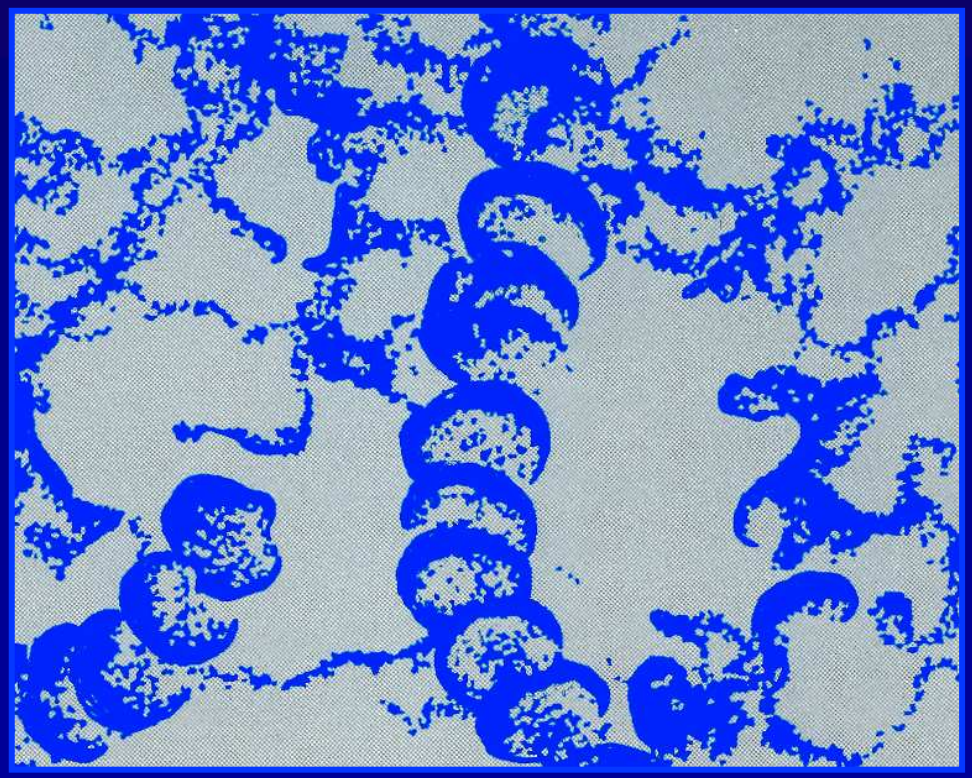
Pneumococci & streptococci
Testing and clinical implications of susceptibility changes



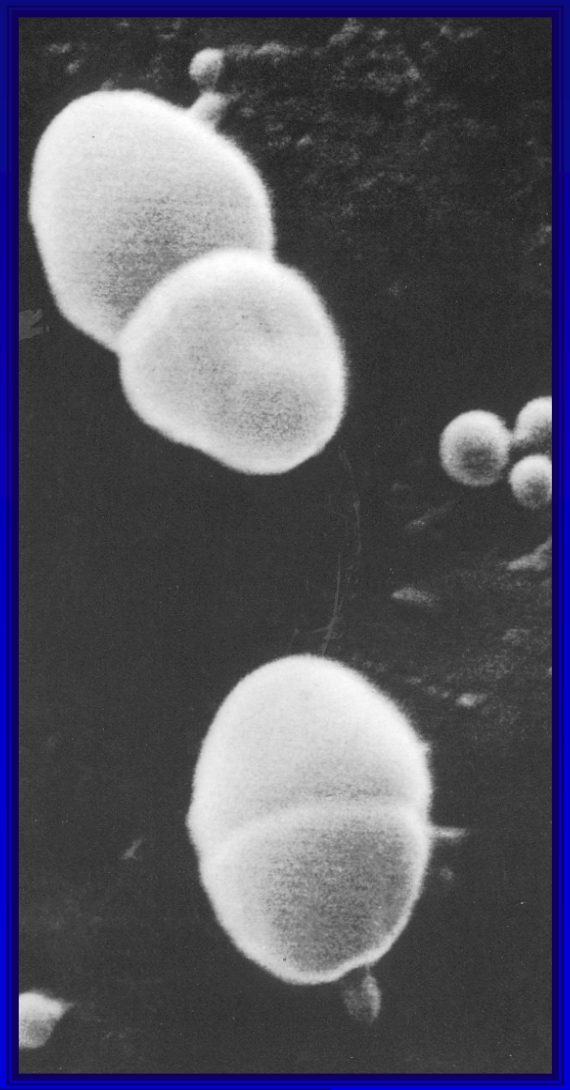
Pierrette Melin

Medical microbiology
University Hospital
of Liege, Belgium

Key questions

- What is the clinical importance of streptococci ?
- What are their resistances to antimicrobial agents ?
- What are the clinical implications for the clinical microbiology lab ?

