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

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Brussels, Belgium
&
International Society of Antiinfective Pharmacology

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

http://www.isap.org
The ideal antibiotic ...
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

• 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
What was the situation in 2010?

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


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**Ciris BloConcept, Gembloux, Belgium
Laboratory for Molecular & Cellular Technology, Queen Astrid Military Hospital, Neder-over-Heembeek, Brussels, Belgium
Department of Molecular and Cellular Interactions, Vrije Universiteit Brussel, Brussels, Belgium
Laboratoire de Microbiologie, Cliniques Universitaires St-Luc, Brussels, Belgium
Laboratorium voor Microbiologie, Universitair Ziekenhuis Brussel, Brussels, Belgium
Clinique des Maladies Infectieuses, Hôpital Erasme, Brussels, Belgium
Laboratoire de Microbiologie, Centre Hospitalier Universitaire Saint-Pierre, Brussels, Belgium
Laboratoire de Microbiologie, Cliniques Universitaires UCL de Mont-Godinne, Yvoir, Belgium

all in the Brussels Region
How was it at day 0 (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
How was it at 0 (P. aeruginosa in HAP)?

**Messages:**
1. Know your local MIC distributions and use appropriate breakpoints to avoid choosing weak antibiotics
Asking the question you always wanted to ask ...

• Does your microbiologist give 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 happen during treatment in case of no eradication?

- 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)

Riou et al. IJAA 2010; 36:513-522
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Messages:
1. Know your local MIC distributions and use appropriate breakpoints to avoid choosing weak antibiotics ...
2. We must eradicate ...

Riou et al. IJAA 2010; 36:513-522
Eradication is already an old story ...

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 properties of antibiotics

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

- Time-dependent ("T > MIC")
  \(\rightarrow\) \(\beta\)-lactams (all)

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

- Total daily dose-dependent ("AUC / MIC")
  \(\rightarrow\) fluoroquinolones (for global efficacy) and all others
β-lactams: how much time above MIC?

- Cefotaxime
- Neutropenic mice
- K. pneumoniae
- Pulmonary infection

100% - Maximal effect?

Log_{10} cfu per lung at 24 hours vs. Time above MIC (%)

Static dose?

40%
Here is a proposal ...

Moderately severe infection in a non-immunospressed patient

Severe infection in an immunosuppressed patient

100 % ?

C

Log$_{10}$ cfu per lung at 24 hours

Time above MIC (%)
But how much above the MIC?

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 in clinical practice: literature review *

<table>
<thead>
<tr>
<th>drug</th>
<th>no. of studies</th>
<th>main indications</th>
<th>main conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>piperacillin</td>
<td>5 (^a)</td>
<td>cIAI / VAP / septicaemia / various infections</td>
<td>equivalence but superiority if (\uparrow) MIC</td>
</tr>
<tr>
<td>ceftazidime</td>
<td>2 (^b)</td>
<td>VAP / pneumonia/ melioidosis/ cystic fibrosis</td>
<td>superiority mainly with resistant isolates</td>
</tr>
<tr>
<td>cefriaxone</td>
<td>1 (^c)</td>
<td>sepsis</td>
<td>superiority</td>
</tr>
<tr>
<td>meropenem</td>
<td>1 (^d)</td>
<td>VAP</td>
<td>superiority</td>
</tr>
</tbody>
</table>

* Full papers in peer-reviewed Journals only with evaluable clinical end-point(s)

\(a\) Grant 2002; Buck 2005; Lau 2006; Rafati 2006; Lorente 2009

\(b\) Rappaz 2000; Angus 2000; Nicolau 2001; Lorente 2007; Hubert 2009

\(d\) Lorente 2006 (Note: meropenem is unstable and may, therefore, not be recommended for continuous infusion without specific precautions)
Continuous infusion of β-lactams in clinical practice: literature review *

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<tr>
<td>penicillin G</td>
<td>1 (^a)</td>
<td>serious infections</td>
<td>favorable</td>
</tr>
<tr>
<td>oxacillin</td>
<td>1 (^b)</td>
<td>burn wound cell.</td>
<td>faster cure</td>
</tr>
<tr>
<td>ampicillin</td>
<td>2 (^c)</td>
<td>septicemia (infants)</td>
<td>equivalence or superiority (practical)</td>
</tr>
<tr>
<td>ceftazidime</td>
<td>3 (^d)</td>
<td>neutropenic fever and infections</td>
<td>favorable (2) unfavorable (1)</td>
</tr>
</tbody>
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* Full papers in peer-reviewed Journals only with evaluable clinical end-point(s)

\(^a\) Walton 2007  
\(^b\) Schuster 2009  
\(^c\) Colding 1982; Colding 1982  
\(^d\) Daenen 1995; Vinks 1997; Marshall 2000
### Continuous infusion of β-lactams in clinical practice: literature review *

