What do we know on PK/PD of β-lactams

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Transparency declaration

Research grants from:

- Astra-Zeneca – Cerexa (avibactam, ceftaroline, meropenem)

- Region wallonne with Eumedica as industrial sponsor (temocillin)
What do we know on PK/PD of β-lactams

Let’s try to lift the veil together ...
Main questions to be addressed

- Which PK/PD profile?
- Which value for PK/PD indices?
- Which optimal therapeutic scheme?
- Which adaptations for specific patients’ populations?
- What about new molecules?
PK/PD parameters for antibiotics

**C<sub>max</sub>**

Patient = host → PK

Bacteria = pharmacological target → PD

AUC

t > MIC

Concentration (mg/L)

Time (h)

MIC
β-lactams are time-dependent antibiotics

IN VITRO, $E_{\text{max}}$ at 4 x MIC

Craig & Ebert, Scand J Infect Dis. 1991; 74:63-70
β-lactams are time-dependent antibiotics

IN VITRO, $E_{\text{max}}$ at 4 x MIC

Craig & Ebert, Scand J Infect Dis. 1991; 74:63-70

cefotaxime
neutropenic mice
K. pneumoniae
lung infection
**β-lactams are time-dependent antibiotics**

**IN VITRO,** $E_{\text{max}}$ at 4 x MIC

**IN VIVO,**
- Static effect if T> MIC = 40%

*Cefotaxime neutropenic mice K. pneumoniae lung infection*

_Craig & Ebert, Scand J Infect Dis. 1991; 74:63-70_
β-lactams are time-dependent antibiotics

**IN VITRO,** $E_{\text{max}}$ at 4 x MIC

- **IN VIVO,**
  - Static effect if $T > \text{MIC} = 40\%$
  - $E_{\text{max}}$ if $T > \text{MIC} > 70\%$

Maximize the time of exposure

**Craig & Ebert, Scand J Infect Dis. 1991; 74:63-70**
The free fraction is bioavailable for activity

vascular space

plasma protein binding

blood cell binding,
diffusion into blood cells,
binding to intracellular biological material

eextravascular space

binding to extracellular biological material

tissue cell binding,
diffusion into tissue cells,
binding to intracellular biological material
Highly protein-bound β-lactams

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>% Protein Binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>flucloxacillin</td>
<td>&gt; 90 %</td>
</tr>
<tr>
<td>temocillin</td>
<td>~ 85 %</td>
</tr>
<tr>
<td>cefazolin</td>
<td>74-86 %</td>
</tr>
<tr>
<td>ceftriaxone</td>
<td>83-96%</td>
</tr>
</tbody>
</table>

→ Most affected by variations in serum protein content
Main questions to be addressed

- Which PK/PD profile?
- Which value for PK/PD indices?
- Which optimal therapeutic scheme?
- Which adaptations for specific patients’ populations?
- What about new molecules?
PK/PD targets based on animal studies

Percentage of the dosing interval over which the unbound (free) drug concentration remains above the minimum inhibitory concentration (MIC) of the infecting pathogen ($fT>MIC$) for various β-lactams after bolus dosing in animal infection models.

<table>
<thead>
<tr>
<th>β-lactams</th>
<th>$fT&gt;MIC$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bacteriostatic effect</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>35%-40%</td>
</tr>
<tr>
<td>Penicillins</td>
<td>30%</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>20%</td>
</tr>
</tbody>
</table>

Sinnollareddy et al, Clinical and Experimental Pharmacology and Physiology 2012; 39:489–496
PK/PD targets based on clinical studies

PK/PD targets proposed in publications dealings with critically-ill patients

<table>
<thead>
<tr>
<th>β-lactams</th>
<th>PK/PD target</th>
<th>Most often proposed target</th>
<th>% of cited targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>piperacillin-tazobactam</td>
<td>50 % T &gt; 1 x MIC</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>ceftazidime</td>
<td>100 % T &gt; 4-5 x MIC</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>cefepime</td>
<td>50-60 or 100 % T &gt; MIC</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>meropenem</td>
<td>40 % &gt; MIC</td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>

Delattre et al, submitted for publication
The authors “would advocate a PD target of 100%T > 1 x MIC for intermittent dosing, as this is likely to result in a concentration 4xMIC for 40-70% of the dosing interval as required for the different classes of β-lactams”.