STREPTOCOCCUS PNEUMONIAE



- Lower respiratory tract infections, pneumonia
  - the single most important bacterial pathogen
- Otitis media
  - Main cause in children
  - Hearing impairment if reccurrence
- Meningitis
  - Life-threatening (children, elderly)
  - Neurologic sequelae
- Sepsis

The challenging pathogens

In hospital

- *S.aureus* (MRSA, GISA, VRSA)
- *Enterococci* (GRE)
- *Enterobacteriaceae* (ESBL, carbapenemase, FQ)
- MDR-*P.aeruginosa*
- MDR-*Acinobacter baumanii*

In community

- MDR-*S.pneumoniae*
- CA-MRSA
- *Salmonella* (ESBL, FQ)
- *Campylobacter* (FQ, macrolides)
- Helicobacter pylori
- MDR-*M.tuberculosis*

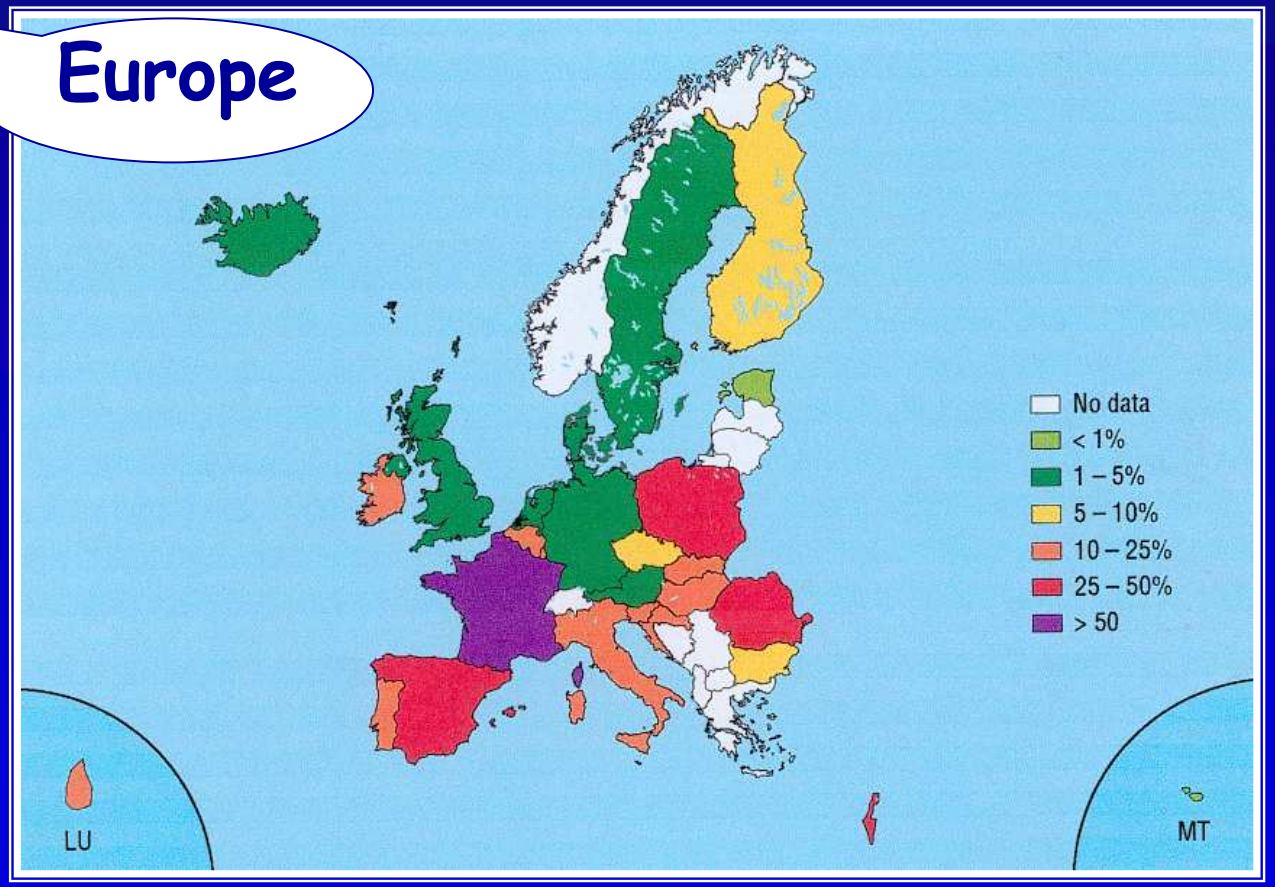
STREPTOCOCCUS PNEUMONIAE

- Emergence of antimicrobial resistance
  - Treatment failures
  - Increased morbidity/mortality
  - Increased duration of diseases
  - Costs

Key role for laboratory :
To recognize « Resistant » organisms !!

