Strategies to combat resistance: Focus on pharmacokinetics/pharmacodynamics with applications to β-lactams

Delhi – 16 February 2011
Strategies to combat resistance: focus on pharmacokinetics/pharmacodynamics with applications to β-lactams

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http://www.facm.ucl.ac.be  http://www.isap.org
Antibiotic treatment: What does the clinician want?

- Best therapeutic effects
- No or minimal toxic effect

"The" drug

Delhi, 16 February 2011
 Strategies to combat resistance: focus on PK/PD
Delhi, 16 February 2011

The ideal antibiotic ...

- the molecule
- brilliant and clear solutions
- chemistry
- microbiology
- therapy
- patient’s cure
Is the molecule always ideal?

the ideal molecule

brilliant and clear solutions

chemistry microbiology therapy

patient’s cure
Main causes of antibiotic failures...
Adapted from Pechère J.C., 1988, 1993, 1998

• False failures
  – erroneous diagnosis
  – underlying disease uninfluenced by antibiotics
  – unjustified lack of patience
  – inactivation of the antibiotic

• Pharmacological failures
  – insufficient amount or drug inappropriately administered
  – no attention paid to pharmacodynamic parameters
  – in situ inactivation or lack of drainage

• Patient related failures
  – compliance failure (broadly speaking)
  – inappropriate administration route (broadly speaking)
  – immunodepressed hosts

• Micro-organism related failures
  – wrong pathogen
  – resistance acquired during treatment
  – insufficient bactericidal activity
  – inoculum effect
In a nutshell ... so far …

- Microbiology parameters: MIC!
- Pharmacodynamic parameters
- PK/PD as applied to beta-lactams: Time-above MIC
- The problems if you underdose
- Take home message
Microbiology

identification

susceptibility

by disc or other techniques

at which drug concentration do we inhibit growth?
What do I do in my country (in relation to microbiology)?

- Survey the level of resistance of *P. aeruginosa* and *S. pneumoniae* from selected hospitals and relate it to therapy ¹
- Examine the mechanisms of resistance acquisition (with special reference to efflux pumps) ²

Assess new antibiotics and novel approaches (immunotherapy) ³

- Examine the susceptibility to biocides ¹

Supported by
1 Regional authorities and the Fund for Industrial Research
2 Fund for Scientific and Medical Research
3 Pharmaceutical Industry and small/medium enterprises
What is the situation at day 0 with P. aeruginosa in HAP?

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

Riou et al. IJAA 2010; 36:513-522
What is the situation at day 0 with *P. aeruginosa* in HAP?

- **Amikacin**
- **Ciprofloxacin**
- **Meropenem**
- **Piperacillin/Tazobactam**
- **Cefepime**
- **Ceftazidime**

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

Riou *et al.* IJAA 2010; 36:513-522
Moving on ...

• Does your microbiologist discuss infection cases in ICU with you?

1. Each case
2. Few cases
3. Upon asking
4. Never
Asking the question you always wanted to ask ...

• Does your microbiologist gives MIC of antibiotics apart from sensitivity in ICU infections?

1. Each case
2. Few cases
3. upon asking
4. Never
Asking the question you always wanted to ask ...

• Does your microbiologist gives MIC of antibiotics apart from sensitivity in ICU infections?

1. Each case
2. Few cases
3. upon asking
4. Never

No, MIC is not the acronym for "Minimal Interest to the Clinician"!
What did the textbooks say about antibiotic dosages and schedules in the 70’s?

1. Stay above the MIC... but how much?
2. Remain around for a while... but how long?
3. Hope it works... against everything?
4. Hope it is not toxic... can’t do much...
In a nutshell ... so far ...

• Microbiology parameters: MIC!
• **Pharmacodynamic parameters**
• PK/PD as applied to beta-lactams: Time-above MIC
• The problems if you underdose
• Take home message
Pharmacokinetics

Dosage

Serum concentration varying over time

Concentration at the site of infection

Concentration at other sites
Pharmacodynamics

Dosage

Serum concentration varying over time

Concentration at the site of infection

Therapeutic effects

Concentration at other sites

Toxic effects

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Strategies to combat resistance: focus on PK/PD
PK / PD : why does it improve the use of antibiotics?

