Antibiotic resistance

- why?
- mechanisms
- Belgian situation (as an example)

With the support of Wallonie-Bruxelles-International
Antibiotic resistance: why?

A simple application of Darwin’s concepts ...

Selection pressure → gene → enzyme / nucleoprotein → function
Antibiotic resistance: why?

A simple application of Darwin’s concepts …

to a highly changeable material

- typical infectious foci contain as much as $10^6 - 10^9$ organisms
- most bacteria are VERY quickly (20 min…) multiplying with a high level of errors ($10^{-6} - 10^{-8}$)
- pathogenic bacteria easily exchange genetic material

Selection pressure

Rapid acquisition and dissemination of resistance determinants
Antibiotic resistance: why?

Gene

Enzyme / nucleoprotein

Function

Resistance ↪ if
• High consumption and
• Inappropriate use

No selection pressure

No antibiotic
Antibiotic resistance: why?

- Resistance ♦ if
  - High consumption
  - Inappropriate use

High and inappropriate antibiotic consumption;
A lot of surviving bacteria
A simple experiment …

Exposure of E. aerogenes to anti-Gram (-) penicillin (temocillin) to 0.25 MIC for 14 days with daily readjustment of the concentration based on MIC détermination

<table>
<thead>
<tr>
<th>Strains</th>
<th>Initial</th>
<th>TEM-Exposed</th>
<th>Revertant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC (mg/L)</td>
<td>MIC (mg/L)</td>
<td>MIC (mg/L)</td>
</tr>
<tr>
<td></td>
<td>TEM</td>
<td>FEP</td>
<td>MEM</td>
</tr>
<tr>
<td>2114/2 c</td>
<td>8</td>
<td>2</td>
<td>0.25</td>
</tr>
<tr>
<td>2502/4 c</td>
<td>8</td>
<td>2</td>
<td>0.125</td>
</tr>
<tr>
<td>3511/1 c</td>
<td>32</td>
<td>2</td>
<td>0.125</td>
</tr>
<tr>
<td>7102/10 d</td>
<td>512</td>
<td>32</td>
<td>1</td>
</tr>
</tbody>
</table>

a figures in bold indicate values > the R breakpoint for Enterobacteriaceae (EUCAST for MEM [8] and FEP [4]; BSAC and Belgium for TEM [16])
b dot blot applied with antiOmp36 antibody; signal quantified for grey value after subtraction of the signal of a porin-negative strain (ImageJ software); negative values indicate a signal lower than the background
c ESBL TEM 24 (+) ; d ESBL (-) and AmpC (+) [high level] ; e Intermediate (I) according to EUCAST

Nguyen et al., presented at the 8th ISAAR, Seoul, Korea, 8 April 2011
A simple experiment …

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Nguyen et al., presented at the 8th ISAAR, Seoul, Korea, 8 April 2011

sub-MIC concentrations create resistance!
Thus, you need to do something …

• "HIT HARD & HIT FAST ?"

Paul Ehrlich:
‘Frapper fort et frapper vite’ (Hit hard and early) –
Address to the 17th International Congress of Medicine, 1913
PK /PD and resistance in Europe in 1999

"Inadequate dosing of antibiotics is probably an important reason for misuse and subsequent risk of resistance.

A recommendation on proper dosing regimens for different infections would be an important part of a comprehensive strategy.

The possibility of approving a dose recommendation based on pharmacokinetic and pharmacodynamic considerations will be further investigated in one of the CPMP* working parties…"

* Committee for Proprietary Medicinal Products – European Medicines Agency
Antibiotic resistance: the PK/PD way

Resistance ↑ if
• High consumption
  and
• Inappropriate use

Appropriate dose of antibiotic;
No surviving bacteria
Antibiotic resistance: mechanisms

1. « fighting » strategy

Wild strain

Antibiotic inactivation (biotransformation)