Global antibiotic resistance in *S.pneumoniae*

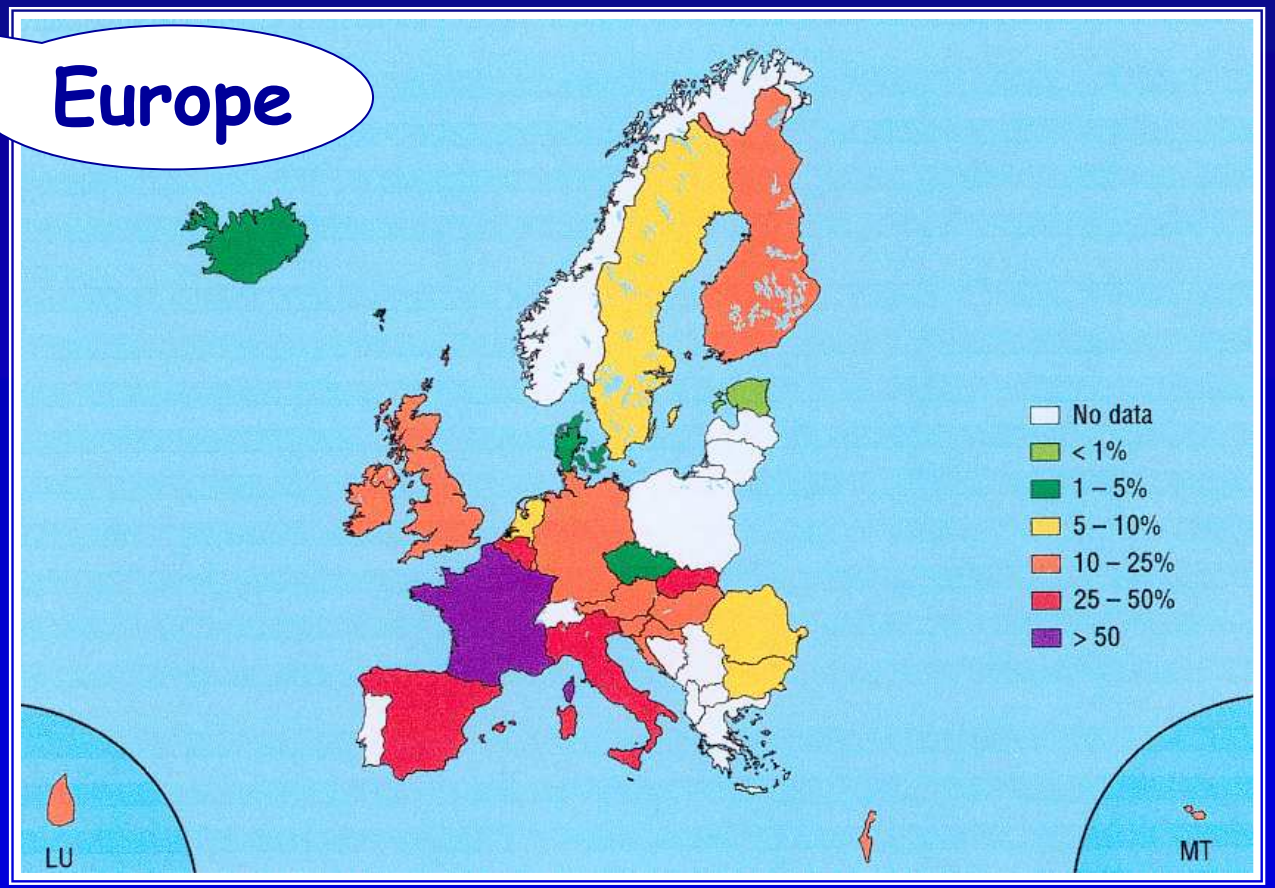
Non-S to penicillin



Invasive isolates non-S to penicillin in 2002 - EARSS

Global antibiotic resistance in *S.pneumoniae*