The basics:

- anti-infective drug usage has long been irrational or not scientifically based on a pharmacodynamic point of view
  - search for low doses for fear of toxicity
  - “errors” in drug dosages at registration
  - misunderstanding of “optimal schedules”

- pharmacokinetics was mostly used to establish “drug presence” rather than to correlate dosing with efficacy

pharmacodynamics of antiinfective drugs was largely “terra incognita” 20 years ago
How did it start?

A bunch of good guys met in Stockholm in 1989...
What did they think all about?

- Population pharmacokinetics
- Tissue concentrations
- Efficacy/toxicity ratios
- AUIC and fluoroquinolones
- Postantibiotic effect and β-lactam infusion
- Once-daily dosing of aminoglycosides
Pharmacodynamics: influence of time and concentration...

Craig et al.
Pharmacokinetics - Pharmacodynamics

Pharmacokinetics
conc vs time

Pharmacodynamics
conc vs effect

PK/PD
effect vs time

from Derendorf,
ISAP workshop
PK/PD in action in the Regulatory in the USA

**PK/PD - Potential Benefits**

- Facilitate Early Selection of Lead Drug Candidate (e.g., Pre-Clinical Screening)
- Select Appropriate Dosage Regimen (e.g., Phase 1/2)
- Better Understand Clinical / Microbiological Outcome (e.g., Phase 3)
- More Efficient Drug Development Program

http://www.fda.gov/cder/present/anti-infective798/biopharm/index.htm
More questions …

• Do you agree with the benefit of "HIT HARD and HIT FAST"?

1. No
2. Yes
More questions ...

• Do you agree the benefit of "HIT HARD & HIT FAST ?"

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

"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
PK / PD in action for science and clinics

Some achievements:

- once-daily dosing of aminoglycosides
  registration or reregistration in several countries
  - amikacin, netilmicin (from bid to qd)
  -  isepamicin (registered essentially for qd dosing)

- 24h AUC / MIC and C_{max} / MIC ratios used as guides
  for phase II / III trials, for treatment optimization
  and for registration of new antimicrobials
  - moxifloxacin
  - telithromycin

- Time above MIC as "gold standard" for β-lactams
PK-PD properties of antibiotics

Most available antibiotics can be divided in 3 main groups with respect to PK/PD properties:

- Time-dependent (" T > MIC ")
  → β-lactams (all)

- Concentration-dependent (" Cmax / MIC" )
  → aminoglycosides and, for eradication, fluoroquinolones

- Total daily dose-dependent (" AUC / MIC " )
  → fluoroquinolones (for global efficacy) and all others
Relationship between peak/MIC and efficacy of cefotaxime towards *Klebsiella pneumoniae* in murine pneumonia (after W.A. Craig *)

![Graph showing the relationship between peak/MIC ratio and log_10 CFU per Lung at 24 Hours.](image)

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000
Relationship between time above MIC (T>MIC) and efficacy of cefotaxime towards *Klebsiella pneumoniae* in murine pneumonia (after W.A. Craig * )

\[ R^2 = 94\% \]
In a nutshell ... so far ...

- Microbiology parameters: MIC!
- Pharmacodynamic parameters
- **PK/PD as applied to beta-lactams:** Time-above MIC
- The problems if you underdose
- Take home message
β-lactams: \( T > \text{MIC} \) … but ...

You know it is "time above MIC", but…

- How much / How frequent?  
  (Static dose vs maximum effect?)
- The same for all beta-lactams?  
  (Free fractions of the drug (\( Fu \))?)
- The same for all micro-organisms?
- The same for all infections?
- Can you apply to all patients?
How much time above MIC?

- **Static dose?**
  - 40%
  - $R^2 = 94\%$

- **100% - Maximal effect?**

- cefotaxime
- neutropenic mice
- *K. pneumoniae*
- pulmonary infection
Here is a proposal ...

