

Therapeutic Monitoring of β -lactam Antibiotic Therapy: An Unmet Medical Need?

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Disclosures

I am a consultant, speakers bureau member or have received research funding from:

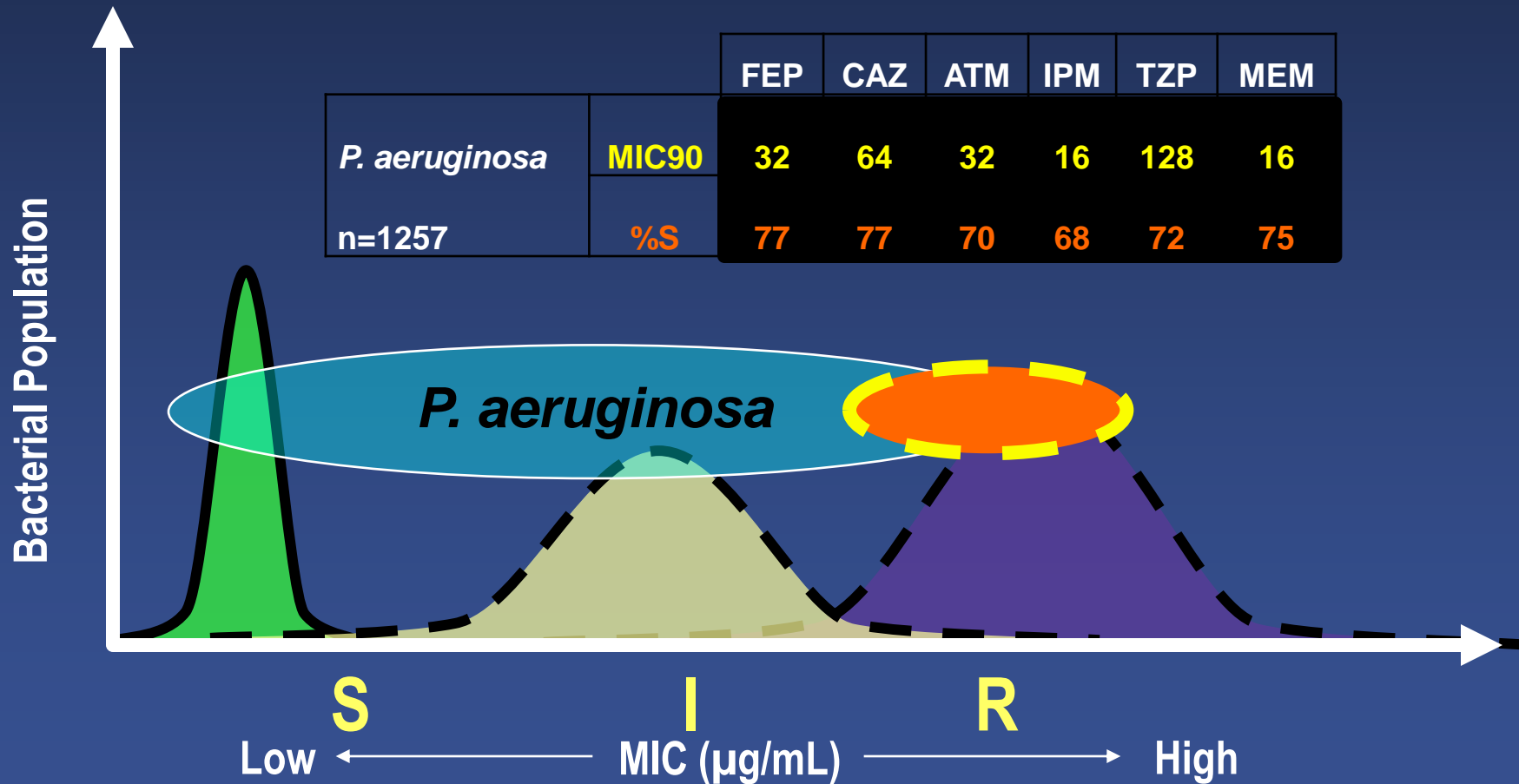
Abbvie, Cepheid, Merck, Paratek, Pfizer, Wockhardt,
Shionogi, Spero, Tetrphase

