Achieving pharmacokinetic/pharmacodynamic (PK/PD) targets of \( \beta \)-lactams in critically ill patients at first dose:

*Can we do it with standard dosing?*

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General Considerations

PK/PD parameter predictive of β-lactam efficacy?

Concentration vs. time profile

**T>MIC**
Time during which concentrations are above the minimal inhibitory concentration (MIC)

Maximize the exposure time
% of Time? Threshold?

%fT>MIC required for β-lactams

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**Prevention of Resistance: A Goal for Dose Selection for Antimicrobial Agents**

G. L. Drusano
Division of Clinical Pharmacology, Clinical Research Institute, Albany Medical College and New York State Department of Health, Albany, New York

**Table 1.** Percentage of the dosing interval required for free drug concentrations that exceed the MIC of the pathogen for β-lactam antibiotics.

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Stasis end point</th>
<th>Max kill end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenems</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Penicillins</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>40</td>
<td>60–70</td>
</tr>
</tbody>
</table>

**NOTE.** Data are % of dosing interval. Max kill is the fraction of the dosing interval needed to be covered by free drug to achieve maximal kill of the pathogen; stasis is the fraction of the dosing interval needed to be covered by free drug to prevent pathogen growth. From W. A. Craig (personal communication).
% of Time? Threshold?

Literature review

- Original papers in PubMed published from 2000 to 2015
- Serum or plasma concentrations in critically ill patients
- Search terms:
  - title: piperacillin, ceftazidime, cefepime or meropenem
  - text: pharmacokinetics or PK, pharmacodynamics or PD and minimal inhibitory concentration or MIC

Example for piperacillin: what is the target?

70 papers reviewed…
… 22 usable papers

<table>
<thead>
<tr>
<th>Reported PK/PD targets</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>100%T&gt;1xMIC</td>
<td>14/27</td>
</tr>
<tr>
<td>50%T&gt;1xMIC</td>
<td>9/27</td>
</tr>
<tr>
<td>50%T&gt;4xMIC</td>
<td>3/27</td>
</tr>
<tr>
<td>100%T&gt;4xMIC</td>
<td>1/27</td>
</tr>
</tbody>
</table>
% of Time? Threshold?

Literature review

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Example for piperacillin: which Mics?

70 papers reviewed…
… 22 usable papers

<table>
<thead>
<tr>
<th>Reported MIC data</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual MIC</td>
<td>7/23</td>
</tr>
<tr>
<td>EUCAST</td>
<td>8/23</td>
</tr>
<tr>
<td>CLSI</td>
<td>1/23</td>
</tr>
<tr>
<td>Unknown</td>
<td>7/23</td>
</tr>
</tbody>
</table>
% of Time? Threshold?

Literature review

- Original papers in PubMed published from 2000 to 2015
- Serum or plasma concentrations in critically ill patients
- Search terms:
  - title: piperacillin, ceftazidime, cefepime or meropenem
  - text: pharmacokinetics or PK, pharmacodynamics or PD and minimal inhibitory concentration or MIC

Ex. Piperacillin

<table>
<thead>
<tr>
<th>Reported MIC data</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual MIC</td>
<td>30%</td>
</tr>
<tr>
<td>EUCAST</td>
<td>35%</td>
</tr>
<tr>
<td>CLSI</td>
<td>4%</td>
</tr>
<tr>
<td>Unknown</td>
<td>31%</td>
</tr>
</tbody>
</table>

!Lack of clinical outcome data!

Impossible to assess and/or compare the clinical efficacy of the PK/PD targets
The authors “would advocate a PD target of 100%T>1xMIC 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”.

(Minerva Anestesiol 2011;77:1-2) REVIEW

Continuous infusion vs. bolus dosing: implications for beta-lactam antibiotics

MOHD HAFIZ ABDUL AZIZ 1, C. E. STAATZ 2, C. M. J. KIRKPATRICK 3, J. LIPMAN 4, 5, J. A. ROBERTS 4, 6
The ‘Houston’ Target

Maximal killing: $100\% T > 4x\text{MIC}$

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Figure 1. The relationship between microbiological success and $T > 4.3 \times \text{MIC}$, determined by univariate logistic regression analysis. Probability $= e^{L}/(e^{L} + 1)$, where $L = 0.064699x - 3.9234$; OR = 645, $P = 0.006$.

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FIG. 2. Observed microbiologic responses to various meropenem exposures. Data are presented as the means ± standard deviations of the bacterial burden. WT, wild type; AmpC, ceftazidime-resistant (AmpC) mutant.
The ‘Houston’ Target

Maximal killing: 100%T > 4xMIC

100%fT > 4xMIC for microbiological success

**Figure 1.** The relationship between microbiological success and $T > 4.3 \times \text{MIC}$, determined by univariate logistic regression analysis. Probability is $e^L/(e^L + 1)$, where $L = 0.064699x - 3.9234$; OR = 645, $P = 0.006$. 

**D**

$\frac{fC_{\text{min}}}{\text{MIC}} = 6$ to suppress resistance emergence

**FIG. 2.** Observed microbiologic responses to various meropenem exposures. Data are presented as the means ± standard deviations of the bacterial burden. WT, wild type; AmpC, ceftazidime-resistant (AmpC) mutant.
Objectives of the Study

In critically-ill patients receiving a first dose of β-lactam:

1. Do we reach ‘Australian double target’
   \((100\%\text{T}>1\times\text{MIC} \sim 40-70\%\text{T}>4\times\text{MIC})\) with the standard dosage?