Moderately severe infection in a non-immunospressed patient

Severe infection in an immunosuppressed patient

100%?
Fig. 7. Relationship between the change in log_{10} CFU per thigh or lung for various pathogens following 24 h of therapy with different doses of penicillins ($\Delta$), cephalosporins ($\bigcirc$) and carbapenems ($\square$).
The same for all microorganisms?

T> MIC for static effect

<table>
<thead>
<tr>
<th>Drug</th>
<th>Enterobacteriaceae</th>
<th>S. pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone (free)</td>
<td>38 (34-42)</td>
<td>39 (37-41)</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>38 (36-40)</td>
<td>38 (36-40)</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>36 (27-42)</td>
<td>39 (35-42)</td>
</tr>
<tr>
<td>Cefpirome</td>
<td>35 (29-40)</td>
<td>37 (33-39)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>22 (18-28)</td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>24 (17-28)</td>
<td></td>
</tr>
</tbody>
</table>

Craig et al.
How do you adjust the dose for a given "Time > MIC"?

- Read the package insert and follow dosage recommendations
  - somewhat blind and simple but may be effective

- Run a simple calculation based on known pharmacokinetics
  - see example on next slide

- Monte-Carlo simulations and target attainment approaches
  - for the expert … but regulatory authorities use it a lot
Calculation of concentration over time for a typical $\beta$-lactam

<table>
<thead>
<tr>
<th>time (hours)</th>
<th>serum concentration for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 g</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>1.5</td>
</tr>
<tr>
<td>12</td>
<td>0.75</td>
</tr>
</tbody>
</table>

* Single administration; half-life 2h; $V_d = 0.2 \text{ l/kg}$
### Reading the results against the MIC of the offending organism (100 % Time > MIC)

<table>
<thead>
<tr>
<th>time (hours)</th>
<th>serum concentration for 0.5 g</th>
<th>1 g</th>
<th>2 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>25</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>12.5</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>12</td>
<td>25</td>
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<td>8</td>
<td>3</td>
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<td>3</td>
<td>6</td>
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<tr>
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<td>3</td>
</tr>
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* Single administration; half-life 2h; V<sub>d</sub> = 0.2 l/kg
Reading the results against the MIC of the offending organism (100 % Time > MIC)

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<td>12</td>
<td>0.75</td>
</tr>
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</table>

A calculator for different:
- dosages
- half-life (clearance)
- volumes of distributions will be available on our web site (see address on last slide)

* Single administration unique; half-life 2h ; \( V_d = 0.2 \text{ l/kg} \)
Simple optimisation of IV β-lactams for "difficult" organisms

- 2 g every 12 h
  - T > MIC = 100 % if MIC ≤ 3 mg/L!

- 2 g every 8 h
  - T > MIC = 100 % if MIC ≤ 12 mg/L

More frequent administrations is the best way to increase the activity of β-lactams in difficult-to-treat infections...

PK / PD breakpoint for

IV β-lactams: MIC = 8 µg/ml
To be practical

In an environment where susceptibilities are compromised (MICs > 4 mg/L) but still "acceptable" (MIC < 16 mg/L) *

• cefepime: 2 g every 8 h
• ceftazidime: 2 g every 8 h
• meropenem: 2 g every 8 h
• imipenem: 1 g every 6 h

* see discussion about breakpoints later on ...

International labelling (SmPC)

Doses up to 2 g three times daily in adults ...may particularly be suited for treating nosocomial infections due to *Pseudomonas aeruginosa* or *Acinetobacter* spp.
To be practical

In an environment where susceptibilities are compromised (MICs > 4 mg/L) but still "acceptable" (MIC < 16 mg/L) *

- cefepime: 2 g every 8 h
- ceftazidime: 2 g every 8 h
- meropenem: 2 g every 8 h
- imipenem: 1 g every 6 h

* see discussion about breakpoints later on ...

The label of all EU countries limit the dose of imipenem to 4 g/day!
Target Concentration for $\beta$-lactams: continuous infusion

Figure 2 Relationship between concentration of ceftazidime and kill rate

The relationship follows a Hill-type model with a relatively steep curve; the difference between no effect (growth, here displayed as a negative kill rate) and maximum effect is within two to threefold dilutions. The maximum kill rate is attained at around four times the minimum inhibitory concentration (MIC). Modified with permission from [16].