- Antibiotic inactivation
  - Inactive antibiotic
  - Active antibiotic

- Target
- Porin
- Modified antibiotic
- Degradation enzyme

• β-lactamases
  (S. aureus, H. influenzae, E. coli, P. aeruginosa, …)
• aminoglycoside-inactivating enzymes
  (enterobacteriaceae)
• macrolide-inactivating enzymes
  (E. coli)
Antibiotic resistance: mechanisms

2. « escaping » strategy

- **Wild strain**
- **Target modification**

- **Antibiotic**
- **Target**
- **Porin**

- **Altered target**

- **Active antibiotic**
- **Useless antibiotic**

- **Quinolone target mutation**
  (GyrA et ParC subunits of the enzymes responsible for ADN supercoiling/decoiling)
  (S. aureus, S. pneumoniae, P. aeruginosa, …)

- **Ribosome methylation at the site of macrolides binding**
  (S. aureus, S. pneumoniae)

- **Mutation of PBP (target for β-lactams)**
  (S. aureus [= MRSA !], S. pneumoniae)
Antibiotic resistance: mechanisms

3. «avoiding» strategy

Wild strain  Alternative target or multiplication of the target

- production of an altered peptidoglycan not recognized by glycopeptides (enterococci, …)
- production of a thicker cell wall, saturating glycopeptide binding (S. aureus [VISA])
Antibiotic resistance: mechanisms

4. « elimination » strategy

Wild strain → impermeabilization → Reduced amount Of antibiotic

- Active antibiotic
- Modified porin
- mutation of the OprD porin reducing the penetration of various antibiotics in *Pseudomonas aeruginosa*
Antibiotic resistance: mechanisms

4. « elimination » strategy

Wild strain

impermeabilization

Active antibiotic

Reduced amount Of antibiotic

- mutation of the OprD porin reducing the penetration of various antibiotics in *Pseudomonas aeruginosa*

- responsible for « intrinsic » resistance of *P. aeruginosa* to a large number of antibiotics

antibiotic

target

porin

Modified porin
Antibiotic resistance: mechanisms

4. « elimination » strategy

- overexpression of wide spectrum efflux pumps conferring cross-resistance to a large number of antibiotics in *Pseudomonas aeruginosa* and *E. coli*
- overexpression of narrow spectrum pumps conferring resistance to a given class of antibiotics in *S. aureus* and *S. pneumoniae*
Antibiotic resistance: mechanisms

4. « elimination » strategy

- **Wild strain**
- **Efflux pump**
  - Overexpression of wide spectrum efflux pumps conferring cross-resistance to a large number of antibiotics in *Pseudomonas aeruginosa* and *E. coli*.
  - Overexpression of narrow spectrum pumps conferring resistance to a given class of antibiotics in *S. aureus* and *S. pneumoniae*.

**Active antibiotic**

**Reduced amount of antibiotic**

**Efflux pump**

- Responsible for « intrinsic » resistance of *P. aeruginosa* to a large number of antibiotics.
Antibiotic transport through bacterial membranes

Gram(+)  
- Antibiotic transport
- Cytoplasmic membrane
- Transporter: MFS, RND, ABC, MATE

Gram(-)  
- Antibiotic transport
- Pore
- Porin
- Outer membrane
- Periplasmic space
- Cytoplasmic membrane
- Transporter: MFS, RND, ABC

## Antibiotic efflux in Gram (+)

<table>
<thead>
<tr>
<th>organism</th>
<th>family</th>
<th>pump</th>
<th>antibiotic</th>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td>β-lactams</td>
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<td>Fluoroquinolones</td>
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<td>Macrolides</td>
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<td>Sulfamides</td>
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<td>S. aureus</td>
<td>ABC</td>
<td>MsrA</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>NorA</td>
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<td></td>
<td></td>
<td>TetK-L</td>
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<td>S. pneumoniae</td>
<td>MSF</td>
<td>MefA</td>
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<td></td>
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<td>MefE</td>
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<td></td>
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<td>TetK-L</td>
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## Antibiotic efflux in Gram (-)

