What's new in group B streptococcus screening and guidelines?

OLD & NEW TOOLS

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CONTENT

- **Introduction & burden**
  - History and historical context of perinatal GBS disease
  - Early and contemporary epidemiology
  - Pathogenesis and risk factors
- **Prevention strategies**
  - Maternal intrapartum chemoprophylaxis
    - Evolution of policies, effectiveness and concerns
    - Towards a European consensus and revised Belgian guidelines
  - Maternal immunization
- **Screening : old and new tools**
- **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

Group B streptococcal diseases in neonates

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

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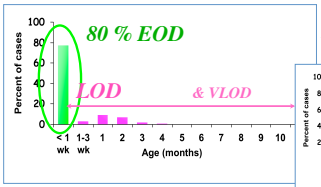
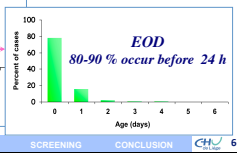


A. Schuchat, Clin Microb Rev 1998;11:497-513



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

- Maternal morbidity
  - Along pregnancy
  - Peripartum
- Serious diseases among elderly and adults with underlying diseases
  - Significant mortality

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GBS EOD vertical transmission

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

60 - 40 % → Non-colonized newborns
40 - 60 % → Colonized newborns

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GBS EOD vertical transmission

GBS colonized mothers

60 - 40 % → Non-colonized newborns
40 - 60 % → Colonized newborns

96 - 98 %
Asymptomatic

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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

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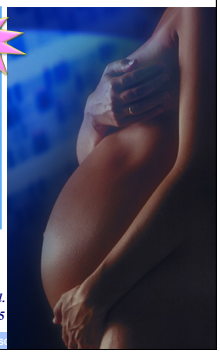
Additional Risk Factors for Early-Onset GBS Disease

- 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

Risk factors

*: No difference in occurrence either in GBS Positive or Negative women, except intrapartum fever

Lorquet S., Melin P. & al. J Gynecol Obstet Biol Reprod 2005



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

Meningitis

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

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

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

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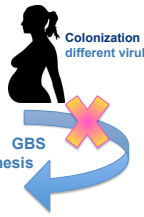
- Universal antenatal screening-based strategy
- Risk-based strategy
- No guideline

GUIDELINES FOR PREVENTION OF GBS PERINATAL DISEASE

Which prevention strategy for GBS perinatal diseases ?

- Intrapartum antibioprophylaxis
- Immunoprophylaxis
  Key strategy
  « nearly within reach »

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



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

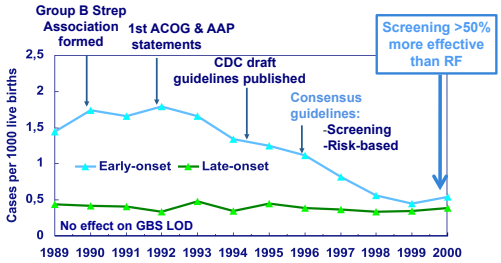
GBS pathogenesis

Preventing transmission

Intrapartum antibioprophylaxis
> 4 (2) hours before delivery

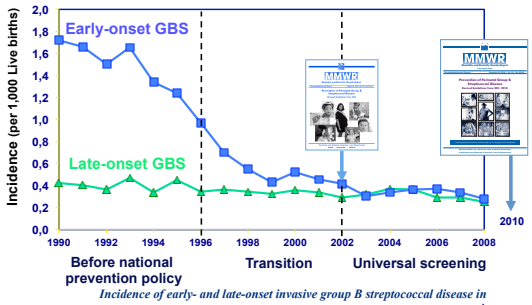
Highly effective in preventing GBS EOD *(1st clinical trials in late 80s)*

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, revision ongoing 2013
    - Germany, 1996, revised 2008
    - Switzerland, 2007
  - Risk-based strategy
    - UK, the Netherlands, Denmark
- **No guidelines**
  - Bulgaria, …