Continuous infusion of β-lactams: an overview...

- The exact role of continuous infusion of β-lactam antibiotics in the treatment of severe infections remains unclear...

- However, increasing evidence is emerging that suggests potential benefits
  - better attainment of pharmacodynamic targets for these drugs
  - More reliable pharmacokinetic parameters in seriously ill patients
  - when the MIC of the pathogen is ≥4 mg/L (empirical therapy where the susceptibility of the pathogen is unknown)

- Clinical data supporting continuous administration are less convincing, but
  - Some studies have shown improved clinical outcomes from continuous infusion
  - none have shown adverse outcomes.
  - clinical and bacteriological advantage are visible in seriously ill patients requiring at least 4 days of antibiotic therapy.

- Seriously ill patients with severe infections requiring significant antibiotic courses (≥4 days) may be the subgroup that will achieve better outcomes with continuous infusion.

Continuous infusion in practice

1. loading dose: the correct scheme *

\[ C_t = \frac{D_l}{V_d} \]

**Target serum concentration**

**Volume of distribution**

**Loading dose**

\ \text{loading dose (in mg) = } C_t \ (\text{mg/L}) \times V_d \ (L) \\]

The loading dose is only dependent upon the volume of distribution and is directly influenced by the weight of the patient and his/her medical situation.

Typical volumes of distribution of a β-lactam are between 0.2 L/kg (volunteers) and 0.4-0.5 L/kg (Intensive Care and burned patients)

* assuming linear pharmacokinetics (almost always the case for β-lactams)
Continuous infusion in practice
1. loading dose: a simplified (useful) scheme

- Because β-lactams have a low intrinsic toxicity, transient overshooting may not be a major problem…
- Conventional treatments (discontinuous) is by means of bolus or short infusions…
- Why not giving the loading dose as a single bolus or short infusion of a classical dose (1-2 g)?
Continuous infusion in practice
2: infusion: the correct scheme *

\[ C_{ss} = \frac{K_0}{\text{Cl}} \]

**Target serum concentration**

**Clearance** *

\[ \text{daily dose} \ (\text{in mg}) = 24 \times \text{clearance} \ (L/h) \times C_{ss} \]

* during the infusion, the necessary dose (in 24h or per min) is only dependent upon the clearance and **not** the weight of the patient

* assuming linear pharmacokinetics (almost always the case for β-lactams)
Continuous infusion in practice: why clearance only?

Once a bath is at the desired level (i.e. after the loading dose), maintaining this level does not depend upon its volume but of the ratio of tap and drain flows (which must be equal: in = out...)

*During the infusion, the necessary dose (in 24h or per min) is only dependent upon the **clearance** and **not** the weight of the patient.
Continuous infusion of β-lactams: a simplified practical scheme for patients with normal renal function

Continuous versus intermittent infusion of temocillin, a directed spectrum penicillin for intensive care patients with nosocomial pneumonia: stability, compatibility, population pharmacokinetic studies and breakpoint selection

Raf De Jongh¹, Ria Hens¹, Violetta Basma², Johan W. Mouton³, Paul M. Tulkens²* and Stéphane Carryn²

¹Dienst Voor Intensieve Zorgen, Ziekenhuis Oost-Limburg, B-3600 Genk, Belgium; ²Unité de Pharmacologie Cellulaire et Moléculaire, Université Catholique de Louvain, B-1200 Bruxelles, Belgium; ³Afdeling Medische Microbiologie en Infectieziekten, Canisius Wilhelmina Ziekenhuis, NL-6500 GS Nijmegen, The Netherlands

- loading dose: 2 g
- infusion: 4 g/day (2.778 mg/min; assumed clearance: 40 ml/min) [drug diluted in 48 ml of water; infusion through motor-operated syringe at a rate of 2 ml/h; temperature 25°C or lower].
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Pharmacokinetics of temocillin
4 g/day
(as an example)

Concentration at equilibrium (total):
73 ± 3
(40 - 142)


Data on 6 g/daily are prepared for publication
Problems with continuous infusion ...