β -Lactam Antimicrobials: The Backbone of Therapy

- Penicillins, Cephalosporins, Carbapenems
 \pm β -Lactamase inhibitor combinations
- Most frequently used agents in hospital
- Used to treat wide range of severity of illness: Sepsis \rightarrow
Urinary tract infections
- Considerations for use:
 - *In vitro* potency \rightarrow Gram+, Gram- and anaerobic
 - Clinical efficacy \rightarrow Sepsis, Pneumonia, Urinary, ...
 - Safety profile \rightarrow Well established
 - Flexibility in dosing \rightarrow Dose, Dosing Interval, Duration of Infusion

Pseudomonas aeruginosa: A Problematic Pathogen for the Ages

Impact of Resistance Mechanism on *In Vitro* Potency
→ MIC Distributions

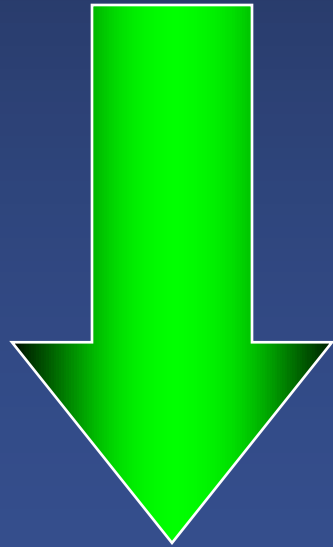


Appropriate Antimicrobial Therapy

- Matches antibiotic susceptibilities of the organism to the antibiotic used

“S” = Success

Improved Outcomes = Reductions in:



Hospital and infection-related mortality

Infection-related morbidity

Length of hospital stay

Days of antimicrobial therapy

Cost of hospitalization

Kollef, et al. *Chest*. 1999; 115:462-474.

Engemann, et al. *Clin Infect Dis*. 2003; 36:592-598.