2. Which dose do we need to reach the ‘Houston’ target
   \((100\%\text{T}>4\times\text{MIC})\)?
Critically ill septic patients treated with a first dose of:

- piperacillin [4g] \((n=22)\),
- ceftazidime [2g] \((n=18)\),
- cefepime [2g] \((n=19)\) or
- meropenem [1g] \((n=19)\)

infused over 30 minutes

* Taccone FS et al. Crit Care 2010;14:R126
Modeling and Simulations (1/2)

- **PK data**
  - Population modeling  (Delattre *et al.* Clin Biochem 2012;45:780-6)
    - Two-compartment model
    - Population estimates (basic model):

<table>
<thead>
<tr>
<th></th>
<th>Piperacillin</th>
<th>Ceftazidime</th>
<th>Cefepime</th>
<th>Meropenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1 (L for 70kg)</td>
<td>24</td>
<td>20</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>CL (L/h for 70kg)</td>
<td>6.8</td>
<td>3.5</td>
<td>4.5</td>
<td>7.5</td>
</tr>
</tbody>
</table>

V1, central volume of distribution; CL, total body clearance

- Simulations: NONMEM
  
  For each β-lactam → 1000 patients
Modeling and Simulations (2/2)

- Target MIC

EUCAST “S” breakpoints for *Pseudomonas* spp.*

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>EUCAST breakpoints for <em>Pseudomonas</em> spp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin</td>
<td>S ≤ 16 mg/L</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>S ≤ 8 mg/L</td>
</tr>
<tr>
<td>Cefepime</td>
<td>S ≤ 8 mg/L</td>
</tr>
<tr>
<td>Meropenem</td>
<td>S ≤ 2 mg/L</td>
</tr>
<tr>
<td></td>
<td>R &gt; 16 mg/L</td>
</tr>
<tr>
<td></td>
<td>R &gt; 8 mg/L</td>
</tr>
</tbody>
</table>

S, susceptibility; R, resistance

*2016-01-01, v 6.0; [http://www.eucast.org](http://www.eucast.org)*

Last access: April 1, 2016
The ‘Australian’ Targets (1/3)

100%T > 1xMIC ~ 40-70%T > 4xMIC

“S” breakpoint from EUCAST for Pseudomonas spp.: 16 mg/L for piperacillin, 8 mg/L for ceftazidime
The ‘Australian’ Targets (1/3)

100%T>1xMIC ~ 40-70%T>4xMIC

Piperacillin 4g q6h, 0.5-h infusion

Ceftazidime 2g q8h, 0.5-h infusion

“S” breakpoint from EUCAST for *Pseudomonas* spp.: 16 mg/L for piperacillin, 8 mg/L for ceftazidime
The ‘Australian’ Targets (2/3)

100%T>1xMIC ~ 40-70%T>4xMIC

Ceftazidime 2g q8h, 0.5-h infusion

Cefepime 2g q8h, 0.5-h infusion

Meropenem 1g q8h, 0.5-h infusion

"S" breakpoint from EUCAST for Pseudomonas spp.: 8 mg/L for cefepime, 2 mg/L for meropenem
Are 'Australian' targets reached?

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?

For 1,000 critically-ill septic patients treated with a first dose of β-lactam:

<table>
<thead>
<tr>
<th></th>
<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</td>
<td>4g [q6h]</td>
<td>560 (56%)</td>
<td>257 (26%)</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>2g [q8h]</td>
<td>871 (87%)</td>
<td>307 (31%)</td>
</tr>
<tr>
<td>Cefepime</td>
<td>2g [q8h]</td>
<td>628 (63%)</td>
<td>128 (13%)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1g [q8h]</td>
<td>592 (59%)</td>
<td>555 (55%)</td>
</tr>
</tbody>
</table>

NO at first dose except for meropenem
The ‘Houston’ Target …

Required median first doses to reach 100% at 4 × MIC

<table>
<thead>
<tr>
<th>Infusion time (h)</th>
<th>Piperacillin</th>
<th>Ceftazidime</th>
<th>Cefepime</th>
<th>Meropenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>0.5</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>12</td>
<td>14</td>
<td>16</td>
</tr>
</tbody>
</table>

- **Required dose** (25%-75%)
- **Standard dose**
The ‘Houston’ Target …

<table>
<thead>
<tr>
<th>First dose of β-lactam in critically ill patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard dose</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>0.5h infusion</td>
</tr>
<tr>
<td>Piperacillin</td>
</tr>
<tr>
<td>Ceftazidime</td>
</tr>
<tr>
<td>Cefepime</td>
</tr>
<tr>
<td>Meropenem</td>
</tr>
</tbody>
</table>

Which dose is needed to reach 100% \( T > 4 \times \text{MIC} \)?

~ 50% to 150% increase of the standard dose even with a 3-h infusion
Conclusions

- The ‘Australian’ targets (100%T>1xMIC ~ 40-70%T>4xMIC)
  - Not reached with standard dosing
    (except for meropenem but low target MICs !!)

- The ‘Houston’ target (100%T>4xMIC)
  - Will require a 50-150% increase over standard dose
  - Systematic 3-h infusion?

Increasing the first dose is probably essential to be optimal in severely-ill patients.

100%T>4xMIC : a new Graal ?

The discussion is open…