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

Can we do it with standard dosing ?

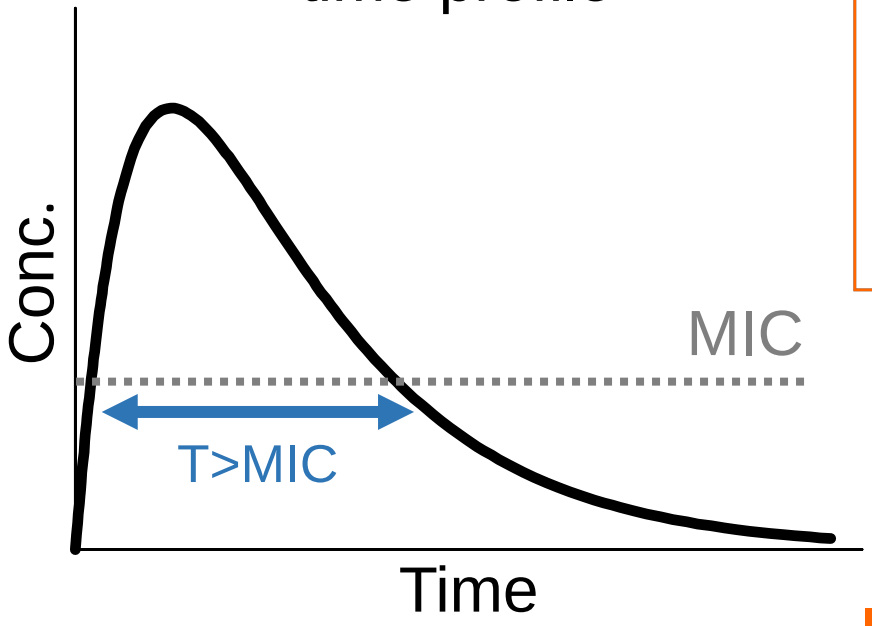
Isabelle K. Delattre[1,7], Fabio S. Taccone[2], Frédérique Jacobs[3], Thierry Dugernier[4], Herbert Spapen[5], Pierre-François Laterre[6], Pierre E. Wallemacq[7], Vincent Tam[8], Françoise Van Bambeke[1], Paul M. Tulkens[1]

[1] Université catholique de Louvain, Louvain Drug Research Institute, Brussels, Belgium
[2] Hôpital universitaire Erasme, Service des soins intensifs, Brussels, Belgium
[3] Hôpital universitaire Erasme, Service des maladies infectieuses, Brussels, Belgium
[4] Clinique St-Pierre, Ottignies, Service des soins intensifs, Brussels, Belgium
[5] Universitair Ziekenhuis Brussel, Service des soins intensifs, Brussels, Belgium
[6] Cliniques Universitaires St-Luc, Service des soins intensifs, Brussels, Belgium
[7] Université catholique de Louvain, Institut de recherche expérimentale et Clinique, Brussels, Belgium
[8] University of Houston, College of Pharmacy, Houston, United States

General Considerations

PK/PD parameter predictive of β-lactam efficacy ?

Concentration *vs.* time profile



T>MIC

Time during with concentrations above the minimal inhibitory concentration (MIC)

Maximize the exposure time

% of Time? Threshold?

%*f*T>MIC required for β-lactams

CID 2003:36 (Suppl 1)

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.

Drug class	Stasis end point	Max kill end point
Carbapenems	20	40
Penicillins	30	50
Cephalosporins	40	60–70

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

Reported PK/PD targets	
100%T>1xMIC	14/27
50%T>1xMIC	9/27
50%T>4xMIC	3/27
100%T>4xMIC	1/27

% of Time? Threshold?

Literature review

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Example for piperacillin: which Mics ?

70 papers reviewed…

… 22 usable papers

Reported MIC data	
Actual MIC	7/23
EUCAST	8/23
CLSI	1/23
Unknown	7/23

% of Time? Threshold?

Literature review

- Original papers in PubMed published from 2000 to 2015
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  - text: pharmacokinetics or PK, pharmacodynamics or PD and minimal inhibitory concentration or MIC

Ex. Piperacillin

Reported MIC data	
Actual MIC	30%
EUCAST	35%
CLSI	4%
Unknown	31%

!Lack of clinical outcome data!