Delattre et al, ECCMID 2016
A pop-PK study at first dose

1000 simulated patients

Delattre et al, ECCMID 2016

30-03-2017
Can we reconcile these targets (at first dose) ?

Is a PK/PD target of 100%T>1xMIC likely to result in a concentration 4xMIC for 40-70% of the dosing interval, as required for the different classes of β-lactams?

<table>
<thead>
<tr>
<th>Dosage (0.5h inf.)</th>
<th>No. of patients with 100%T&gt;MIC</th>
<th>No. of patients with 100% T&gt;1xMIC and 40-70%T&gt;4xMIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin 4g [q6h]</td>
<td>560 (56%)</td>
<td>257 (26%)</td>
</tr>
<tr>
<td>Ceftazidime 2g [q8h]</td>
<td>871 (87%)</td>
<td>307 (31%)</td>
</tr>
<tr>
<td>Cefepime 2g [q8h]</td>
<td>628 (63%)</td>
<td>128 (13%)</td>
</tr>
<tr>
<td>Meropenem 1g [q8h]</td>
<td>592 (59%)</td>
<td>555 (55%)</td>
</tr>
</tbody>
</table>

**Delattre et al, ECCMID 2016**

Not at first dose (except for meropenem) ...

**Loading...**

Need for a loading dose ...
Main questions to be addressed

- Which PK/PD profile?
- Which value for PK/PD indices?
- **Which optimal therapeutic scheme?**
- Which adaptations for specific patients’ populations?
- What about new molecules?
Therapeutic schemes to optimize time of exposure

Prolonged time of exposure

Concentration (mg/L)

Time (hr)

1 g IV every 8 hr (1-hr infusion)
1 g IV every 8 hr (4-hr infusion)
1 g IV (1-hr infusion), followed by 2 g IV (23-hr infusion)
Continuous infusion: some limitations ...

Chemical instability
Continuous infusion: some limitations ...

- **Definition:** > 90% intact product (Pharmacopeia)
- **Conditions:** mimicking the total daily dose (commercial product) in 48 mL (motor operated syringe) water without pH adjustment and maintained at a fixed temperature

<table>
<thead>
<tr>
<th>molecule</th>
<th>≤ 6 h</th>
<th>12 h</th>
<th>24 h</th>
<th>&gt; 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>penicillin G</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ampicillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>oxacillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>piperacillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>temocillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cefazolin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cefotaxime</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ceftriaxone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ceftazidime</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cefepine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>imipenem</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>meropenem</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **key:**
  - [37°C](#)
  - [25°C](#)
  - [4°C](#)

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*Servais & Tulkens, AAC 2001;45:2643-7 – Viaene et al. AAC 2002;46:2327-32 - Baririan et al. JAC 2003;51:651*
Main questions to be addressed

- Which PK/PD profile?
- Which value for PK/PD indices?
- Which optimal therapeutic scheme?
- **Which adaptations for specific patients’ populations?**
- What about new molecules?
Critically-ill patients: why are PK of β-lactams altered?

Hosthoff et al, Swiss Med Wkly. 2016;146:w14368
Critically-ill patients: The DALI cohort

Primary aim

- To determine whether contemporary antibiotic dosing for critically-ill patients achieves concentrations associated with maximal activity

Secondary aims

- Comparison of observed antibiotic PK/PD with the clinical outcome of therapy
- Description of the population PK of the individual antibiotics in ICU patients

Roberts et al, BMC Infectious Diseases 2012; 12:152
Proposed subgroups for the primary and secondary aims:

- Patients administered intermittent dosing versus extended or continuous infusions
- Patients with ‘steady-state’ versus ‘non-steady-state’ pharmacokinetics (‘non-steady-state’ defined as antibiotics commenced within 24-h prior to sampling)
- Patients with different levels of sickness severity as measured by SOFA, APACHE and PIRO Scores
- Different admission diagnoses
- Different indications for antibiotic therapy
- Presence of surgery within the 24-hours prior to sampling
- Different total body weight
- Different levels of renal function and presence of extracorporeal renal support techniques
Critically-ill patients: The DALI cohort

Roberts et al, CID 2014; 58:1072–83

Most often, optimal PK/PD target not reached
Critically-ill patients: The DALI cohort

Continuous infusion > intermittent bolus
Especially in patients with respiratory tract infection and high SOFA score

Abdel Aziz et al, JAC 2016; 71: 196–207
Renal insufficiency: why are PK of β-lactams altered?

**Intermittent**
- IHD: Intermittent haemodialysis
- IUF: Isolated Ultrafiltration

**Hybrid**
- SLEDD: Sustained (or slow) low efficiency daily dialysis
- SLEDD-F: Sustained (or slow) low efficiency daily dialysis with filtration

**Continuous**
- CVVH: Continuous veno-venous haemofiltration
- CVVHD: Continuous veno-venous haemodialysis
- CVVHDF: Continuous veno-venous haemodiafiltration
- SCUF: Slow continuous ultrafiltration

**Flow Rates**
- Blood flow: >200 ml/min
- Dialysate flow: > 500 ml/min
- High clearance but intermittent

- Blood flow: <200 ml/min
- Dialysate flow: < 34 ml/min
- Low clearance
Continuous renal replacement therapy

Conventional doses: CEF: 2g x 3; TZP: 4 g x 4; MEM: 1g x 3

PK/PD target

Drug elimination

In general, conventional dose appropriate
BUT TDM remains useful to readjust in specific patients

1Beumier et al, Critical Care 2014, 18:R105; 2Economou et al, http://dx.doi.org/10.1016/j.ijantimicag.2017.01.009
Discontinuous renal replacement therapy

Temocillin; 1 g for 24h (in the SmpC: 1g/48h)

→ Current dosing suboptimal

Vandecasteele, Bastos et al; IJAA 2015; 46:660–665
Obese patients: why are PK of β-lactams altered?

- Increased intestinal absorption of lipophilic antibiotics
- Obesity-associated kidney failure
- Reduced hepatic metabolism due to fatty infiltration
- Variable effect of cytochrome P450 enzymes
- Delayed gastric emptying leading to decreased absorption

Increase in serum antibiotic concentration

Decrease in serum antibiotic concentration

Increased glomerular filtration rate

Increased volume of distribution

Al-Dorzi et al, Curr Opin Infect Dis. 2014;27:165-73
Obese patients: why are PK of \( \beta \)-lactams altered?

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
<th>Hydrophilic antibiotics</th>
<th>Lipophilic antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generally have low volume of distribution.</strong></td>
<td>Are primarily cleared in kidneys.</td>
<td>Generally have high volume of distribution.</td>
</tr>
<tr>
<td><strong>Have lower intracellular and tissue penetration.</strong></td>
<td></td>
<td>Are primarily cleared in the liver.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Have higher intracellular and tissue penetration.</td>
</tr>
</tbody>
</table>

| Changes in obesity | | Obesity increases the antibiotic volume of distribution. | Obesity have variable effects on hepatic clearance. |
|--------------------|--------------------------|---------------------------------------------------|
| **Obesity has little effect of the antibiotic volume of distribution.** | | | |
| **Renal clearance is generally increased in obesity unless renal impairment is present.** | | |

<table>
<thead>
<tr>
<th>Dosing in obesity</th>
<th>Ideal or adjusted body weight is generally used for dosing ( ^a ).</th>
<th>Total body weight is generally recommended for dosing ( ^a ).</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Examples of antibiotics</th>
<th>(( \beta )-lactams (penicillins, cephalosporins, carbapenems))</th>
<th>Fluoroquinolones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td></td>
<td>Macrolides</td>
</tr>
<tr>
<td>Vancomycin</td>
<td></td>
<td>Tigecycline</td>
</tr>
<tr>
<td>Colistin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Broad spectr. β-lactams: non critically-ill obese patients

Hites et al, Nutrition & Diabetes 2014;4:e119

Conventional dosing inadequate if increased renal function
Critically-ill AND obese: a ‘big’ problem ...