<table>
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<th>antibiotic</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>β-lactams</td>
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<tr>
<td><strong>E. coli</strong></td>
<td>ABC</td>
<td>MacAB-TolC</td>
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</tr>
<tr>
<td></td>
<td>MFS</td>
<td>ErmAB-TolC</td>
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<tr>
<td></td>
<td></td>
<td>TetA-E</td>
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</tr>
<tr>
<td></td>
<td>RND</td>
<td>AcrAB-TolC</td>
<td></td>
</tr>
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<td></td>
<td>AcrCD-TolC</td>
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<td></td>
<td></td>
<td>AcrEF-TolC</td>
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<tr>
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<td>SMR</td>
<td>ErmE</td>
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...and the list is much longer
# Antibiotic efflux in Gram (-)

<table>
<thead>
<tr>
<th>organism</th>
<th>family</th>
<th>pump</th>
<th>antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. aeruginosa</td>
<td>MFS</td>
<td>TetA,C,E</td>
<td>β-lactams Aminoglycosides Fluoroquinolones Macrolides Tetracyclines Trimethoprim Sulfamides</td>
</tr>
<tr>
<td></td>
<td>RND</td>
<td>MexAB-OprM</td>
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<td></td>
<td></td>
<td>MexCD-OprJ</td>
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<td></td>
<td></td>
<td>MexEF-OprN</td>
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<td></td>
<td></td>
<td>MexJK-OprM</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MexXY-OprM</td>
<td></td>
</tr>
</tbody>
</table>
Antibiotic resistance in bacteria responsible for respiratory tract infections: how is doing Belgium at the beginning of the XXI century?
A recent study on pneumococci ...

**Bacteria:**
146 samples of *S. pneumoniae* isolated in 2004-2007 from patients in 4 large hospitals in the Region of Brussels with a diagnostic of community acquired pneumonia

**Susceptibility testing:**
- MICs (microdilution)
- Resistance through active efflux
  - for macrolides: comparison between erythromycin and clindamycin
  - for quinolones: addition of reserpine

Epidemiological survey of antibiotic resistance in a Belgian collection of CAP isolates of *Streptococcus pneumoniae* (SP)
**S. pneumoniae** susceptibility for patients with CAP

- **Penicillin**
  - Cumulative percentage
  - MIC
  - Susceptible
  - Decreased susceptibility (EUCAST)
  - Resistant (CLSI)

- **Amoxicillin**
  - Cumulative percentage
  - MIC
  - Susceptible
  - Decreased susceptibility (EUCAST)
  - Resistant (CLSI)

- **Cefuroxime**
  - Cumulative percentage
  - MIC
  - Susceptible
  - Decreased susceptibility (EUCAST)
  - Resistant (CLSI)
S. pneumoniae susceptibility for patients with CAP

**Erythromycin**

**Clarithromycin**

**Telithromycin**

- **susceptible**
- **decreased susceptibility (EUCAST)**
- **resistant (CLSI)**
S. pneumoniae susceptibility for patients with CAP

- Ciprofloxacin
  - Susceptible
  - Decreased susceptibility (EUCAST)
  - Resistant (CLSI)
  - With efflux (reserpine)

- Levofloxacin
  - Susceptible
  - Decreased susceptibility (EUCAST)
  - Resistant (CLSI)

- Moxifloxacin
  - Susceptible
  - Decreased susceptibility (EUCAST)
  - Resistant (CLSI)
  - With efflux (reserpine)
**S. pneumoniae**: clinical attitude to cope with the increase of resistance

<table>
<thead>
<tr>
<th>Antibiotic class</th>
<th>Resistance mechanism</th>
<th>Clinical attitude</th>
</tr>
</thead>
</table>
| β-lactams        | • Target modification causing a progressive reduction in susceptibilities | • increase the dose (« I » strains)  
• change AB class (« R » strains) |
| macrolides       | • Target modification causing a marked change in susceptibility  
• efflux | • Prefer ketolide  
(higher affinity for the mutated target; less subjected to efflux)  
or 16-membered macrolides  
(miocamycine; less susceptibles to efflux)  
• change AB class |
| fluoroquinolones | • target modification  
• efflux | • Select the molecule with highest intrinsic activity  
(ciprofloxacine <<< levofloxacine  
< moxifloxacine)  
• Change AB class |
| tetracyclines    | • modification de la cible  
• efflux | • change antibiotic class |
Other useful local data useful for the next steps of our journey...