↓

Impossible to assess and/or compare the clinical efficacy of the PK/PD targets

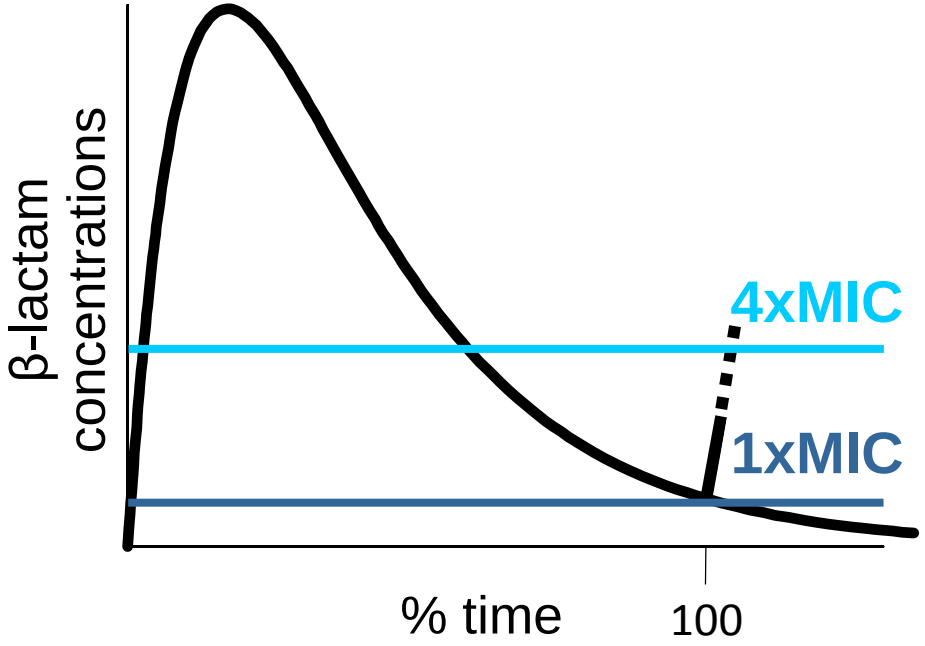
The ‘Australian’ Hypothesis

(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 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*”.



100%T > 1xMIC

~

40-70%T > 4xMIC

The 'Houston' Target

Maximal killing: 100%T > 4xMIC

Journal of Antimicrobial Chemotherapy (2002) **50**, 425–428
DOI: 10.1093/jac/dkf130

JAC

Pharmacodynamics of cefepime in patients with Gram-negative infections

Vincent H. Tam[1,2], Peggy S. McKinnon[1], Ronda L. Akins[1]*, Michael J. Rybak[1,3] and George L. Drusano[2]†

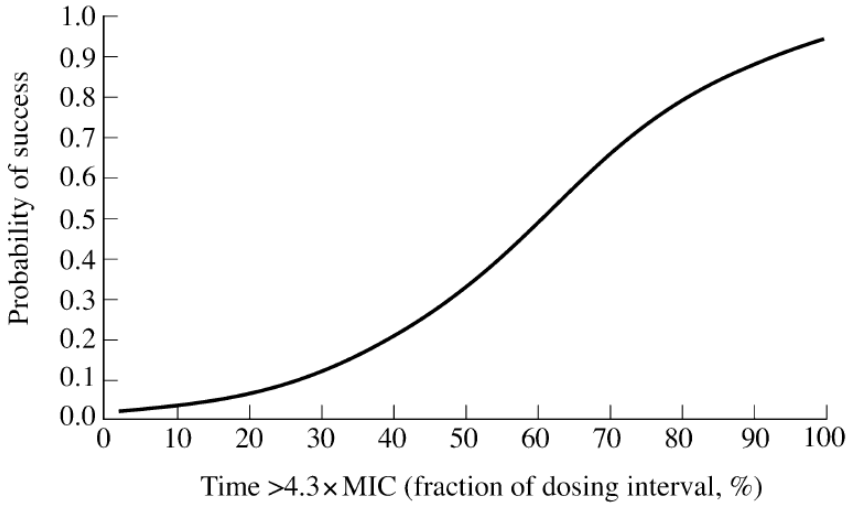


Figure 1. The relationship between microbiological success and $T >$ 4.3 × MIC, determined by univariate logistic regression analysis. Probability = $e^L/(e^L + 1)$, where $L = 0.064699x - 3.9234$; OR = 645, $P = 0.006$.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2005, p. 4920–4927
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.12.4920–4927.2005

Vol. 49, No. 12

Optimization of Meropenem Minimum Concentration/MIC Ratio To Suppress In Vitro Resistance of *Pseudomonas aeruginosa*

Vincent H. Tam,[1]* Amy N. Schilling,[1] Shadi Neshat,[2] Keith Poole,[2] David A. Melnick,[3] and Elizabeth A. Coyle[1]