Alobaid et al, IJAA 2016; 47: 259–268
Broad spectrum β-lactams: critically-ill obese patients

No major change in concentration

Hites et al, AAC 2013; 57:708-15
Broad spectrum β-lactams: critically-ill obese patients

No major change in concentration...

But we need more data in morbidly obese patients

Hites et al, AAC 2013; 57:708-15
CF patients: why are PK of β-lactams altered?

**Absorption**
- ↑ gastric acid
- ↓ secretion pancreatic enzymes

**Distribution**
- ↑ plasma volume (pulmonary HT)
- ↓ albumin / lipoproteins
- ↑ \(\gamma\)-globulins / fatty acids

**Elimination**
- ↑ glomerular filtration
- ↑ tubular secretion

**PK**
- delayed absorption
- increased Vd
- accelerated elimination

*Prandota, Drugs 1988; 35:542-578*
CF patients: how are PK of β-lactams altered?

Table 1—Pharmacokinetics of β-Lactam Antibiotics in Patients with Cystic Fibrosis Compared with Those in Normal Subjects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Volume of Distribution (%)</th>
<th>Clearance Rate (%)</th>
<th>Half-life (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin</td>
<td>↑ 37</td>
<td>↑ 21</td>
<td>↑ 24</td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>↑ 37</td>
<td>↑ 78</td>
<td>↓ 19</td>
</tr>
<tr>
<td>Dicloxacillin</td>
<td>↑ 297</td>
<td></td>
<td>↑ 17</td>
</tr>
<tr>
<td>Ticarcillin</td>
<td>↑ 25</td>
<td></td>
<td>↓ 8</td>
</tr>
<tr>
<td>Azlocillin</td>
<td>↑ 29</td>
<td>↑ 22</td>
<td>↓ 20</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>↑ 57</td>
<td></td>
<td>↓ 47</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>↑ 39</td>
<td>↑ 40</td>
<td>↓ 28</td>
</tr>
<tr>
<td>Ceftazadime</td>
<td>↑ 20</td>
<td>↑ 42</td>
<td>↓ 28</td>
</tr>
<tr>
<td>Imipenem</td>
<td>↑ 20</td>
<td>↑ 5</td>
<td>↓ 20</td>
</tr>
</tbody>
</table>

Vd and clearance generally increased → risk of under-dosing

Lietman, Chest 1988; 94:115S-119S
β-lactam PK/PD in adult CF patients

Pharmacokinetic data in CF patients.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Clearance (L/h)</th>
<th>Volume of distribution (L)</th>
<th>Half-life (h)</th>
<th>Protein binding (f_u)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam [6] *</td>
<td>6 ± 1.1</td>
<td>10.95 ± 1.26</td>
<td>1.54 ± 0.17</td>
<td>0.56</td>
</tr>
<tr>
<td>Cefepime [8] *</td>
<td>8.47 ± 3.45</td>
<td>14.9 ± 5.78</td>
<td>1.64 ± 0.36</td>
<td>0.2</td>
</tr>
<tr>
<td>Ceftazidime [9] **</td>
<td>5.37 (3.35–12.8)</td>
<td>9.14 (2.77–19.9)</td>
<td>1.48 (0.49–1.78)</td>
<td>0.1</td>
</tr>
<tr>
<td>Meropenem [10] *</td>
<td>15.9 ± 1.9</td>
<td>19.6 ± 2.2</td>
<td>0.86 ± 0.05</td>
<td>0.2</td>
</tr>
<tr>
<td>Piperacillin–tazobactam [11]**</td>
<td>8.78 (6.39–12.1)</td>
<td>8.13 (5.16–10.8)</td>
<td>0.69 (0.34–1.19)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

* Mean ± standard deviation.
** Median (range).