- Clearance estimates
- Variations in clearance (ICU)
- Volume of distribution (ICU, burned patients, ...)
- Non-linear clearance
- drug instability
Problems with continuous infusion ...

- Clearance estimates
- Variations in clearance (ICU)
- Volume of distribution (ICU, burned patients, ...)
- Non-linear clearance
- **drug instability**

!! carbapenems are unstable (3-4h max.)

you may like to monitor the serum levels if MICs $\geq 4$ (also for discontinuous administration)
Carbapenems stability

doi:10.1093/jac/dkq044
Advance publication 21 February 2010

Stability of meropenem and doripenem solutions for administration by continuous infusion

Karine Berthoin¹, Cécile S. Le Duff², Jacqueline Marchand-Brynaert², Stéphane Carryn¹,³
and Paul M. Tulkens¹*

![Graph showing the influence of time on the % of original concentration of carbapenem solutions at different temperatures.](image)
Meropenem Infusion in the Critically-Ill

Thus even resistant bugs / bugs with extremely high MIC also can be taken care with prolonged (3h) infusion of meropenem

Cefepime by prolonged (3 – 4h) infusion

Steady-state pharmacokinetics and pharmacodynamics of cefepime administered by prolonged infusion in hospitalised patients

S. Christian Cheatham a, Katherine M. Shea b, Daniel P. Healy c, Melissa L. Humphrey d, Megan R. Fleming a, Matthew F. Wack e, David W. Smith f, Kevin M. Sowinski d, Michael B. Kays d, +

a St Francis Hospital, Department of Pharmacy, Beech Grove, IN, USA
b Seton Family of Hospitals, University Medical Center at Brackenridge, Austin, TX, USA
c James L. Winkle College of Pharmacy, University of Cincinnati Academic Health Center, Cincinnati, OH, USA
d Purdue University College of Pharmacy, Department of Pharmacy Practice, W7555 Myers Building, WHS, 1001 West Tenth Street, Indianapolis, IN 46202-2879, USA
e Infectious Diseases of Indiana, Indianapolis, IN, USA
f Clarian Health Partners, Inc., Methodist Hospital, Indianapolis, IN, USA
Fig. 2. Probability of target attainment (PTA) at 60% $fT > MIC$ for six prolonged infusion regimens of cefepime at specific minimum inhibitory concentrations (MICs). The dotted line indicates a PTA $\geq 90\%$. $fT > MIC$, time for which the free drug concentration remains above the MIC; q8h, every 8 h; q12h, every 12 h; q6h, every 6 h.
To be practical:
3 h infusion for "difficult" organisms and for patients with normal renal function

1. Loading dose (in 30 min)
   - 2 g (cefepime / meropenem)*

2. Followed immediately by an 3 h infusion
   - 2 g (cefepime / meropenem)*

3. Repeat step 2 every 8 h

* piperacillin/tazobactam: loading dose: 4.5 g; infusion: 4.5 g every 6 h
* imipenem: loading dose max. 1 g; infusion: 1 g every 6h (max.)
Clinicians tend to ask only (and clinical microbiologists to provide only) "S – I – R" answers based on accepted breakpoints …

But, what is a breakpoint?
Clinical breakpoints

Clinical breakpoints are for everyday use in the clinical laboratory to advise on patient therapy.

In EUCAST tables, the I-category is not listed. It is implied as the values between the S-breakpoint and the R-breakpoint.

For a breakpoint listed as S<=1 mg/L and R>8 mg/L the intermediate category is 2-3 (technically >1 - 8) mg/L.

For a breakpoint listed as S>=22 mm and R<18 mm the intermediate category is 18-21 mm.