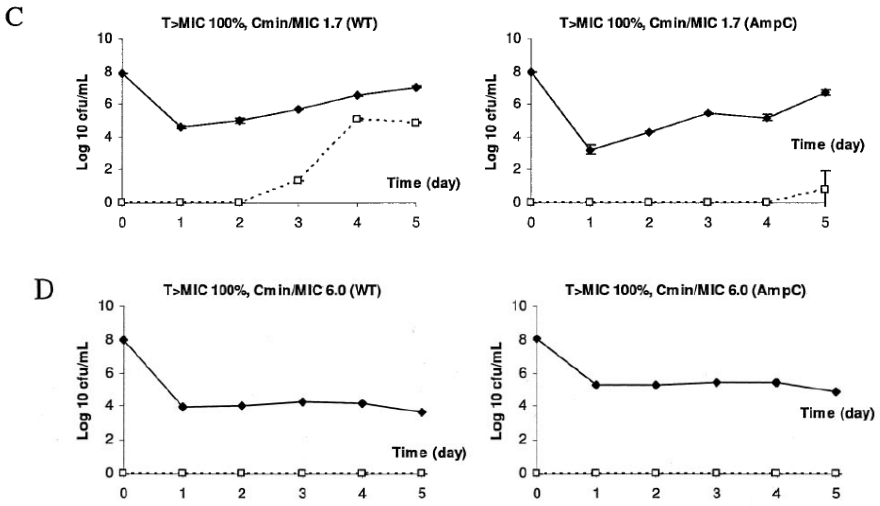


FIG. 2. Observed microbiologic responses to various meropenem exposures. Data are presented as the means ± standard deviations of the bacterial burden. WT, wild type; AmpC, ceftazidime-resistant (AmpC) mutant.

The 'Houston' Target

Maximal killing: 100%T > 4xMIC

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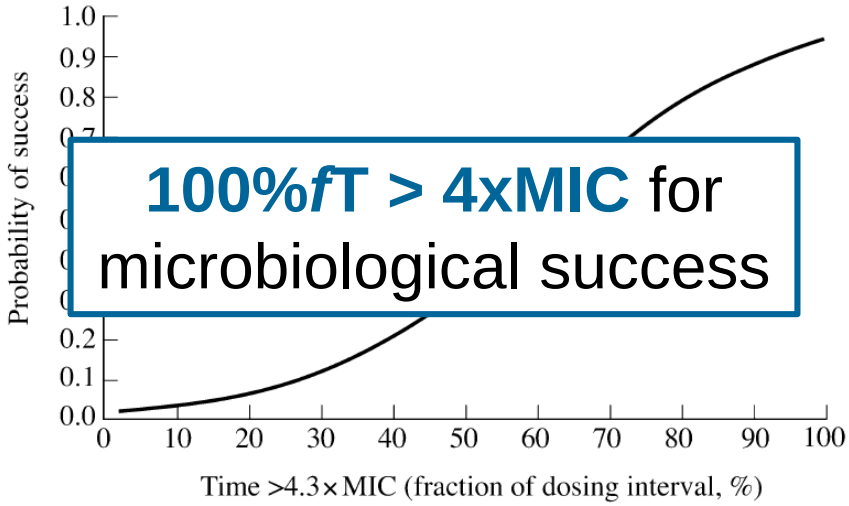

100%*f*T > 4xMIC for microbiological success

Figure 1. The relationship between microbiological success and $T > 4.3 \times$ 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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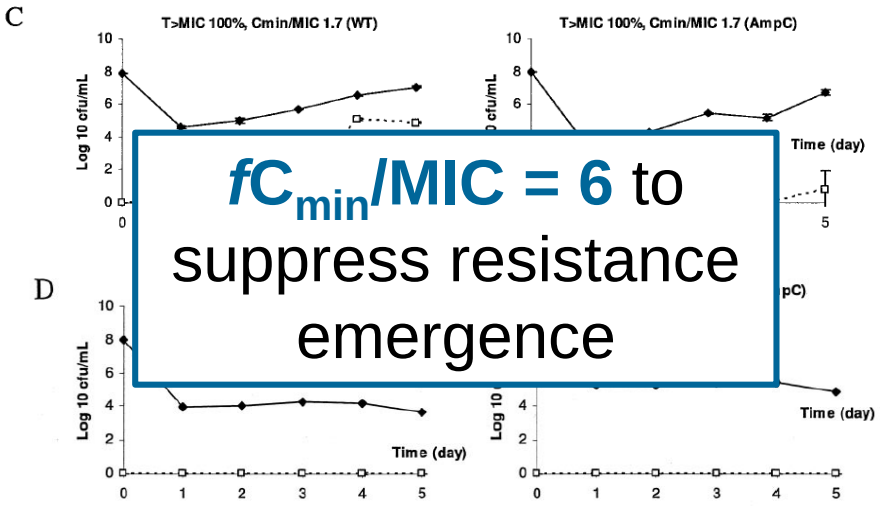


***f*C$_{min}$/MIC = 6** to suppress resistance emergence

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.