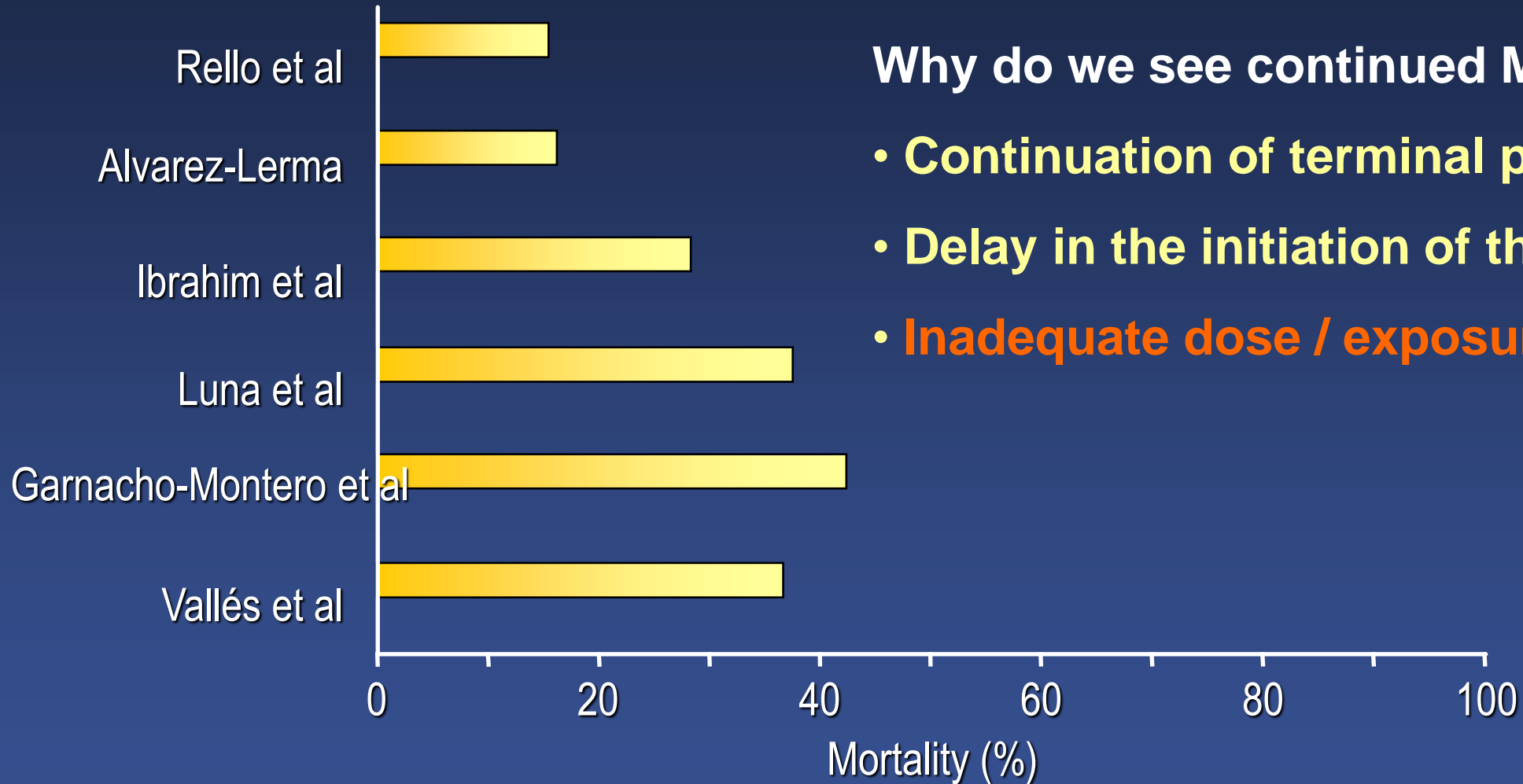
Lodise, et al. *Clin Infect Dis*. 2002; 34:922-929.

Toubes, et al. *Clin Infect Dis*. 2003; 36:724-730.

Pelz, et al. *Intensive Care Med*. 2002. 28:692-697.

Song, et al. *Infect Control Hosp Epidemiol*. 2003; 24:251-256.

When “S” Does NOT = Success



Why do we see continued Mortality?

- Continuation of terminal process
- Delay in the initiation of therapy
- Inadequate dose / exposure

DALI: Defining Antibiotic Levels in Intensive Care Unit Patients

- Prospective, multinational pharmacokinetic point-prevalence study including 8 **β -lactam antibiotics**¹
 - 248 patients treated for infection, 16% did not achieve 50% $fT > MIC$ and these patients were 32% less likely to have a positive clinical outcome (odds ratio [OR], 0.68; $P = .009$).
 - Positive clinical outcome was associated with increasing **50% $fT > MIC$** and **100% $fT > MIC$** ratios
- 42 patients from 26 ICUs receiving **vancomycin**²
 - Target trough concentrations were achieved in 57% of patients, but more frequently in patients receiving continuous infusion (71% v. 39%; $P = 0.038$)
- PK variability and exposures of **fluconazole, anidulafungin, and caspofungin**³
 - 33% receiving fluconazole did not attain the PD target of $fAUC/MIC$

¹Roberts JA et al. Clin Infect Dis 2014;58(8):1072-83

²Blot S et al. Crit Care. 2014;18(3):R99

³Sinnollareddy MG et al. Crit Care. 2015;19(1):758

Therapeutic Drug Monitoring (TDM)

- Testing that measures the amount of medicine in your **blood**.
- Executed to make sure the amount is both safe and effective.

