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

Bangalore – 14 February 2011
Strategies to combat resistance: focus on pharmacokinetics/pharmacodynamics with applications to β-lactams

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&
International Society of Antiinfective Pharmacology

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

- "The" drug
- Best therapeutic effects
- No or minimal toxic effect
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

patient’s cure

chemistry

microbiology

therapy
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

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

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

• 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 static techniques

drug concentration stays constant
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
- Examine the mechanisms of resistance acquisition (with special reference to efflux pumps)
- Assess new antibiotics and novel approaches (immunotherapy)
- Examine the susceptibility to biocides

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?

- **amikacin**
- **ciprofloxacin**
- **meropenem**
- **piperacillin / tazobactam**
- **cefepime**
- **ceftazidime**

**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?

Knowing what YOUR distributions are.
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

Concentration at the site of infection

Concentration at other sites

Serum concentration varying over time

Dosage
Pharmacodynamics

**Dosage** → Serum concentration varying over time → Concentration at the site of infection → Therapeutic effects

Concentration at other sites → Toxic effects
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
- postantibiotic effect and β-lactam infusion
- once-daily dosing of aminoglycosides
- AUIC and fluoroquinolones
Pharmacodynamics: influence of time and concentration...

Craig et al.
But then came the "Bangalore Meeting"

International Society of Anti-Infective Pharmacology
Founded in 1991

7th ISAP International Symposium
Advances in the Pharmacology of Antiinfective Therapy
co-sponsored with Astra Research Centre, India

January 20-22 (Thursday - Saturday), 2000,
National Science Seminar Complex, Indian Institute of Science, Bangalore, Karnataka, India

Craig et al.
But then came the "Bangalore Meeting"

International Society of Anti-Infective Pharmacology

• **Trends & Problems in Therapy with Antibacterial Drugs** (O. Carl, Uppsala, Sweden)
• Pharmacokinetic concepts (O. Carl, Uppsala, Sweden)
• **Pharmacodynamic concepts** (W.A. Craig, Madison, WI)
• **Intracellular pharmacodynamics** (P.M. Tukens, Brussels, Belgium)
• **In vitro** pharmacodynamic models in the development of antibacterials (E. Löwdin, Uppsala, Sweden)
• **Animal models in early evaluation of antibacterial agents** (N. Frimodt-Moller, Copenhagen, Denmark)
• Use of animal models to define pharmacokinetic and pharmacodynamic interactions and optimal doses of antibacterial drugs (W.A. Craig, Madison, WI)
• Slide Presentations on *in vivo* models for the determination of antibacterial efficacy: advantages and limitations (N. Frimodt-Moller, Copenhagen, Denmark & W.A. Craig, Madison, WI)
• **Problems in the treatment of tuberculosis** (J. Nacheva, Baltimore, MD)
• Prediction of clinical efficacy of antitubercular regimens from *in vitro* studies (C. Paramasivan, Chennai, India)
• **Animal efficacy studies of antitubercular agents** (V. Balasubramanian, AstraZeneca R&D Indian Site, Bangalore, India)
• Evaluation of Clinical Efficacy and Optimal dosing from Clinical Trials (C. Drusano, Albany, NY) [talk delivered by W.A. Craig, due to the illness of the speaker]
• **Design of Clinical Studies of Antibacterial Agents for Efficacy and Toxicity** (R. Norby, Lund, Sweden)
• **Can we obtain useful susceptibility reports?** (Naninadekar, ...)
• **Prediction and prevention of emergence of resistance of clinically used antibacterials** (F. Baezuelo, Madrid, Spain)
• Regulatory efficacy requirements of new antibacterial drugs (talk delivered by W.A. Craig, Madison, WI, on behalf of the U.S. Food and Drug Administration)
• **Industrial Aspects of the development of Antibiotics** (J. Edwards, Alderley Park, UK)
• Closing remarks (S. Rosell, Umeå, Sweden & P.M. Tukens, Brussels, Belgium)
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

July 1998
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 $C_{\text{max}} / \text{MIC}$ 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 $\beta$-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 log10 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 * )
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
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?
Bangalore, 14 February 2011

Strategies to combat resistance: focus on PK/PD

How much time above MIC?