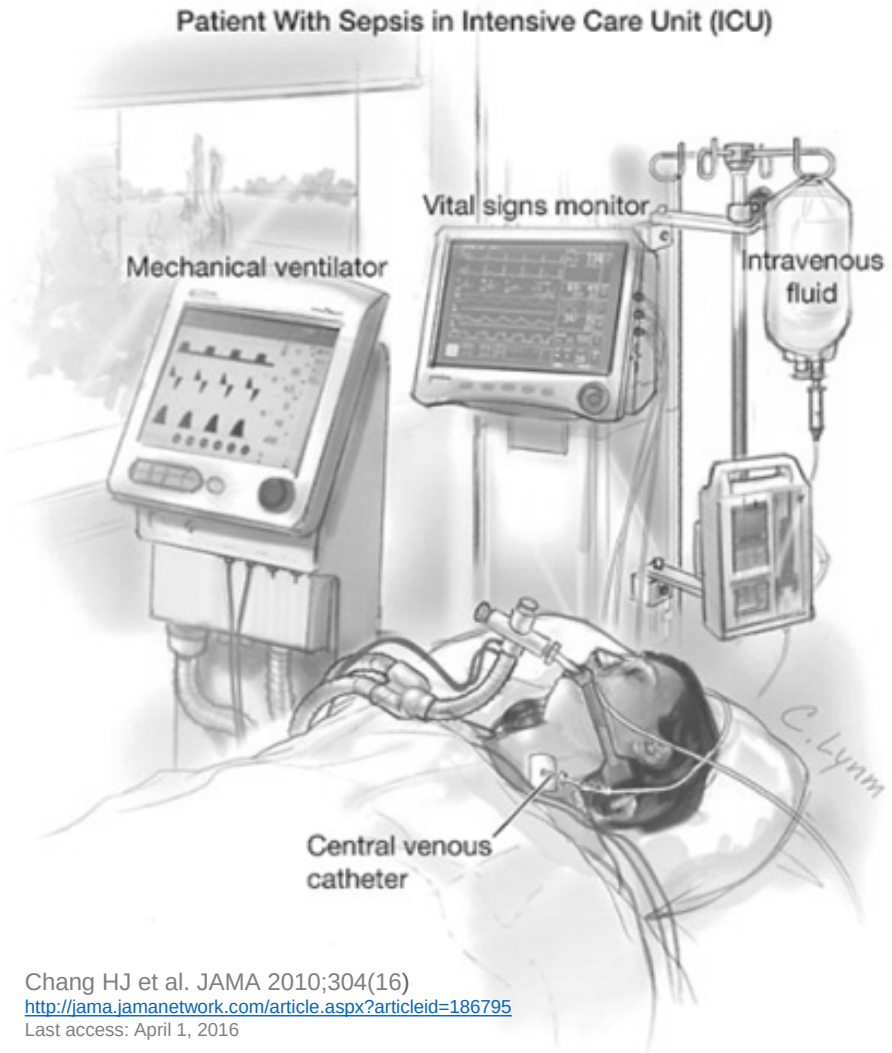
Objectives of the Study

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

1. Do we reach 'Australian double target' **(100%T>1xMIC ~ 40-70%T>4xMIC)** with the standard dosage ?

2. Which dose do we need to reach the 'Houston' target **(100%T>4xMIC)** ?

Patients



Chang HJ et al. JAMA 2010;304(16)
http://jama.jamanetwork.com/article.aspx?articleid=186795
Last access: April 1, 2016

Critically ill septic patients treated with a <u>first dose</u> 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):

	Piperacillin	Ceftazidime	Cefepime	Meropenem
V1 (L for 70kg)	24	20	18	24
CL (L/h for 70kg)	6.8	3.5	4.5	7.5

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.*

	EUCAST breakpoints for *Pseudomonas* spp.	
Piperacillin	**S ≤ 16 mg/L**	R > 16 mg/L
Ceftazidime	**S ≤ 8 mg/L**	R > 8 mg/L
Cefepime	**S ≤ 8 mg/L**	R > 8 mg/L
Meropenem	**S ≤ 2 mg/L**	R > 8 mg/L