- clinical breakpoints - bacteria (v 1.1) - pdf-file for printing (April 27, 2010)
- clinical breakpoints - bacteria (v 1.4) - Excel-file for screen (April 27, 2010)

- clinical breakpoints - fungi (MIC breakpoints)

- definitions of clinical breakpoints and epidemiological cut off values
- procedure for harmonizing and defining breakpoints

Delhi, 16 February 2011

Strategies to combat resistance: focus on PK/PD
The next slides describe the EUCAST procedure for harmonizing European breakpoints and reach rational values.
1. Data on dosing, formulations, clinical indications and target organisms are reviewed and differences which might influence breakpoints are highlighted

2. Multiple MIC-distributions are collected, the wild type MIC distribution is defined and tentative epidemiological cut-off values determined (WT \( \leq X \text{ mg/L} \))

4. Pharmacokinetic / Pharmacodynamic data are collected and evaluated; Monte Carlo simulations are performed and a PK/PD breakpoint calculated based on conventional dosing regimens

5. Clinical data relating outcome to MIC-values, wildtype and resistance mechanisms are assessed in relation to the tentative breakpoint

6. Pk/Pd breakpoints are checked against target species wild type MIC distributions to avoid splitting the wild type population

http://www.eucast.org
7. Tentative breakpoints by the EUCAST Steering Committee are referred to the national breakpoint committees for comments. When steering committee and national committees agree the tentative breakpoints are subjected to the EUCAST consultation process:

8. Consultation process on tentative breakpoints:
   - EUCAST general committee
   - Expert committees (Neisseria, Anaerobes, others)
   - Pharmaceutical industry, AST device manufacturer
   - Others via EUCAST website

9. Rationale document prepared and published on website
### Enterobacteriaceae

<table>
<thead>
<tr>
<th>Carbapenems</th>
<th>MIC breakpoint (mg/L)</th>
<th>Disk content (µg)</th>
<th>Zone diameter breakpoint (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S ≤</td>
<td>R &gt;</td>
<td>S ≥</td>
</tr>
<tr>
<td>Doripenem</td>
<td>1</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>0.5</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Imipenem</td>
<td>2</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Meropenem</td>
<td>2</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>

- The carbapenem breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including the majority of carbapenemases).
- Some strains that produce carbapenemase are categorized as susceptible with these breakpoints and should be reported as tested, i.e. the presence or absence of a carbapenemase does not in itself influence the categorization of susceptibility.
- In many areas, carbapenemase detection and characterization is recommended or mandatory for infection control purposes.
EUCAST and cephalosporins

1. The cephalosporin breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including ESBL, plasmid mediated AmpC). Some strains that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as found, i.e. the presence or absence of an ESBL does not in itself influence the categorization of susceptibility. In many areas, ESBL detection and characterization is recommended or mandatory for infection control purposes.

Why so low?
To exclude ESBL..
What about ESBL?

Beta-lactamases: Classification

- Serine enzymes
  - Group C: AmpC
  - Group A: TEM / SHV /CTX-M
  - Group B
  - Group D: OXA

- Metallo (Zn) enzymes
  - Group B: IMP/VIM

ESBLs
Class A and D of β-lactamases are poorly active on 3rd generation cephalosporins

<table>
<thead>
<tr>
<th>Table 130.1 Functional classification of β-lactamases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Group 1: serine cephalosporinases not inhibited by clavulanic acid</td>
</tr>
<tr>
<td>2d: cloxacillin-hydrolyzing β-lactamases generally inhibited by clavulanic acid</td>
</tr>
</tbody>
</table>

Van Bambeke F, Glupczynski, Y, Mingeot-Leclercq, MP, Tulkens PM
Mechanisms of Action.
So, now you are left with the ESBL...

**Beta-lactamases: Classification**

- **Serine enzymes**
  - Group C
  - AmpC
  - TEM / SHV / CTX-M
  - ESBLs
  - those should be inhibited by tazobactam

- **Metallo (Zn) enzymes**
  - Group D
  - OXA
  - Group B
  - IMP/VIM

Delhi, 16 February 2011
Strategies to combat resistance: focus on PK/PD
An innovative approach for ESBL...

- take a 4\textsuperscript{th} generation cephalosporin (cefepime [PM]) ➔ should cover (partly AmpC) and resist to OXA
- add a β-lactamase inhibitor (tazobactam [TZ]) ➔ will take care of many ESBL

Mouton et al. ICAAC 2010
76 ESBL producing \textit{Enterobacteriaceae} were selected from a variety of clinical specimens.