- cefotaxime
- neutropenic mice
- K. pneumoniae
- pulmonary infection

Static dose?

40%

\( R^2 = 94\% \)

100% - Maximal effect?
Here is a proposal ...

- **40%**
  - Moderately severe infection in a non-immunospressed patient

- **100%**
  - Severe infection in an immunosuppressed patient

Bangalore, 14 February 2011

Strategies to combat resistance: focus on PK/PD
The same for all $\beta$-lactams?

Carbapenems tend to require less time above MIC.

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 ($\triangle$), 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>
How do you adjust the dose for a given "Time > MIC"?

- "out of the package insert" PK data
- Monte-Carlo simulations and target attainment approaches
**Typical pharmacokinetics of an IV β-lactam**

<table>
<thead>
<tr>
<th>time (hours)</th>
<th>serum concentration for (mg/L)</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 unique; half-life 2h; $V_d = 0.2$ l/kg
## Reading the labeling (package insert)

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* Single administration unique; half-life 2h; $V_d = 0.2$ l/kg

Where would you like to be?
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
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* see discussion about breakpoints later on ...

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

- Maximum effect time-kill at 4 x MIC
- Maximum effect in vitro model 4 x MIC
- Effect in endocarditis model 4 x MIC (Xiong et al 1994)
- Effect in pneumonia model dependent on severity of infection


**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 $\beta$-lactams: an overview...

- The exact role of continuous infusion of $\beta$-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 $\geq 4$ 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 ($\geq 4$ days) may be the subgroup that will achieve better outcomes with continuous infusion.

Continuous infusion in practice

1. loading dose: the correct scheme *

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

Loading dose (in mg) = \( C_t \) (mg/L) \* \( V_d \) (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 *

Target serum concentration

\[ C_{ss} = \frac{K_0}{CI} \]

Clearance *

infusion rate

daily dose (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?

* 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

Journal of Antimicrobial Chemotherapy (2008) 61, 382–388
doi:10.1093/jac/dkm467
Advance Access publication 10 December 2007

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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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*

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**Graph:**

- **Influence of time**
  - % of original concentration
  - Time (h): 0, 6, 12, 18, 24
  - Lines represent different conditions:
    - Doripenem 1% 25°C
    - Doripenem 1% 37°C
    - Meropenem 4% 25°C
    - Meropenem 4% 37°C
Meropenem Infusion in the Critically-Ill

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

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

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

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 patients with normal renal function

• 1st administration: loading dose in 30 min
  ➢ 2 g (cefepime / meropenem)*
• followed immediately by an 3 h infusion of
  ➢ 2 g (cefepime / meropenem)*
• 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 6 h (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?
Bangalore, 14 February 2011

Strategies to combat resistance: focus on PK/PD

EUCAST procedure for setting breakpoints

The next slides describe the EUCAST procedure for harmonising European breakpoints and reaching rational values.

http://www.eucast.org

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

http://www.eucast.org
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 \( \leq X \) 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

http://www.eucast.org
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.
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

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

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Molecular class</th>
<th>Preferred substrates</th>
<th>Active β-lactams</th>
<th>Typical examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: serine cephalosporinases not inhibited by clavulanic acid</td>
<td>C</td>
<td>Cephalosporins I and II (&gt;&gt; cephalosporins III, monobactams, penicillins)</td>
<td>Carbapenems</td>
<td>AmpC from gram-negatives; variable upon level of expression</td>
</tr>
<tr>
<td>2d: clavulanin-hydrolyzing β-lactamases generally inhibited by clavulanic acid</td>
<td>D</td>
<td>Penicillins Cloxacillin Cephalosporins I and II</td>
<td>Carbapenems</td>
<td>OXA-1 to -30, PSE-2 from Enterobacteriaceae and <em>P. aeruginosa</em> OXA-11 to -19, 28, 32, 45 are ESBLs in <em>P. aeruginosa</em> (R to Ceph 3) OXA-23, -24, -58 are carbapenemases in <em>Acinetobacter baumannii</em></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 A**
    - TEM / SHV / CTX-M
    - ESBLs
  - **Group C**
  - AmpC
  - **Group D**
    - OXA