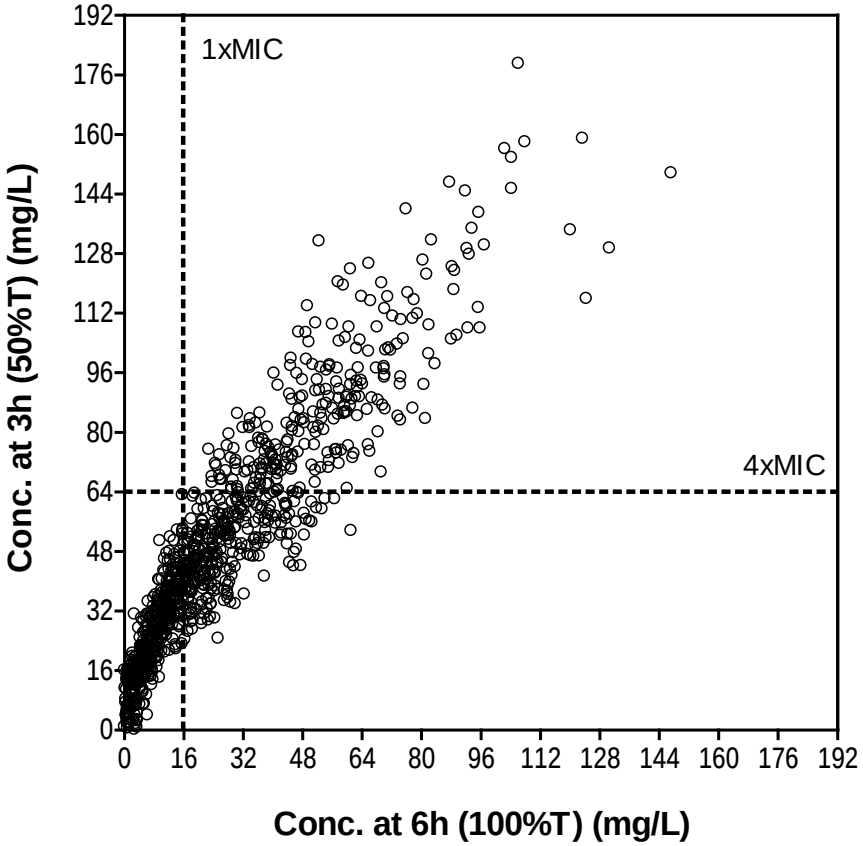
S, susceptibility; R, resistance

* 2016-01-01, v 6.0; http://www.eucast.org
Last access: April 1, 2016

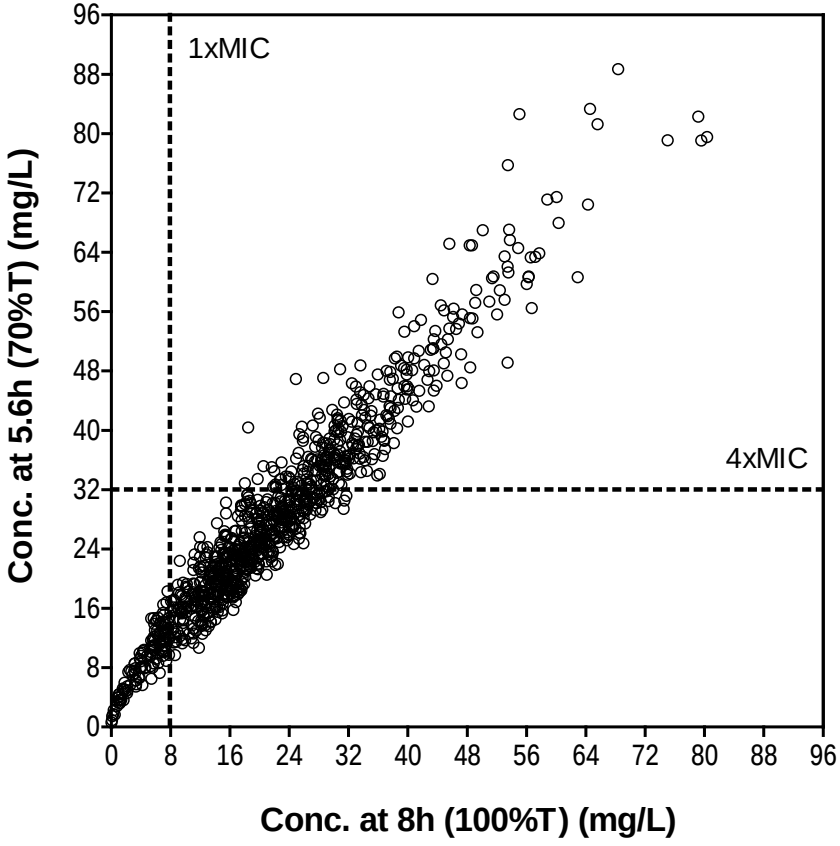
The ‘Australian’ Targets (1/3)