<table>
<thead>
<tr>
<th></th>
<th>%S</th>
<th>%I</th>
<th>%R</th>
<th>MIC\text{50 (mg/L)}</th>
<th>MIC\text{90 (mg/L)}</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM</td>
<td>15</td>
<td>14</td>
<td>71</td>
<td>&gt;32</td>
<td>&gt;32</td>
</tr>
<tr>
<td>PM/TZ 1mg/L</td>
<td>41</td>
<td>34</td>
<td>25</td>
<td>2</td>
<td>32</td>
</tr>
<tr>
<td>PM/TZ 4mg/L</td>
<td>70</td>
<td>25</td>
<td>5</td>
<td>0.5</td>
<td>4</td>
</tr>
<tr>
<td>PM/TZ 16mg/L</td>
<td>93</td>
<td>7</td>
<td>0</td>
<td>0.25</td>
<td>1</td>
</tr>
</tbody>
</table>
An innovative approach for ESBL...

Percentage sensitive (S), intermediate (I) and resistant (R) cefepime (breakpoints EUCAST: ≤1 S – R >8)
An innovative approach for ESBL...

Conclusions:

• The combination of cefepime and tazobactam may offer an alternative treatment option for ESBL harboring strains.

• If the same amount of tazobactam is used as current piperacillin/tazobactam regimens and breakpoint determinations, most strains would be categorized as susceptible.

Mouton et al. ICAAC 2010

In India, due to high ESBL: consider cefepime + tazobactam

• cefepime 3 x 2 g /day
• tazobactam 3 x 0.25 g /day

or 3h infusion
In a nutshell ... so far ...

- Microbiology parameters: MIC!
- Pharmacodynamic parameters
- PK/PD as applied to beta-lactams: Time-above MIC
- **The (hidden) problem if you underdose**
- Take home message
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>
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<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

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Strategies to combat resistance: focus on PK/PD  
79
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<tbody>
<tr>
<td></td>
<td>MIC (mg/L) (^a)</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>
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<td>8</td>
<td>2</td>
<td>0.125</td>
</tr>
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<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>
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sub-MIC concentrations create resistance!
And this happens also with biocides

Exposure of *P. aeruginosa* to sub-MIC concentrations of chlorhexidine

Change in MIC of CHX during exposure to 0.5 MIC with daily concentration readjustment

Typical change in colony size and swarming abilities after 13 days of exposure to 0.5 MIC

Tan *et al*. ECCMID 2011, in press
And in the clinics?

In vivo development of antimicrobial resistance in *Pseudomonas aeruginosa* strains isolated from the lower respiratory tract of Intensive Care Unit patients with nosocomial pneumonia and receiving antipseudomonal therapy

Mickaël Riou¹, Sylviane Carbonnelle¹,², Laëtitia Avrain¹,², Narcisa Mesaros¹,³, Jean-Paul Pirnay⁴, Florence Bilocq⁵, Daniel De Vos⁶,⁷, Anne Simon⁶, Denis Piérard⁸, Frédérique Jacobs⁹, Anne Dediste¹⁰, Paul M. Tulkens¹,*, Françoise Van Bambeke¹, Youri Glupczynski¹
**What happens during treatment?**

- D0: initial isolate
- DL: last isolate obtained
- Individual values with geometric mean (95% CI)
- S (lowest line) and R (highest line) EUCAST breakpoints

* $p < 0.05$ by paired t-test (two-tailed) and Wilcoxon non-parametric test

$^a$ $p < 0.05$ by Wilcoxon non-parametric test only

Note: stratification by time between D0 and DL gave no clue (too low numbers)

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### Example Data

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC (mg/L)</th>
<th>D0</th>
<th>DL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amikacin</strong></td>
<td>8</td>
<td>D0</td>
<td>DL</td>
</tr>
<tr>
<td><strong>Meropenem</strong></td>
<td>0.5</td>
<td>D0</td>
<td>DL</td>
</tr>
<tr>
<td><strong>Piperacillin</strong></td>
<td>32</td>
<td>D0</td>
<td>DL</td>
</tr>
<tr>
<td><strong>Ciprofloxacin</strong></td>
<td>0.0625</td>
<td>D0</td>
<td>DL</td>
</tr>
<tr>
<td><strong>Cefepime</strong></td>
<td>128</td>
<td>D0</td>
<td>DL</td>
</tr>
</tbody>
</table>

Yes, resistance did develop, but we minimized it for meropenem and cefepime.
And what about colistin?