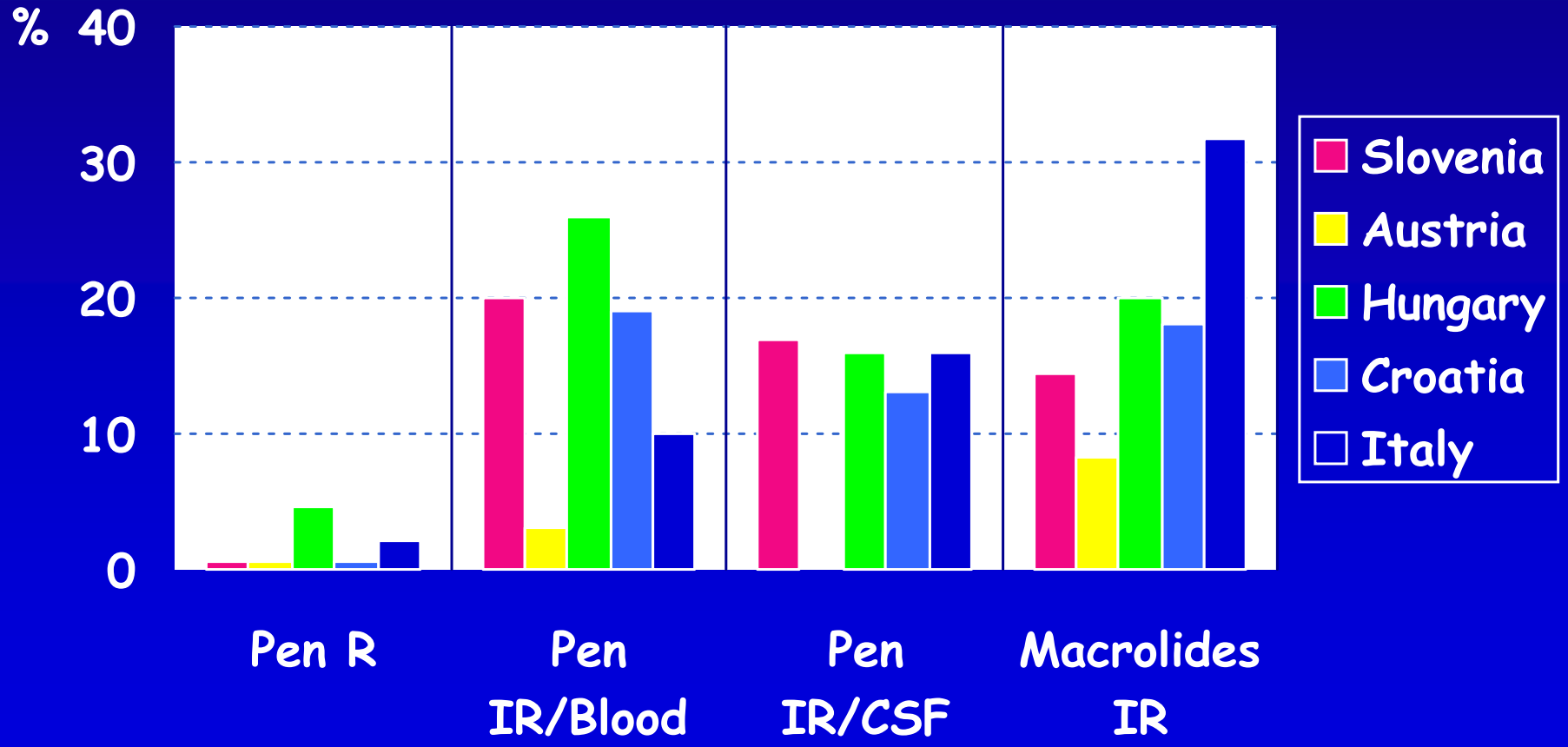
Non-S to erythromycin



Invasive isolates non-S to erythromycin in 2002 - EARSS

Antibiotic resistance (%) in *S.pneumoniae* (Blood/CSF)