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

Piperacillin 4g q6h, 0.5-h infusion



Ceftazidime 2g q8h, 0.5-h infusion

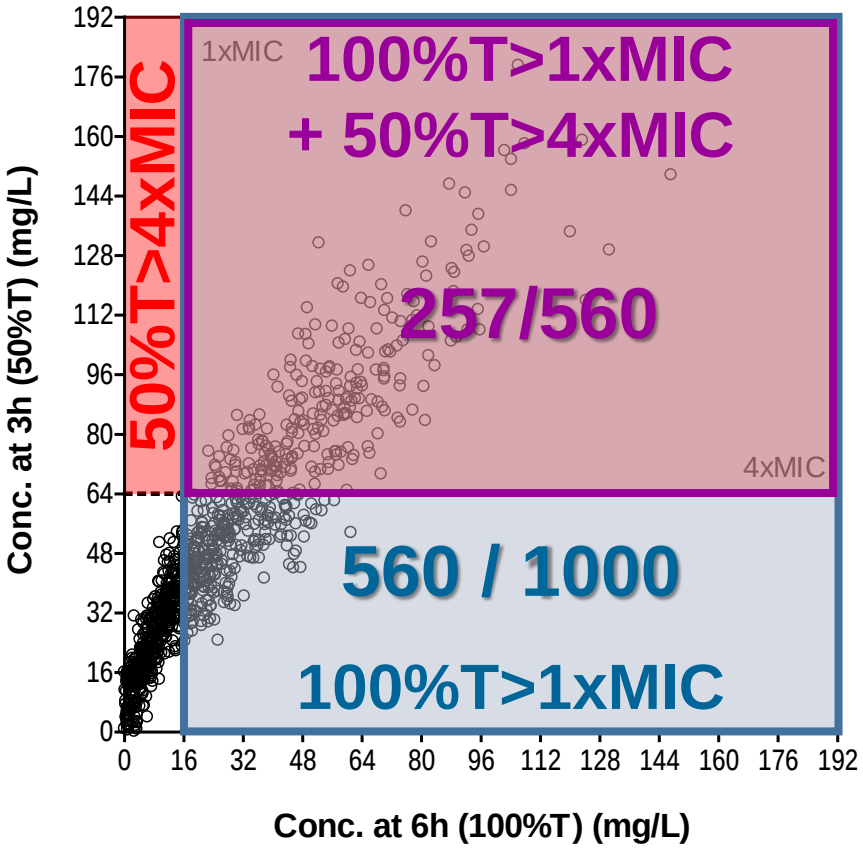


“S” breakpoint from EUCAST for *Pseudomonas* spp.: **16 mg/L** for **piperacillin**, **8 mg/L** for **ceftazidime**

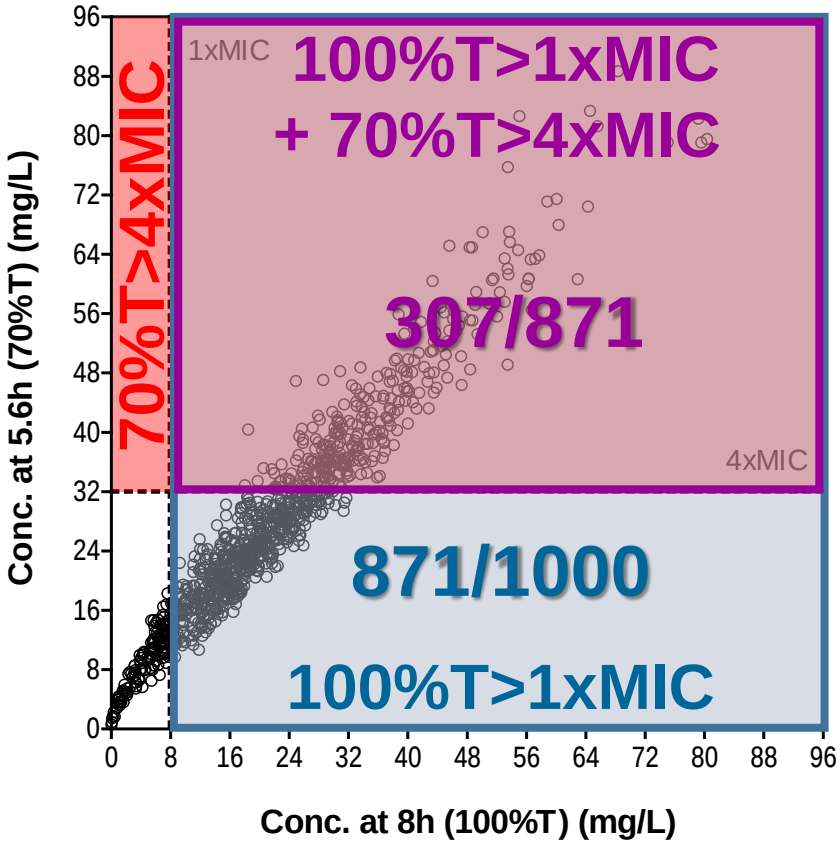
The ‘Australian’ Targets (1/3)