Conventional doses with prolonged administration may be appropriate.
Ceftaroline in CF patients

Bolus 600 mg x 2

**EUCAST S Bkpt**

Bolus 600 mg x 3

Prolonged perf. 600 mg x 2

Prolonged perf. 600 mg x 3

→ Higher dose & prolonged perfusion needed

*Autry et al, Pharmacotherapy 2016; 36:13-18*
Children: why are PK of β-lactams altered?

Adapted from Kearns, NEJM 2003; 349:1157-1167
Meropenem in children with severe infections

Target: $f_T > MIC$ 40%

Higher dose & prolonged perfusion needed

EUCAST S bkpt

Recommended dose (SmpC): 10-20 mg/kg x 3

Kongthavonsakul et al, IJAA 2016; 48:151–157
Piperacillin-tazobactam in children with severe infections

Recommended dose
(SmpC): 80-100 mg/kg x 4

Target: $fT > MIC \ 50\%$

Target: $fT > MIC \ 100\%$

$\rightarrow$ High dose & prolonged perfusion needed

Nichols et al, AAC 2015; 60:522-531
Main questions to be addressed

- Which PK/PD profile?
- Which value for PK/PD indices?
- Which optimal therapeutic scheme?
- Which adaptations for specific patients’ populations?
- What about new molecules?
Ceftazidime/Ceftolozane + Avibactam/Tazobactam...

- **Enhanced activity against Gram-negative bacilli**
- **Stability against β-lactamases**
- **Antipseudomonal activity**
  - **(but lost if AmpC β-lactamase overproduction)**
- **Increased antipseudomonal activity and less susceptibility to AmpC β-lactamase**
  - **BUT risk of convulsions**

Zhanel et al. Drugs. 2014;74:31-51

- **Increased antipseudomonal activity and less susceptibility to AmpC**
  - **Lower risk of convulsions**
  - **Combined with tazobactam**

- **Combined with avibactam**
Ceftazidime-Avibactam for pneumonia

Dose fractionation makes avibactam more potent at lower concentrations

Berkhout et al, AAC 2016; 60:368–375.
Ceftazidime-Avibactam for pneumonia

\[ 50\% \text{ } fT > \text{ CAZ-AVI MIC for ceftazidime and } 50\% \text{ } fT > \text{ CT for avibactam} \]

Best correlation if \( f_{\text{conc}} > 1 \text{ mg/L} \) as a cutoff\(^1\)

Trough level at 0.5 mg/L after administration of 500 mg/2 g ceftazidime\(^2\)

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\(^1\)Berkhout et al, AAC 2016; 60:368 –375; \(^2\)Merdjan et al, Clin Drug Investig. 2015; 35:307-17.
Ceftolozane-Tazobactam for pneumonia

Simulated PK of Ceftolozane/Tazobactam, 2/1 g x 3 (approved dose for IAI: 1/0.5 g)

Xiao et al, J Clin Pharm 2016; 56:56-66
Ceftolozane-Tazobactam for pneumonia

Ceftolozane/Tazobactam, 1/0.5 g

A

B

serum

ELF

Ceftolozane/Tazobactam, 2/1 g

A

B

Xiao et al, J Clin Pharm 2016; 56:56-66

Increase the dose
Take home messages

- β-lactams are time-dependent → prolong time of exposure (continuous or prolonged infusion; frequent administration)

- No consensus so far on PK/PD target but probably optimal exposure needed in critically-ill patients (see next speakers for resistance and toxicity issues)

- Specific patients’ populations
  Under-dosing is frequent → any room for TDM (see next session) ?

- Efforts are made to try rationalizing dosing for new drugs from the beginning
Take home messages

- β-lactams are time-dependent → prolong time of exposure (continuous or prolonged infusion; frequent administration)

- No consensus so far on PK/PD target but probably optimal exposure needed in critically-ill patients (see next speakers for resistance and toxicity issues)

- Specific patients’ populations
  Under-dosing is frequent → any room for TDM (see next session) ?

- Efforts are made to try rationalizing dosing for new drugs from the beginning
What do we know on PK/PD of β-lactams

I hope it will help you to flight for the rest of the day ...