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<th>no. of studies</th>
<th>type of patients</th>
<th>main conclusions</th>
</tr>
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<tr>
<td><strong>3. PK/PD studies in humans (no clinical end-point)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ampicillin</td>
<td>1 a</td>
<td>colorectal surgery</td>
<td>equivalence</td>
</tr>
<tr>
<td>piperacillin</td>
<td>1 b</td>
<td>VAP.</td>
<td>favorable</td>
</tr>
<tr>
<td>temocillin</td>
<td>1 c</td>
<td>non <em>Ps.</em> Gram (-)</td>
<td>pharmacokinet. super.</td>
</tr>
<tr>
<td>ceftazidime</td>
<td>5 d</td>
<td>ICU, clAI, neutropenia, VAP</td>
<td>pharmacokinet. super.</td>
</tr>
<tr>
<td>cefepime</td>
<td>4 e</td>
<td>nosocom. pneum. and severe Gram(-) infect.</td>
<td>equivalence or superiority (practical)</td>
</tr>
<tr>
<td>imipenem</td>
<td>1 f</td>
<td>surgery (various indic.)</td>
<td>equivalence</td>
</tr>
<tr>
<td>meropenem</td>
<td>3 g</td>
<td>neutropenic fever and infections</td>
<td>favorable (2) – unfavorable (1)</td>
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a Martin 1998 -- b Boselli 2008 -- c De Jongh, 2008

d Lipman 1999; Buyck 2002; Dalle 2002; Cousson 2005; Mariat 2006
e Georges 1999; Jaruratanasirikul 2002; Boselli 2003; Roos 2006 (Note: cefepime solutions develop color upon storage and may not be suitable for human use)
f Sakka 2007; g Thalhammer 1999; Langgartner 2008; Roberts 2009 (Note: both imipenem and meropenem are unstable and may, therefore, not be recommended for continuous infusion without special precautions)
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: 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)?
Problems with continuous infusion ...

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

you may like to monitor the serum levels if MICs ≥ 4 (also for discontinuous administration)
**β-lactam stability in a nutshell...**

* Servais & Tulkens, AAC 200;45:2643-7 – Viaene et al. AAC 2002;46:2327-32 - Baririan et al. JAC 2003;51:651
  other references for individual drugs in in Berthoin et al. (in preparation).
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*
Carbapenems in 3h infusion: target attainment rate *

*probability of attaining the target of 40% $T > MIC$ by MIC for $d$ meropenem as a 30-min and 3-h infusion at the simulated dosage regimens

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.)
Continuous infusion with vancomycin?

1. loading dose

\[ C_t = \text{Dosis} / V_d \]

\[ \text{Dosis} = C_t \times V_d \]

**target level:** 27.5 mg/L

\[ Vd \text{ (L/kg):} \quad 0.7 \]

\[ \text{dose (mg/kg):} \quad 19.25 \text{ mg/kg} \]

* 0.39 tot 0.97 L/kg

Continuous infusion of vancomycin …

2. infusion

\[ C_{ss} = \frac{\text{infus. rate}}{\text{Cl}_{van}} \]

\[ \text{infus. rate} = C_{ss} \times \text{Cl}_{van} \]

target level: 27.5 mg/L

\[ \text{Cl}_{van} : 0.65 \times \text{Cl}_{creatinin} \]

infus. rate: 1.78 mg x min\(^{-1}\)
(for Clcr = 0.1 L x min\(^{-1}\))

daily dose: 2.57 g
Results

concentration of vancomycin as a function of the time in patients treated with continuous infusion

Variability of vancomycin concentration during continuous infusion (typical patients)

Ampe et al., in preparation
"Pros" of continuous infusion
(beta-lactams / vancomycine)

• A more rational way of administering beta-lactams (and also applicable to other antibiotics for which the impact of concentration [once above x-fold the MIC] is low)

• Can be easier to use in hospital setting *

• "Monitoring made easy" and more reliable *

• Can help containing costs *

* not addressed in this talk, but ask questions…
"Cons" of continuous infusion
(beta-lactams / vancomycin)

- The stability of each beta-lactam MUST be critically assessed under the conditions of practical use…

- Compatibility issues may make things quite complex unless a dedicated line is used *

- Use of motor-operated pumps (or pumps with similar reliability) is probably essential *

- High serum levels maintained for prolonged periods may be associated with toxicities (for vancomycin, levels > 28 mg/L have been associated with renal toxicity; for beta-lactams, levels > 80 mg/L have been associated with convulsions [cefepime]) *

* not addressed in this talk, but ask questions…
Continuous infusion of antibiotics ...

A BRILLIANT IDEA....

But do not forget the problems...
In a nutshell ... so far ...

- Microbiology parameters: MIC!
- Pharmacodynamic parameters
- PK/PD as applied to beta-lactams and vacomycin
- 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>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC (mg/L)</td>
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</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>
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<tr>
<td>7102/10 d</td>
<td>512</td>
<td>32</td>
<td>1</td>
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^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

Nguyen T *et al.* unpublished
**A simple experiment …**

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<td>2048&gt; 128</td>
<td>16</td>
<td>32</td>
<td>4</td>
<td>0.5</td>
</tr>
<tr>
<td>2502/4 c</td>
<td>8</td>
<td>2</td>
<td>0.125</td>
<td>8192</td>
<td>4</td>
<td>0.25</td>
<td>4096</td>
<td>1</td>
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Nguyen T et al. unpublished
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 what about colistin?

You first need to consider the MIC distribution.

Here are the data of EUCAST for *Pseudomonas*.
Do you ever reach the epidemiological cut-off?

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

CMS
- $t_{1/2} \approx 2.3$ h.

Colistin:
- $t_{1/2} \approx 14.4$ h.
- $C_{\text{max}}$ (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; 53:3430-6
Do you hit all your inoculum?

Population analysis profiles of K. pneumoniae isolates

Poudyal et al. JAC 2008; 62:1311-1318

Problem #2: Heteroresistance is frequent with colistin

Poudyal et al. JAC 2008; 62:1311-1318
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

Slides are available from http://www.facm.ucl.ac.be