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

Piperacillin 4g q6h, 0.5-h infusion



Ceftazidime 2g q8h, 0.5-h infusion

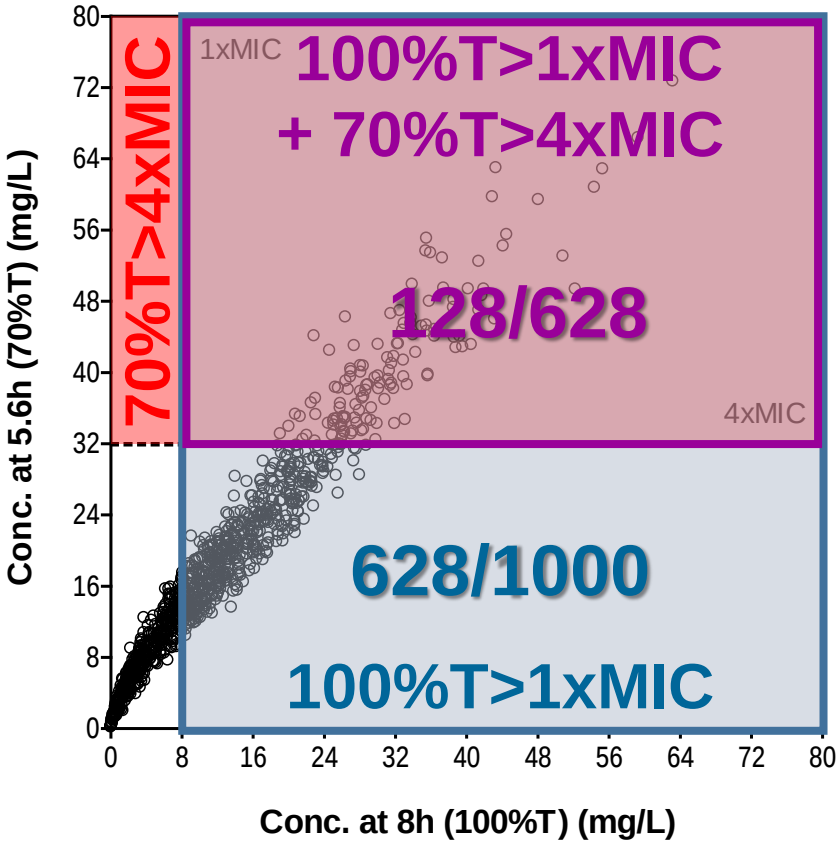


“S” breakpoint from EUCAST for *Pseudomonas* spp.: **16 mg/L** for **piperacillin**, **8 mg/L** for **ceftazidime**

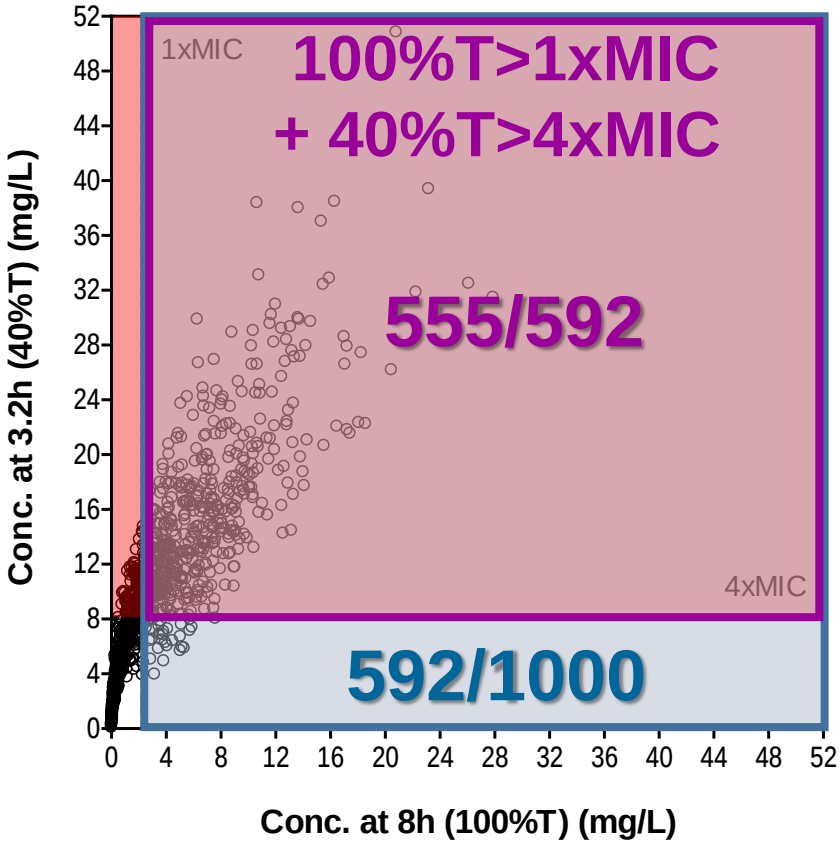
The ‘Australian’ Targets (2/3)

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

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 ?