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

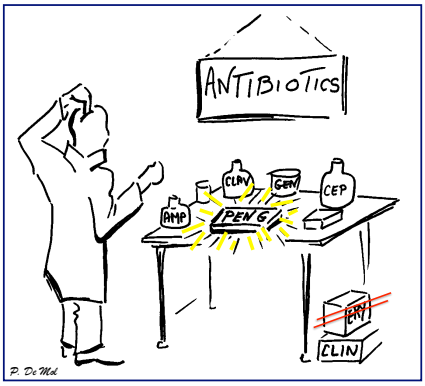
if NO

if YES

Intrapartum prophylaxis NOT indicated

Gynecologists
Obstetricians
Microbiologists
Midwives
Neonatalogists

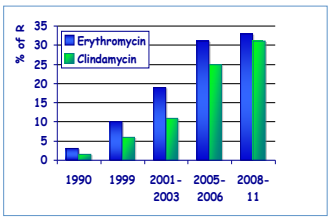
Adhesion to a common protocol is a key of success
Multidisciplinary collaboration is mandatory



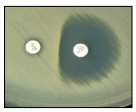
Concerns : Clinically relevant antimicrobial resistance

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

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



- Denmark 4%
- Spain 20%
- Others 15-35% or even more



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

Concerns : Clinically relevant antimicrobial resistance

- **Increase of** resistance to erythromycin and clindamycin
- **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
    - No clinical impact ?

Noriyuki Nagano et al, AAC 2008

  - **Very few in the U.S., Canada**
  - **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**

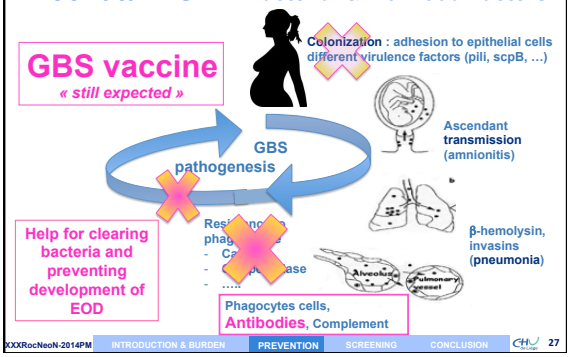
Remaining burden of GBS EOD
Missed opportunities

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

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



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

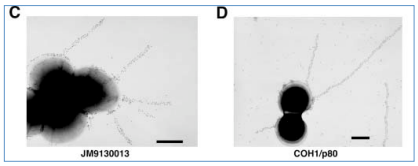
- Comparaison of genomes from 8 different GBS serotypes

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

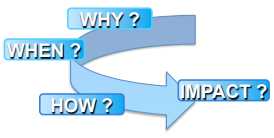


Vaccine 31S (2013) D1–D2
Contents lists available at ScienceDirect
Vaccine
journal homepage: www.elsevier.com/locate/vaccine

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



Specimen collection
Processing
Culture or non culture approach?

SCREENING FOR GBS COLONIZATION

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)

Antenatal GBS culture-based screening

Goal of GBS screening

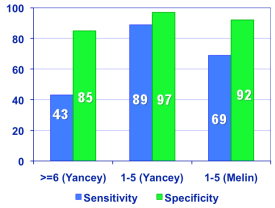
To predict GBS vaginal (rectal) colonization at the time of delivery

- **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)*



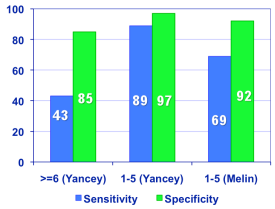
Not 100 % as colonization is dynamic

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**

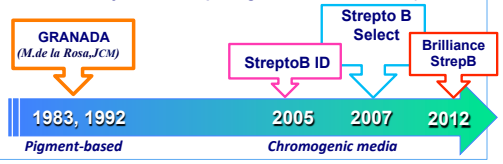
Need for more accurate predictor of intrapartum GBS vaginal colonization