Focus on *Pseudomonas aeruginosa*
**What is the problem?**

**Pseudomonas aeruginosa:** resistance and therapeutic options at the turn of the new millennium

N. Mesaros¹, P. Nordmann², P. Plésiat³, M. Roussel-Delvallez⁴, J. Van Eldere⁵, Y. Glupczynski⁶, Y. Van Laethem⁷, F. Jacobs⁸, P. Lebecque⁹, A. Malfroot¹⁰, P. M. Tulkens³ and F. Van Bambeke¹

**ABSTRACT** (summarized)

*Pseudomonas aeruginosa* is a major cause of nosocomial infections.

It resists to many antibiotics, either intrinsically (because of constitutive expression of β-lactamases and efflux pumps, combined with low permeability of the outer-membrane) or following acquisition of resistance genes (e.g., genes for β-lactamases, or enzymes inactivating aminoglycosides or modifying their target), over-expression of efflux pumps, decreased expression of porins, or mutations in quinolone targets.

Susceptibility testing is therefore crucial in clinical practice.

Empirical treatment usually involves combination therapy, selected on the basis of known local epidemiology.

Innovative therapeutic options for the future remain scarce.

**Accepted:** 24 November 2006

*Clin Microbiol Infect* 2007; 13: 560–578
What can you do?

- Survey the level of resistance in Brussels Hospitals and relate it to therapy
- Examine the mechanisms of resistance acquisition (with special reference to efflux pumps)
- Assess new antibiotics and novel approaches (immunotherapy)
- Examine the susceptibility to biocides
Impact of therapy on the development of in vitro antimicrobial resistance in *Pseudomonas aeruginosa* strains isolated from lower respiratory tract of Intensive Care Units (ICU) patients with nosocomial pneumonia

Supported by the
- "Région Bruxelloise/Brusselse Gewest" (Research in Brussels)
- FNRS (post-doctoral fellowships)
- FRSM
What did we do?

Initial collection:
- 144 patients
- 233 isolates

Screening for confirmed VAP / HCAP:
- 104 patients
- 199 isolates

35 patients with D0 isolate(s) only:
- 38 isolates

69 patients with multiple successive samples:
- 161 isolates

Clonality analysis:
- Non clonal isolates (10) (only initial isolate kept)

Locations:
- Erasme
- UZ Brussel
- St-Luc
- St Pierre
- UCL
- Queen Astrid Military Hospital
Characteristics of the patients

Total population (n=104)

<table>
<thead>
<tr>
<th>Age</th>
<th>lowest</th>
<th>geom. mean</th>
<th>mean±SD</th>
<th>median</th>
<th>highest</th>
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</thead>
<tbody>
<tr>
<td>years</td>
<td>1.2</td>
<td>54.1</td>
<td>60.0 ± 19.3</td>
<td>63.1</td>
<td>85.0</td>
</tr>
<tr>
<td>Ventilated</td>
<td>yes</td>
<td>no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no. of patients</td>
<td>74</td>
<td>30</td>
<td></td>
<td></td>
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</tbody>
</table>

Enrolment based upon

- report of the isolation of *P. aeruginosa* as single or predominant microorganism from the lower respiratory tract [endotracheal or bronchial aspirates, broncho-alveolar lavages] and/or from pleural fluid, and
- radiological confirmation of the pneumonia (presence of infiltrates).

Cystic fibrosis patients systematically excluded.
What is the situation at day 0?

**MIC (mg/L : 0.0156 to 512 mg/L)**

- **EUCAST bkpt > R**
- **CLSI bkpt ≥ R**
What is the situation at day 0?