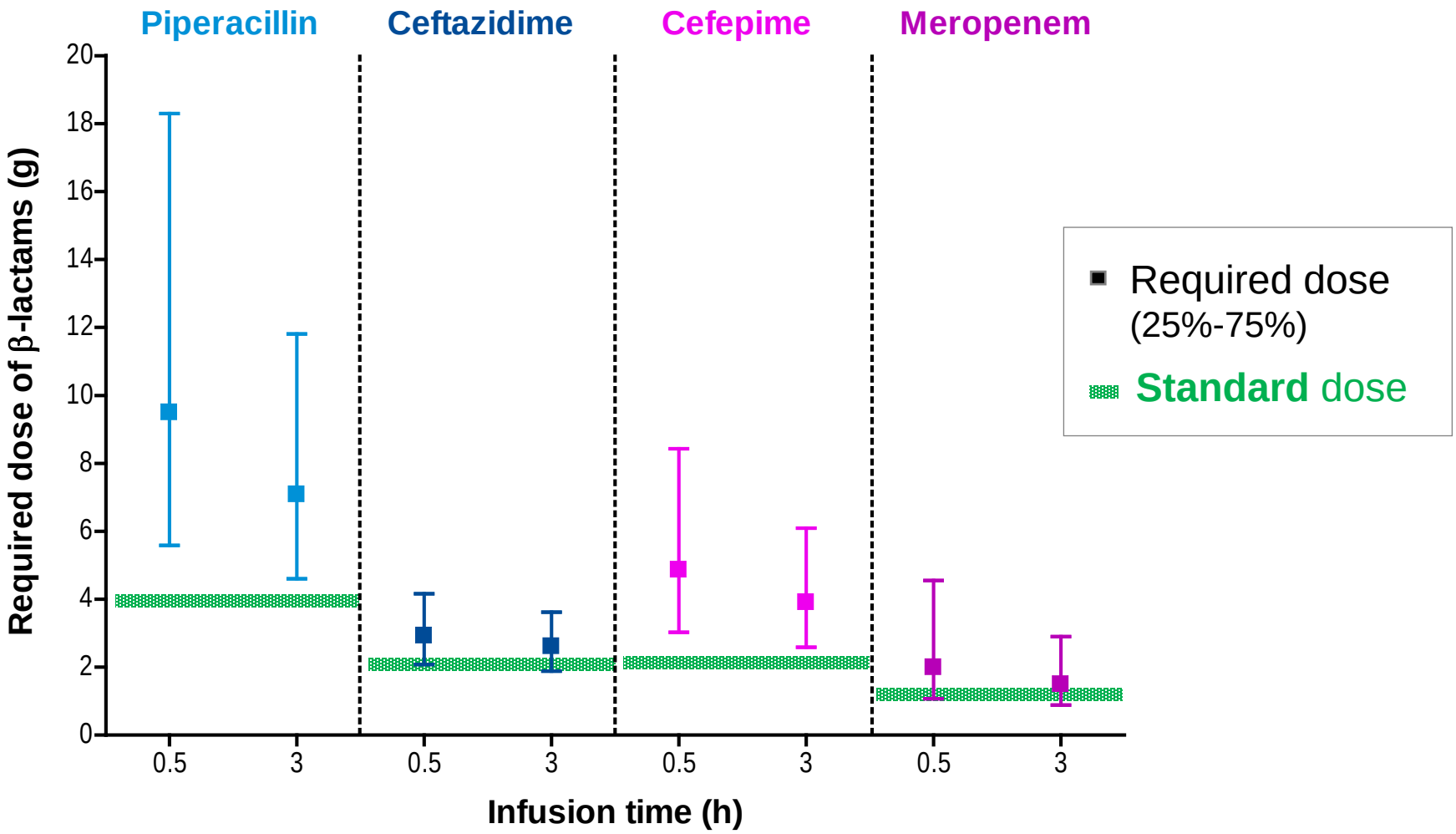
Is a PK/PD target of 100%T>1xMIC likely to result in a concentration 4xMIC for 40-70% of the dosing interval as required for the different classes of β-lactams?

For **1,000** critically-ill septic patients treated with a first dose of β-lactam:					
	Dosage (0.5h inf.)	no. of atients with **100%T>MIC**		no. of patients with **100% T>1xMIC and 40-70%T>4xMIC**	
Piperacillin	4g [q6h]	560	**(56%)**	257	**(26%)**
Ceftazidime	2g [q8h]	871	**(87%)**	307	**(31%)**
Cefepime	2g [q8h]	628	**(63%)**	128	**(13%)**
Meropenem	1g [q8h]	592	**(59%)**	555	**(55%)**

NO at first dose except for meropenem

The ‘Houston’ Target …

Required median first doses to reach 100% at 4 x **MIC**



The ‘Houston’ Target …

Which dose is needed to reach 100%T>4xMIC?

First dose of β-lactam in critically ill patients					
	Standard dose	Optimal median dose			
	0.5h infusion	0.5h infusion		3h infusion	
Piperacillin	**4g** (q6h)	9.5g	**x 2.4**	7.1g	**x 1.8**
Ceftazidime	**2g** (q8h)	2.9g	**x 1.5**	2.6g	**x 1.3**
Cefepime	**2g** (q8h)	4.9g	**x 2.5**	3.9g	**x 2.0**
Meropenem	**1g** (q8h)	2.0g	**x 2.0**	1.5g	**x 1.5**

~ 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 ?

https://walexperience.com/wp-content/uploads/2014/10/IL-SANTO-GRAAL.jpg

The discussion is open…