In case of known IgE mediated penicillin allergic women
    - Determination of clindamycin susceptibility for GBS positive screening
- IAP for all GBS positive pregnant women
  - documented by antenatal testing (or intrapartum testing if performed)

Revised Belgian guidelines

(Superior Health Council, 2015)

(Neonatologists, obstetricians, microbiologists, midwives)

Main recommendentions

- Mahieu L, Langhendries JP, Cossey V, De Praeter C, Lepage P, Melin P.

  Management of the neonate at risk for early-onset Group B streptococcal disease (GBS EOD): new paediatric guidelines in Belgium.

  Acta Clin Belg. 2014 Oct;69(5):313-9.

Prevention strategy for GBS EOD

TOWARDS A EUROPEAN CONSENSUS ?

Conference held in June 2013, Florence, Italy

A European working party: Neonatologists, obstetricians, microbiologists

Representing countries
- with screening-based IAP,
- with risk-based IAP strategies
- or nothing

Towards « European Consensus »

Decision taken by the European working party

Main recommendations

- Universal screening at time of delivery
  - 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 prenatal screening in known penicillin allergic women
  - Determination of clindamycin susceptibility if GBS positive screening

Towards « European Consensus »

Decision taken by the European working party

Main recommendations

- Provisionally , for countries with antenatal screening
  - Improved antenatal screening method
    - Use of Lim broth for transportation
    - Use of selective differential media

Di Renzo GC, Melin P, Berardi A, et al
Intrapartum GBS screening and antibiotic prophylaxis: a European consensus conference.
J Matern Fetal Neonatal Med. 2014 Aug 27:1-17

Prevention of GBS EOD and LOD

Prevention of maternal diseases

VACCINE

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

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

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 Vaccines

GBS Protein-based Vaccine

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

Protein-based Vaccines

Protein	Protective Ab (in mouse)	associated serotypes
Alpha-like proteins		
Alpha	Yes	Ia, Ib et II
Alp1		Ia
Rib	Yes	III
Alp2	Yes	V, VIII
Alp3	Yes	V, VIII
Beta C protein	Yes	Ib
C5a peptidase	Yes	All
Sip (1999)	Yes	All
BPS	Yes	All

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

Protein-based Vaccines

Reverse vaccinology approach
Knowledge of complete GBS genome

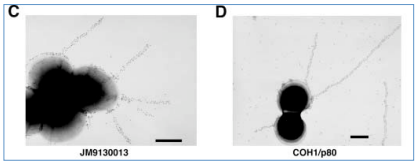
- Comparaison of genomes from 8 different GBS serotypes

D.Maione et al, Science 2006

- 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



Vaccine 31S (2013) D1–D2
Contents lists available at ScienceDirect
Vaccine
journal homepage: www.elsevier.com/locate/vaccine

Editorial

Introduction: Addressing the challenge of group B streptococcal disease

Vaccine 31S, 2013

- Introduction, *Rappuoli & Black*
- GBS Review, *Carol Baker*
- Overview GBS epidemiology, *Paul Heath*
- GBS epidemio and vaccine needs, *Melin & Efstratiou*
- GBS epidemiology in developping 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

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
- Toward a European consensus

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
    - Yes but costs, logistic, …
    - Need for more clinical and cost effectiveness trials
    - No result for clindamycin susceptibility

Thank you !