You first need to consider the MIC distribution.

Here are the data of EUCAST for \textit{Pseudomonas}.

![MIC distribution graph for \textit{Pseudomonas aeruginosa} showing the MIC (mg/L) on the x-axis and the percentage of microorganisms on the y-axis. The cut-off point is indicated.]

4217 observations (12 data sources)

Clinical breakpoints: S ≤ 4 \text{mg/L}, R > 4 \text{mg/L}.
And what about colistin?

Dosage (colistine methane sulfonate [CMS]): 240 mg every 8h (= 3 x 10^6 UI)

CMS
• \( t_{1/2} \sim 2.3 \text{ h} \),

Colistin:
• \( t_{1/2} \sim 14.4 \text{ h} \).
• \( C_{\text{max}} \) (pred.)
  • 1st dose: 0.60 mg/L
  • s.s.: 2.3 mg/L.

Plachouras et al. AAC 2009; E-pub 11 May

Problem #1:
Low initial blood levels suggest the necessity of a loading dose
And what about colistin?

Population analysis profiles of K. pneumoniae isolates

Problem #2: Heteroresistance is frequent with colistin

Poudyal et al. JAC 2008; 62:1311-1318
Retrospective cohort **clinical study of 258 patients**

- **52.3% isolates were polymyxin–only-susceptible**
- Remainder were susceptible to colistin & at least 1 other antibiotic
Patients with polymyxin-only-susceptible infections

Amongst the combinations of colistin with other antibiotics, only Colistin+Meropenem combination was an independent factor ($P = 0.017$)
- for cure of infection &
- better infection outcome

• In how many patients are you implementing "once-daily dosing" of aminoglycosides?

1. 0%
2. 25%
3. 50%
4. 75%
5. 100%
Pharmacokinetic and toxicological evaluation of a once-daily regimen versus conventional schedules of netilmicin and amikacin

Paul M. Tulkens

Laboratoire de Chimie Physiologique, Université Catholique de Louvain, and International Institute of Cellular and Molecular Pathology, Brussels, Belgium

In conclusion, these very sensitive tests of nephro- and oto-toxicity suggest that od dosing of amikacin or netilmicin is, if anything, safer than bd or tid dosing.
And what do we do now with toxicity?

We work on polymyxins with the help of Debaditya Das ... from Kolkata!

Comparative analysis of the potential of polymyxin B and gentamicin to cause apoptosis and necrosis in cultured renal LLC-PK1 cells: concentration-dependent studies with incubated and electroporated cells

Oral presentation (Session: "Antimicrobial pharmacology: from bench to bedside" -- Saturday, 7 May 2011: 16:30)
“Take home” message

- dosage is key to success and protection against resistance...
- dosage should match bacterial susceptibility... and knowledge of MIC is essential
- for β-lactams, get TIME > MIC to reach maximal efficacy ... and dose appropriately...
  ➔ 3h infusion of meropenem and cefepime may help
- Use of correct breakpoints will also help in avoiding the use of "weak antibiotics" ... or to decide dosage escalation to avoid emergence of resistance ...
- New combinations tailored to local needs (viz. cefepime + tazobactam) with 3h infusion) are useful ...
WHO statement 2000

The most effective strategy against antibiotic resistance is:

• “to unequivocally destroy microbes”
• “thereby defeating resistance before it starts”

WHO Overcoming Antimicrobial Resistance, 2000
And a few sights from Belgium...
I hope the future will be fine with you...

http://www.isap.org

http://www.facm.ucl.ac.be

All slides are available from here