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

*Those should be inhibited by tazobactam*
An innovative approach for ESBL...

- take a 4\textsuperscript{th} generation cephalosporin (cefepime [PM]) ➔ should cover (partly AmpC) and resist to OXA
- add a \(\beta\)-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\textsubscript{50} (mg/L)</th>
<th>MIC\textsubscript{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)

Mouton et al. ICAAC 2010
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.

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

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

Bangalore, 14 February 2011
Strategies to combat resistance: focus on PK/PD
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
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 MIC (mg/L)</th>
<th>TEM-exposed MIC (mg/L)</th>
<th>Revertant MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TEM</td>
<td>FEP</td>
<td>MEM</td>
</tr>
<tr>
<td>2114/2</td>
<td>8</td>
<td>2</td>
<td>0.25</td>
</tr>
<tr>
<td>2502/4</td>
<td>8</td>
<td>2</td>
<td>0.125</td>
</tr>
<tr>
<td>3511/1</td>
<td>32</td>
<td>2</td>
<td>0.125</td>
</tr>
<tr>
<td>7102/10</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 dotblot 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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<td>2</td>
<td>0.25</td>
<td>2048</td>
</tr>
<tr>
<td>2502/4  c</td>
<td>8</td>
<td>2</td>
<td>0.125</td>
<td>8192</td>
</tr>
<tr>
<td>3511/1 c</td>
<td>32</td>
<td>2</td>
<td>0.125</td>
<td>4096</td>
</tr>
<tr>
<td>7102/10 d</td>
<td>512</td>
<td>32</td>
<td>1</td>
<td>16384</td>
</tr>
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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 Avrain², Narcisa Mesaros³, Jean-Paul Pirnay⁴, Florence Bilocq⁵, Daniel De Vos⁶,⁷, Anne Simon⁸, Denis Piérard⁹, Frédérique Jacobs⁵, Anne Dediste⁶, 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)

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 *Pseudomonas*.
And what about colistin?

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

CMS
- t_{1/2} ~ 2.3 h,

Colistin:
- t_{1/2} ~ 14.4 h.
- Cmax (pred.)
  - 1st dose: 0.60 mg/L
  - s.s.: 2.3 mg/L.

Problem #1:
Low initial blood levels suggest the necessity of a loading dose

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

Colistin therapy for microbiologically documented multidrug-resistant Gram-negative bacterial infections: a retrospective cohort study of 258 patients

Matthew E. Falagas\textsuperscript{a,b,c,*,} Petros I. Rafailidis\textsuperscript{a,b}, Elda Ioannidou\textsuperscript{a}, Vangelis G. Alexiou\textsuperscript{a}, Dimitrios K. Matthaiou\textsuperscript{a}, Drosos E. Karageorgopoulos\textsuperscript{a}, Anastasios Kapaskelis\textsuperscript{a,b}, Dimitra Nikita\textsuperscript{d}, Argyris Michalopoulos\textsuperscript{a,e}

- Retrospective cohort \textbf{clinical study of 258 patients}
- \textbf{52.3\% isolates were polymyxin–only-susceptible}
- Remainder were susceptible to colistin & at least 1 other antibiotic
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

Patients with polymyxin-only-susceptible infections

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

1. 0%
2. 25%
3. 50%
4. 75%
5. 100%
Thank you!


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.
“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