Types of Medicine	Medicine Names
Infectious Diseases	vancomycin, aminoglycosides, voriconazole
Cardiovascular	digoxin, procainamide, lidocaine
Anti-seizure	phenytoin, phenobarbital, valproic acid
Autoimmune diseases	cyclosporine, tacrolimus
Psychiatric	lithium

TDM: General Criteria for Use

β -lactams

- | | |
|---|------------|
| • Narrow therapeutic index | • NO |
| • Defined therapeutic range & toxicity threshold | • YES & NO |
| • Good relationship btwn blood [c] & clinical/toxic effects | • YES & NO |
| • Poor relationship between drug dose & blood [c] | • NO |
| • Significant inter-individual variation | • YES |
| • Serious consequences for under- or over-dosing | • YES |
| • Subject to drug-drug interactions | • NO |
| • When toxicity mimics indication for the drug | • NO |

TDM: Factors that Influence Results

Drug	
	Formulation
	Route of Administration
	Dosing regimen
	Pharmacokinetics (Vd, T1/2, metabolites)

Patient	
	Age
	Body Composition
	Renal function
	Hepatic function
	Medication adherence
	Pregnancy
	Protein Status
	Pharmacogenetics
	Disease / Malignancies

TDM: Factors that Influence Results

Specimen	
	Collection tube / preservatives
	Time collected relative to dose
	Storage
	Handling

Other	
	Concomitant medications
	Supplements
	Diet
	Clerical errors

Analytical methods	
	Assay availability / type
	Pre-analytical processing
	Sensitivity
	Specificity
	Matrix effects

REVIEW



Diagnostic and medical needs for therapeutic drug monitoring of antibiotics

Claude Mabilat¹ · Marie Françoise Gros¹ · David Nicolau² · Johan W. Mouton³ · Julien Textoris¹ · Jason A. Roberts^{4,5,6} · Menino O. Cotta^{4,5,6} · Alex van Belkum⁷ · Isabelle Caniaux¹

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REVIEW OF THERAPEUTICS

PHARMACOTHERAPY 

A guide to therapeutic drug monitoring of β -lactam antibiotics

Andrew J. Fratoni | David P. Nicolau  | Joseph L. Kuti 

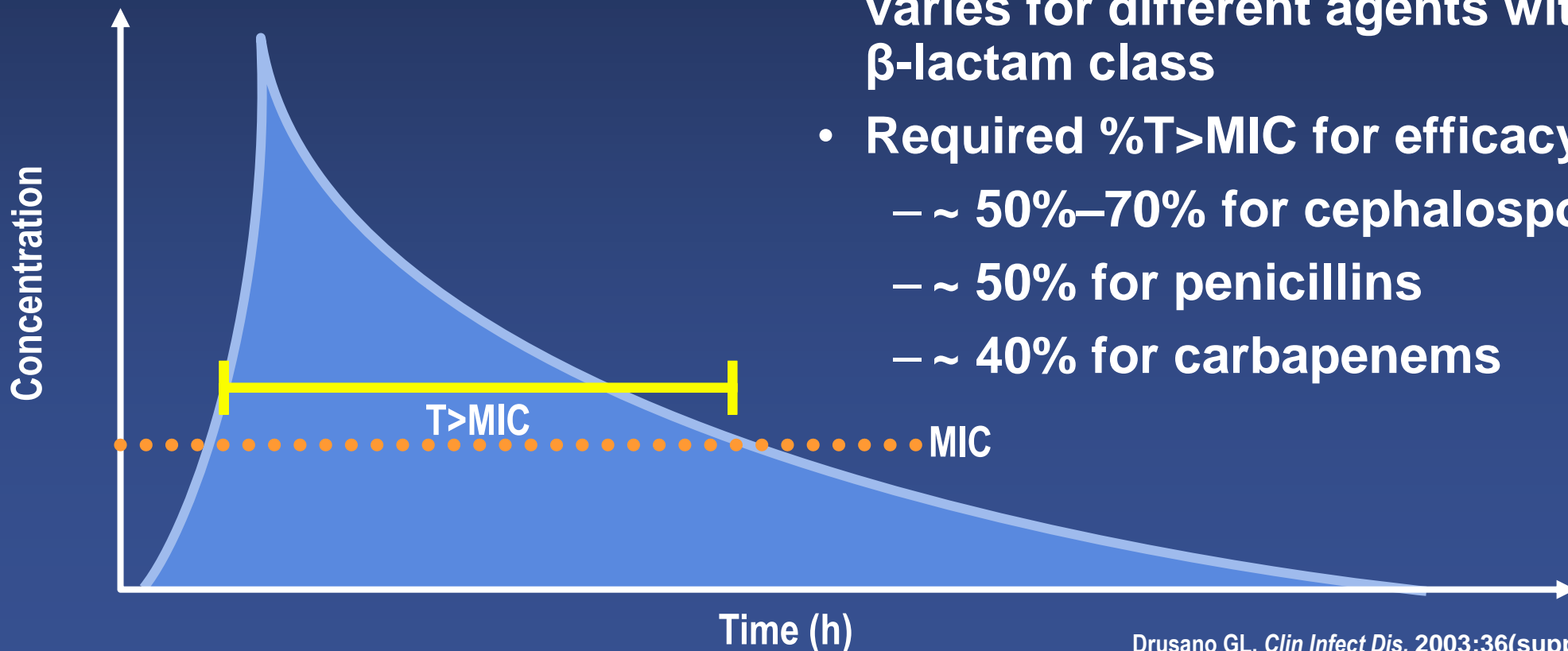
Pharmacotherapy. 2021;41:220–233.

