RESISTANCE TESTING CHALLENGES
AND SOLUTIONS
WITH EMPHASIS ON PATIENT CARE

Pierrette Melin
Medical microbiology, University hospital of Liege, Belgium
Clinical Microbiology Laboratories
Current Challenges

Specimen collection

RESISTANCE:
- Detection / method-dependant
- Level of in vitro expression
- Predictive value
- Microbiological & therapeutic interpretations

Patient’s optimized management

Identification
AST

Specimen Analysis: Relevant Pathogens

Cost effective & timely
Decreasing resources!
A few years of wonder and then ...

INCREASE
OF FAILURES

Very high levels
of Resistance

emergence + spread + escalation

« Difficult to treat » patients
Some of the XXI\textsuperscript{st} century-Challenges in infectious diseases

- **Microorganisms**
  - Increasing antimicrobial Resistance
  - Resistance determinant
  - « Pathogens » evolution

- **Patients and medical improvements**
  - Critical care
  - Immuno-compromised
  - Nosocomial infections
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*
Appropriate therapy saves lives

- Early inappropriate therapy
  - Increase of mortality in severe infection
- Infection with antibiotic-R bacteria
  - Increase of risk of inappropriate therapy
- Antibiotic-R organisms
  - More commonly associated with inadequate therapy
- Streamlining therapy to narrow spectrum drug
  - Saving costs

Appropriate therapy saves lives

- **Target empiric therapy** to likely pathogens,
  - based on hospital, regional, specific epidemiology.

- **Target definitive therapy** to known pathogens,
  - based on accurate, quantitative S results
Who / What do we treat?

- Patient?
- Disease?
- Bug?
Main goals of anti-infective therapy

- Clinical cure of patients
- Eradicating the pathogens
- To avoid development of resistance
- To avoid transmission

By giving «supposedly» or proven effective antibiotic

Choices often based on results in terms of «S» or «Non S»
SIR, bacteria are not simply « S » or « Non S »

- Varies over a wide range
- May be quantified by MIC
- May result in overdosing or underdosing
  - Risk of R development
  - Unnecessary costs
  - Increase morbidity/mortality
- Standard definition of Resistance
ACCURATE DETECTION of clinically & epidemiologically significant R-determinants

COST-EFFECTIVE to patient care & infection control
Are AST results clinically relevant & reliable?
Therapeutic predictive values

- Many variables affecting results
  - Standardization
  - *In vitro // in vivo*?
- Current breakpoints
  - S, I, R
    - NCCLS, BSAC, SFM, Japanese, ....
Different interpretative criteria

*P. aeruginosa* ATCC 27853, same MIC yet different categories
Are AST results clinically relevant - reliable?
Therapeutic predictive value

- Many variables affecting results
  - Standardization / in vivo?
- Current breakpoints
  - S, I, R
    - NCCLS, BSAC, SFM, Japanese, ...
  - Safety or efficacy?
  - Evolution // pharmacology-pharmacodynamics?
    - β-lactams, aminoglycosides, FQ
- Expression of resistance? Detection?

ART vs. AST
**MIC determinations and PK/PD model**

- **Ser. Conc**
- **PEAK**
- **Cmax**
- **AUC**
- **TIME > MIC**
- **MIC**
- **Time**

טלון:
- **MIC**
- **PK/PD**
- תוצאות

**AUC**

**TIME > MIC**

**MIC**
**Practical recommendations for PK/PD-optimized therapy**

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B-lactams</strong></td>
<td>- remain &gt; MIC for at least 50% of the time</td>
</tr>
<tr>
<td></td>
<td>- Fractionate the dose</td>
</tr>
<tr>
<td><strong>Aminoglycosides</strong></td>
<td>- Obtain Cmax/MIC ratio of at least 8</td>
</tr>
<tr>
<td></td>
<td>- Administer once daily</td>
</tr>
<tr>
<td><strong>Fluoroquinolones</strong></td>
<td>- Obtain a 24-H AUC/MIC ratio &gt; 125</td>
</tr>
<tr>
<td></td>
<td>- Obtain Cmax/MIC ratio of at least 8</td>
</tr>
<tr>
<td></td>
<td>- Do not overfractionate the daily dose</td>
</tr>
<tr>
<td></td>
<td>- Consider lowering breakpoints for older FQ</td>
</tr>
<tr>
<td><strong>Etc.</strong></td>
<td></td>
</tr>
</tbody>
</table>
**AST methods routinely used in Belgium (E. faecium EQC-ISP 2003)**