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**

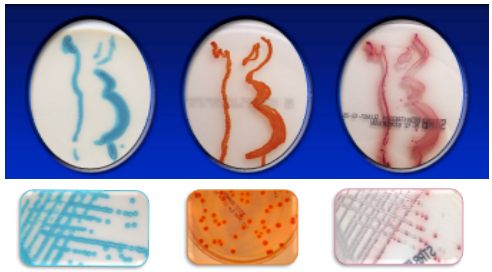
Use of differential agar media

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

Standard procedure

Vagino-rectal swab or
Vaginal & rectal swabs

Inoculate swab(s) in 1 Lim broth

LIM broth

Overnight And subculture following — *at 35-37°C to one of the media*

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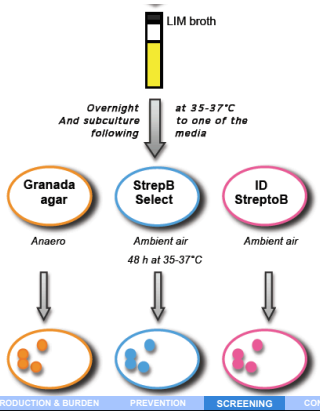

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Crucial conditions to optimize SCREENING

- 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)

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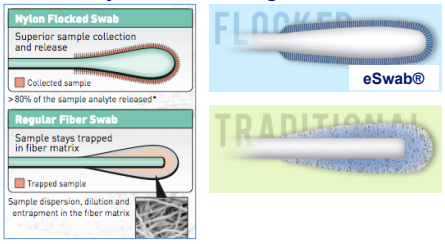
Crucial conditions to optimize SCREENING

Transport-collection system & transport-storage condition

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



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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**

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Crucial conditions to optimize SCREENING

Transport-collection system & storage condition

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

Rosa-Fraile M. et al. J Clin Microbiol 2005, 43: 928-930

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.

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

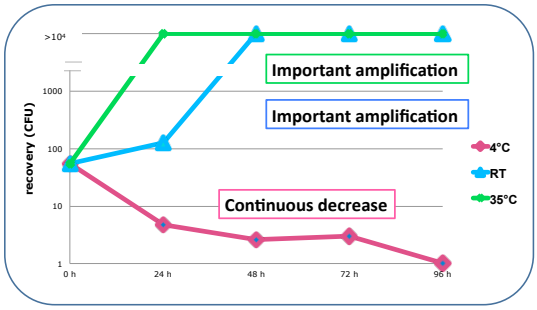
IMPROVEMENT OF TRANSPORT CONDITION OF SWABS FOR GROUP B STREPTOCOCCAL (GBS) SCREENING

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, 2013

- 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)

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) (can be performed as a POCT)

The Xpert GBS™ Advantage: Simplicity
- Fully automated process reduces handling time to just minutes
- Random access for flexibility and workflow optimization
- Rapid results to improve patient management
- Fully integrated reagent and instrument system for accuracy and reproducibility

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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%

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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

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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 !

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Revised Belgian guidelines

(Superior Health Council, expected autumn 2014)

(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 *(if IgE mediated penicillin allergy)*
- Universal screening at time of delivery can 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)

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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

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Towards « European Consensus »

Decision taken by the European working party

Main recommendentions

- **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 recommendentions

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

The Journal of Maternal-Fetal & Neonatal Medicine

Intrapartum GBS screening and antibiotic prophylaxis: a European Consensus Conference.

Journal:	*The Journal of Maternal-Fetal & Neonatal Medicine*
Manuscript ID:	DJMF-2014-0242
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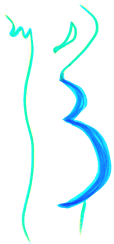
Complete List of Authors:	Di Renzo, Gian Carlo; University Hospital of Perugia, Dept. of Ob/Gyn and Centre for Perinatal Medicine Melin, Pierrette; University Hospital of Liege, Department of Clinical

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**

Thank you !