EARSS 1999-2002



S.pneumoniae: Mechanisms of resistance

- Resistance to Penicillin
  - Modification of Penicillin Binding Proteins
    - Qualitative & quantitative alteration of the targets
    - Transformation and/or stepwise chromosomally mediated mutations; genes < oral streptococci
    - Decreased susceptibility to all β-lactams
      - Ceph. III and amoxicillin less affected
  - Clonal spread AND local emergence
  - 50 % co-resistance to other agents

S.pneumoniae: Mechanisms of resistance

- **Resistance to Macrolides**
  - Alteration of ribosomal methylase (*ermB* gene)
    - Constitutive or inducible (D test)
    - MLS_B phenotype
  - ATP-dependant efflux pump (*mefE* gene)
- **Resistance to fluoroquinolones**
  - Chromosomal mutations of gene encoding for
    - Topoisomerase IV (*parC*, *parE*)
    - DNA gyrase (*gyrA*, *gyrB*)
  - Efflux

Susceptibility/Resistance testing methods

- Disk diffusion
  - Penicillin : NOT reliable !!
  - Oxa screen
    - NCCLS 1 µg disk (S >= 20 mm)
    - SFM 5 µg disk (S >= 26 mm)
    - No dicrimination between I and R isolates
    - False R and a few false S

Need for true MICs

S.pneumoniae: SIR and penicillin

- S
  - Susceptibility (MIC <= 0.064 mg/L) correlates with clinical outcome with standard dosages
- I
  - Intermediate susceptibility (MIC <= 0.12 - 1 mg/L) requires a high penicillin dose for clinical outcome
- R
  - Resistance (MIC >= 2 mg/L) necessitates alternative therapy

Susceptibility/Resistance testing methods

- MICs in routine
  - Automated microdilution system
    - Vitek 2 (BioMérieux)
    - Risk of underestimation of R
  - Etest
    - The easiest and affordable
    - Detects subtle decreases in S
    - Validated, « reference method »
    - Directly on Gram positive CSF

S.pneumoniae AST algorithm

Respiratory

or

MIC/Etest
Pen G
Amoxicillin
Cefotaxime*

Disc
Erythro
(Clinda.)
SXT
New FQ

If
< 20

Disc
Oxacillin 1µg
« S >= 20 mm »