Therapeutic Drug Monitoring (TDM)

- Do we need TDM for β -lactams?
- If so, in what patient populations?

Pharmacodynamic Principles for β -Lactams

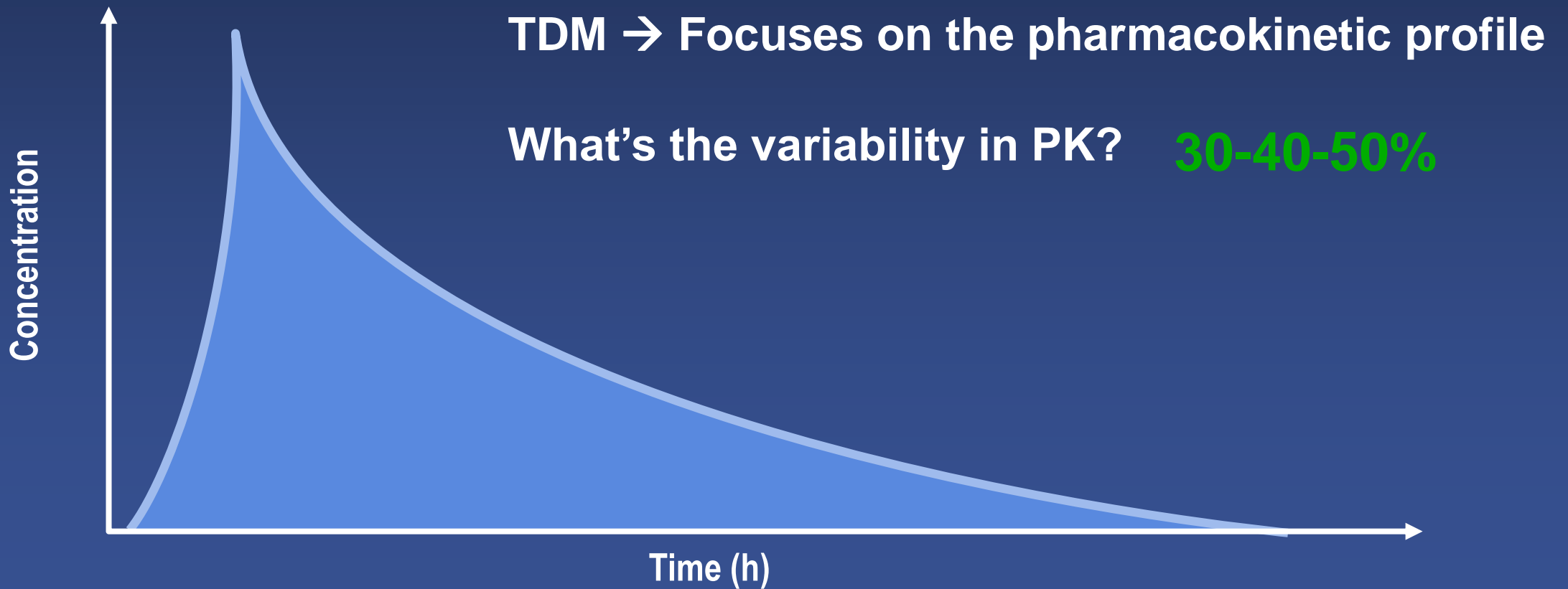
- The time drug concentration exceeds the MIC ($T > MIC$) is predictive of antibacterial effect