- **« Disk » diffusion**
  - Paper discs: 25%
  - Rosco tablets: 50%

- **« MIC » Automated system**
  - Vitek 1: 7.5%
  - Vitek 2: 17%

- **Real MIC Etest**
  - Vancomycin: 25%
## AST methods routinely used

<table>
<thead>
<tr>
<th></th>
<th>D. Diffusion</th>
<th>Vitek/Phoenix</th>
<th>E test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Results</strong></td>
<td>S, I, R</td>
<td>« MIC »</td>
<td>Real MIC</td>
</tr>
<tr>
<td><strong>Cost (Invest./fct)</strong></td>
<td>Low/Low ++</td>
<td>High/high</td>
<td>Low/very high</td>
</tr>
<tr>
<td><strong>Flexibility</strong></td>
<td>Not for fastidious, ...</td>
<td>Workload, TAT, quality</td>
<td>++</td>
</tr>
<tr>
<td><strong>Pro &amp; Contra</strong></td>
<td>False S // Breakpoints</td>
<td>Reproducibility, Software expert</td>
<td>All kinds of organisms, even slow growing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not for +/- fastidious, ...</td>
<td>Large range of MICs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Black box</td>
<td>Time consuming</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R expression ?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limited range of MICs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Vitek**
- Phoenix
- D. Diffusion

**E test**
- **S, I, R**
- **Low/Low**
- **++**
- **Not for fastidious, ...**
- **False S // Breakpoints**
To prevent antimicrobial R = to treat infections effectively

- Detection of Resistance
- Target optimal therapy
  - Choice of the most potent drug in class
  - Giving optimal regimen
    - To maximise effect
    - To enhance bacterial eradication
    - To minimise development of R
- Strategies using PK/PD parameters

Real MIC = one necessary component !!
Improvement expected for clinical microbiology lab.

- Detection of resistance
- Determination of true MICs
- To be cost effective
  - To define clinical circumstances requiring MIC
  - To identify organisms requiring MIC
  - To define organisms, phenotypes or clinical circumstances requiring specific method for detection of R
Clinical circumstances worthy of MICs

- **Patients**
  - ICU or other high risk patients

- **Infections**
  - Endocarditis
  - Meningitidis
  - Cystic fibrosis, other chronic infections, sterile site infections
  - Serious nosocomial infections

*Versus*

SIR adequate for trivial uncomplicated infections
Treatment of streptococcal endocarditis

- **MIC < 0.1 mg/L**
  - Penicillin G for 4 weeks

- **MIC 0.1-0.5 mg/L**
  - Penicillin + gentamicin 2 weeks; penicillin 2 weeks

- **MIC > 0.5 mg/L**
  - Penicillin + gentamicin for 4-6 weeks
Organisms or type of R to detect worthy of Etest MICs

R proned, invasive, virulent

- *S. pneumoniae*
- *N. gonorrhoeae*
- Fastidious bacteria: NF GNB, GPB, etc
- Anaerobes
- Opportunist with no defined interpretative criteria
- Yeasts, fungi
- Confirmation / Detection of R
  - Penicilline (Pneumo)
  - Glycopeptides (staphylo, enterococci)
  - Oxacilline/SA
  - ESBLs, metallo-BLs
Enterococci AST algorithm

Urine, others

- Disc
  - Ampicillin
  - Vancomycin
  - FQ
  - Nitrofurantoin

Blood or sterile site

- Etest/MIC
  - Ampicillin
  - Teicoplanin
  - Vancomycin
  - HL Gentamicin
  - HL Streptomycin

VA<sup>1</sup> or R

VA<sup>R</sup>

Etest primary
- Ampicillin
- Vancomycin

VA<sup>R</sup>

Etest/MIC secondary
- Rifampicin
- Chloramphenicol
- Minocycline
- Linezolid - Synercid
Staphylococci AST algorithm

- **S.aureus**
- **ICU, critical specimen**
- **CNS, urines**

**Vitek**

**MIC Etest**

- **Unusual results**

**Vancomycin I**
- or
- **MIC > 2**
- Or **Teico I / MIC > 4**

**Disc diffusion**
Gram positive Bacilli AST algorithm

Sterile site, pure culture
Multiple positive blood cultures

Corynebacterium sp

Bacillus sp

Etest
Penicillin
Cefotaxime
Vancomycin
FQ

Etest
Penicillin
Clindamycin
Vancomycin
FQ