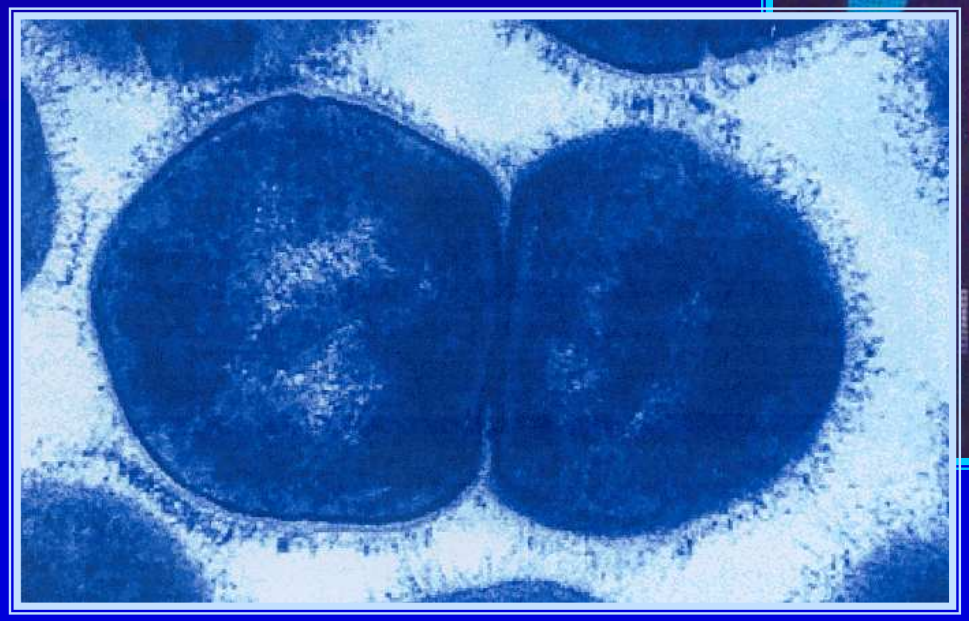
Erythro
(Clinda.)
SXT
New FQ

Blood or sterile site

MIC/Etest
Pen G
Cefotaxime*
Meropenem
Vancomycin
New FQ if non-CSF

* Or Ceftriaxone

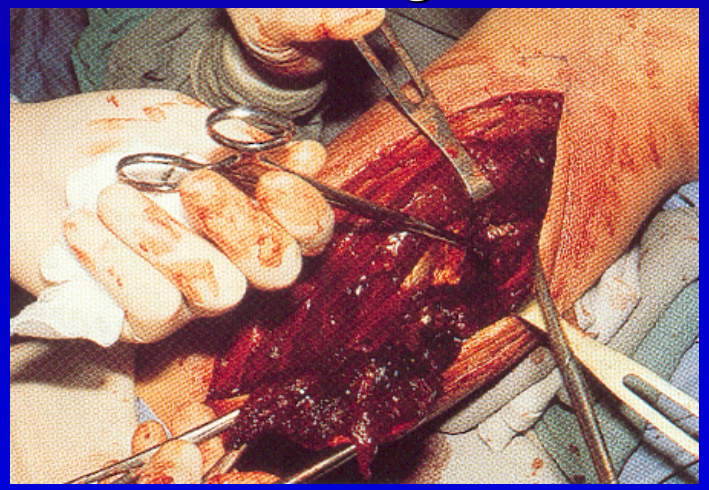
Streptococcus pyogenes



Streptococcus pyogenes

- Pharyngitis and asymptomatic carriage (1-70%)
- Scarlet fever
- Erysipelas
- Streptococcal pyoderma (Impetigo Contagiosa)
- Lymphangitis
- Cellulitis
- Necrotizing fasciitis
  - Myositis, pneumonia
- STSS
- Puerperal sepsis
- Endocarditis
- Postinfectious sequelae
  - Rheumatic fever, poststreptococcal glomerulonephritis

The « flesh eating » bacteria



Streptococcus pyogenes

- Therapeutic options
  - Penicillin,
  - Alternatives may include
    - Macrolides and certain cephalosporins;
    - Vancomycine for pen-allergic patients with serious infections

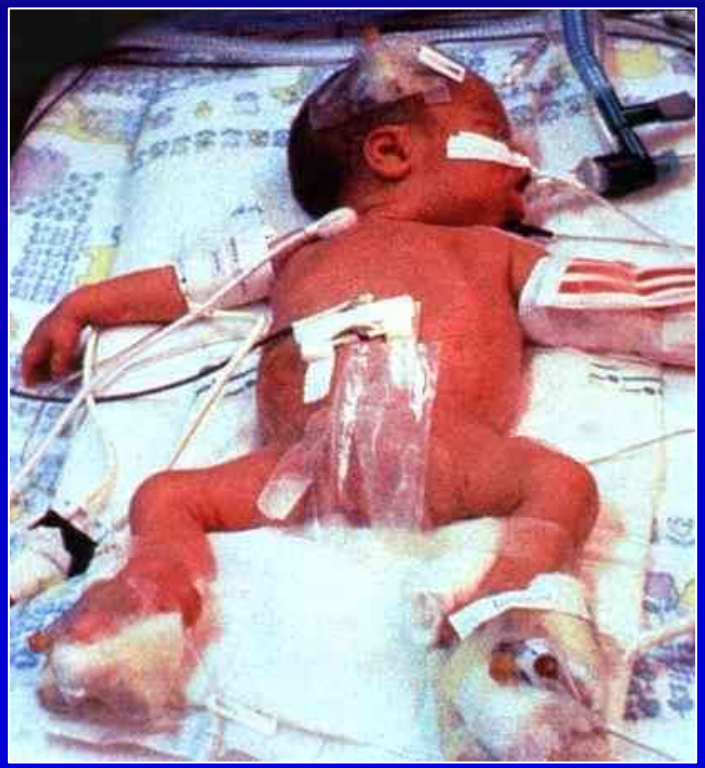
Streptococcus pyogenes

- Penicillin
  - GAS remain 100 % Sensitive
  - = drug of choice
  - S-testing not necessary
- But, reduced efficacy in severe GAS infection
  - High inoculum
  - Decrease in expression of Penicillin Binding Protein (PBP) by GAS in stationary phase