- **Gentamicin**
- **Piperacillin**
- **Ticarcillin**
- **Aztreonam**
- **Colistin**

**MIC (mg/L)**
- **EUCAST bkpt > R**
- **CLSI bkpt ≥ R**
What is the situation at day 0?

| Antibiotic | MIC<sub>50/90</sub> (mg/L) | % Non-susceptible Isolates According to EUCAST | | % Non-susceptible Isolates According to CLSI |
|------------|---------------------------|---------------------------------------------|---------------------------------------------|
|            | Breakpoint<sup>a</sup> (≤ S / R >) mg/L | Isolates I / R | Breakpoint<sup>b</sup> (≤ S / R ≥) mg/L | Isolates I / R |
| AMK        | 4 / 16                      | 8 / 16 | 9 / 8 | 16 / 64 | 1 / 7 |
| CIP        | 0.25 / 8                    | 0.5 / 1 | 7 / 23 | 1 / 4 | 4 / 18 |
| MEM        | 1 / 16                      | 2 / 8 | 12 / 24 | 4 / 16 | 3 / 24 |
| TZP        | 8 / 128                     | 16 / 16 | 34<sup>c</sup> | 64 / 128 | 7 / 12 |
| FEP        | 8 / 64                      | 8 / 8 | 46<sup>c</sup> | 8 / 32 | 17 / 30 |
| CAZ        | 4 / 64                      | 8 / 8 | 39<sup>c</sup> | 8 / 32 | 6 / 33 |
| GEN        | 2 / 64                      | 4 / 4 | 26<sup>c</sup> | 4 / 16 | 10 / 15 |
| PIP        | 8 / 128                     | 16 / 16 | 36<sup>c</sup> | 64<sup>d</sup> / 128 | 0 / 26 |
| TIC        | 64 / 512                    | 16 / 16 | 86<sup>c</sup> | 64 / 128 | 0 / 39 |
| ATM        | 8 / 32                      | 1 / 16 | 68 / 30 | 8 / 32 | 20 / 30 |
| CST        | 2 / 4                       | 2 / 2 | 33<sup>c</sup> | 2 / 8 | 26 / 0 |
Are they cross-resistances at day 0?

<table>
<thead>
<tr>
<th></th>
<th>AMK</th>
<th>CIP</th>
<th>MEM</th>
<th>TZP</th>
<th>FEP</th>
<th>CAZ</th>
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<tbody>
<tr>
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<td>14 / 8</td>
<td>12 / 5</td>
<td>16 / 7</td>
<td>17 / 4</td>
<td>17 / 5</td>
<td>14 / 8</td>
<td>16 / 6</td>
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<td>4 / 0</td>
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<td>22 / 8</td>
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<td>23 / 21</td>
<td>21 / 20</td>
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<td>31 / 24</td>
<td>11 / 0</td>
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<td>40 / 29</td>
<td>23 / 7</td>
<td>28 / 22</td>
<td>25 / 20</td>
<td>18 / 13</td>
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<td>98 / 38</td>
<td>27 / 0</td>
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</tbody>
</table>

Number of isolates (out of 110 initial isolates [D0]) categorized as resistant to the two antibiotics (row – column) using the criteria of EUCAST (first figure) or CLSI (last figure).

- **red-bold**: combinations for which cross-resistance > 25% of isolates
- EUCAST only -- EUCAST and CLSI
But what is the link with PK/PD?

**Dosage**

- $C_{\text{max}}$
- AUC
- half-life

**PK**

**PD**

- dose-response
- $E_{\text{max}}$
- time

**Therapeutic effects**

**Toxic effects**
But what is the link with PK/PD?

**PK**
- $C_{\text{max}}$
- AUC
- half-life

**PD**
- dose-response
- $E_{\text{max}}$
- time

Dosage

Therapeutic effects

Toxic effects

Let's go and see in the section: PK/PD to fight resistance ...

Section 4 B