Streptococcus pyogenes

- In severe infections: Clindamycin more effective
  - Not affected by inoculum or stationary phase
  - Inhibits synthesis of bacterial toxins
  - Facilitates phagocytosis of GAS by inhibiting synthesis of M protein
  - Suppresses PBP Synthesis ⇘ degradation
  - Longer post-antibiotic effect/penicillin
- **Resistance to Macrolides** (+/- 10%)
  - Alteration of ribosomal methylase (*erm*B gene)
    - MLS_B phenotype, constitutive
  - Efflux pump (*mefA* gene)

Streptococcus agalactiae



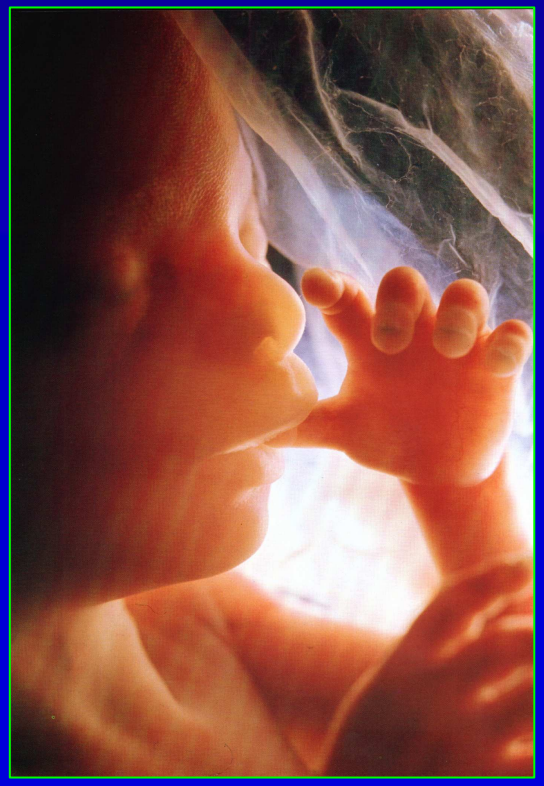
- Asymptomatic colonization
- Neonatal infections
  - EOD & LOD
- Infections during pregnancy
- Adult's infections

Risk factors for neonatal EOD

- Vaginal Colonization
- Obstetrical risks:
  - Prolonged rupture of membranes, Prematurity, Intrapartum fever
- GBS bacteriuria
- Previous infant with GBS infection
- Immunologic risks:
  - Low level specific IgG, etc

How could we prevent neonatal EOD ?

Intrapartum Antibio-prophylaxis



- Gyneco-Obst.
- Pediatrician
- Labo
- Labor & delivery ward

Intrapartum antibio-prophylaxis

(CDC 2002, Belgian HC 2003)

- **Penicillin G**
  - *5 millions U, IV initial dose, + 2,5 millions U IV every 4 hours until delivery*

- **Ampicilline**
  - *2 g IV initial dose, + 1 g IV every 4 h until delivery*
  - **Acceptable** alternative, **but** extended spectrum, may select R strains

Intrapartum antibio-prophylaxis
In case of penicillin-allergy

(CDC 2002, Belgian HC 2003)

- *Patient at low risk for anaphylaxis*
  - Cefazolin
- *Patient at high risk for anaphylaxis*
  - Clindamycin

Therapeutic options

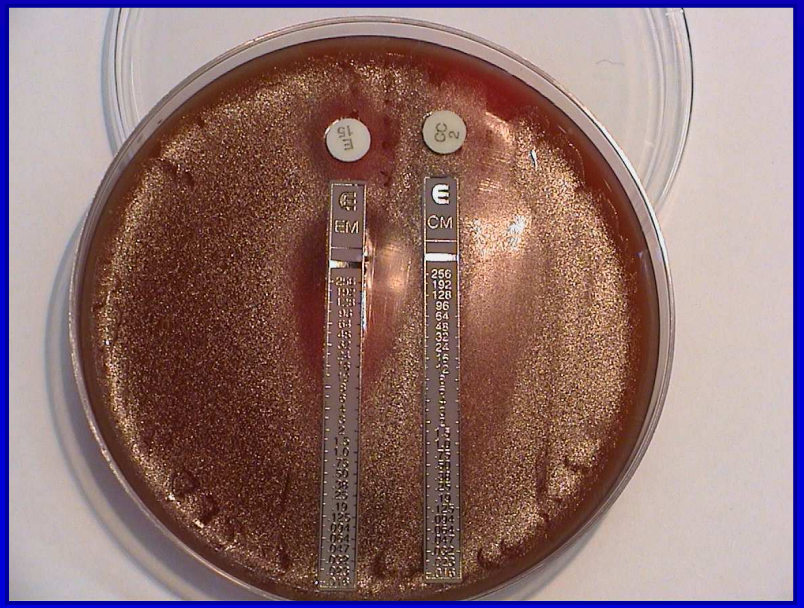
- Empiric
  - Ampicillin + aminoglycoside
- When confirmed
  - Penicilline + aminoglycoside (max 3-5 days)
  - Then Penicillin for 10 to 28 days

GBS susceptibility profile

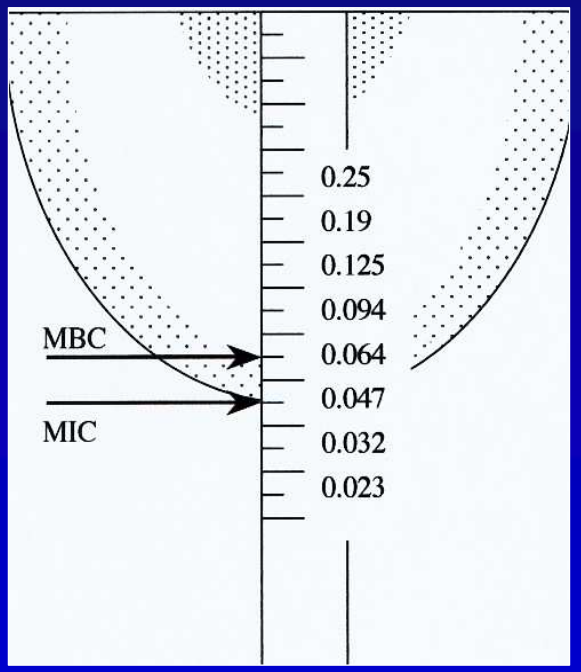
(Belgium)

15 à 30 %, en ↗

50 % $cMLS_B$
30 % $iMLS_B$
20 % M



GBS Penicillin susceptibility and tolerance



No tolerance was observed :

79.3 % of isolates had an MBC/MIC = 1

19 % of isolates had an MBC/MIC = 1.5

1.7 % of isolates had an MBC/MIC = 2

Streptococcus « viridans »

- Bacteremia
- Endocarditis
- Nosocomial infections

β-hemolytic streptococci and streptococcus « viridans »

- Tolerance to β-lactams
  - High MBCs despite low MICs
- Progressive decreases in S to Penicillin in β-hemolytic streptococci
- Pen R in viridans group
- Increasing macrolide, trimeth/sulfa and FQ R

MICs needed for serious infections or critical patients

β-hemolytic streptococci and streptococcus « viridans »

- Disc diffusion
  - Penicillin and FQ
    - Only for β-hemolytic streptococci
- Microdilution and automated systems
  - Growth supplement, CO2, etc
  - Not adapted, except for GBS
- Etest
    - Easy, affordable, convenient
    - Media and atmosphere adapted
    - Detects subtle decreases in S
    - Directly on Gram positive CSF

β-hemolytic and viridans streptococci AST algorithm

Blood or sterile site or « critical » patient

GAS, GBS, GCS & GGS large colonies

Disc
Pen G*
(Cefotaxime)**
Erythromycin
(Clindamycin)
(New FQ)

MIC/Etest
Pen G*
(Cefotaxime)**
Erythromycin
Clindamycin
Vancomycin
(New FQ if non-CSF)

* Pen S = β-lactams S
** or Ceftriaxone