- The optimum level of exposure varies for different agents within the β -lactam class
- Required % $T > MIC$ for efficacy:
 - ~ 50%–70% for cephalosporins
 - ~ 50% for penicillins
 - ~ 40% for carbapenems

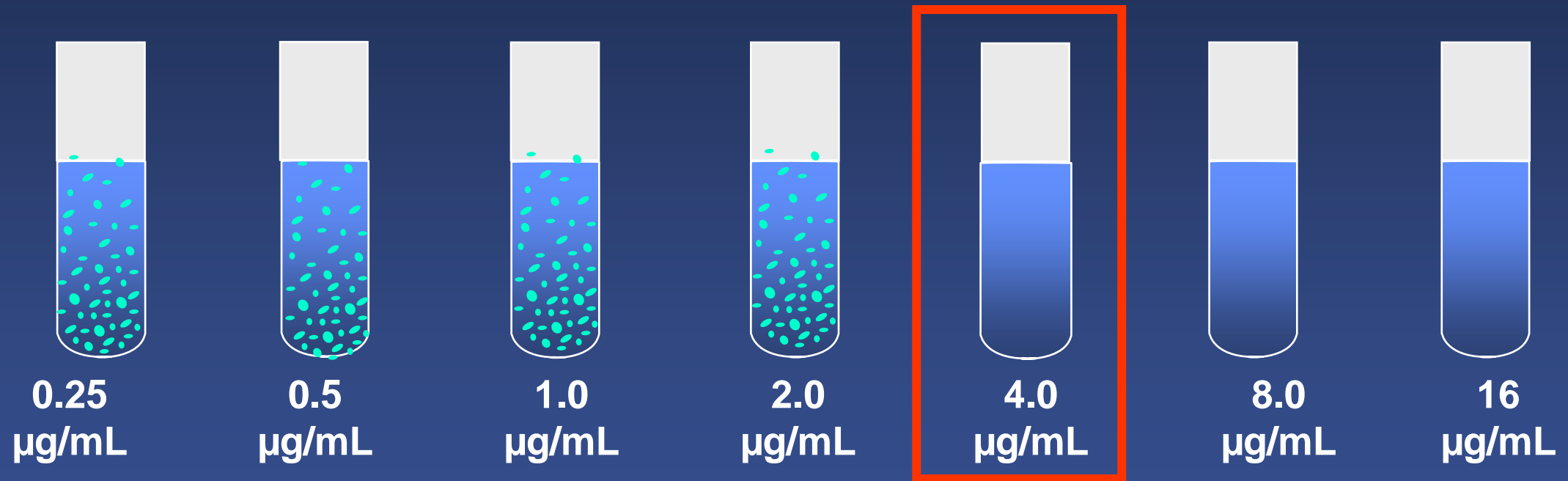
Pharmacodynamic Principles for β -Lactams

- Pharmacokinetics: Concentration-time profile



Drug potency (MIC) is measured by determining lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism after overnight exposure

Known bacterial inoculum, drug concentration, and media placed into each tube

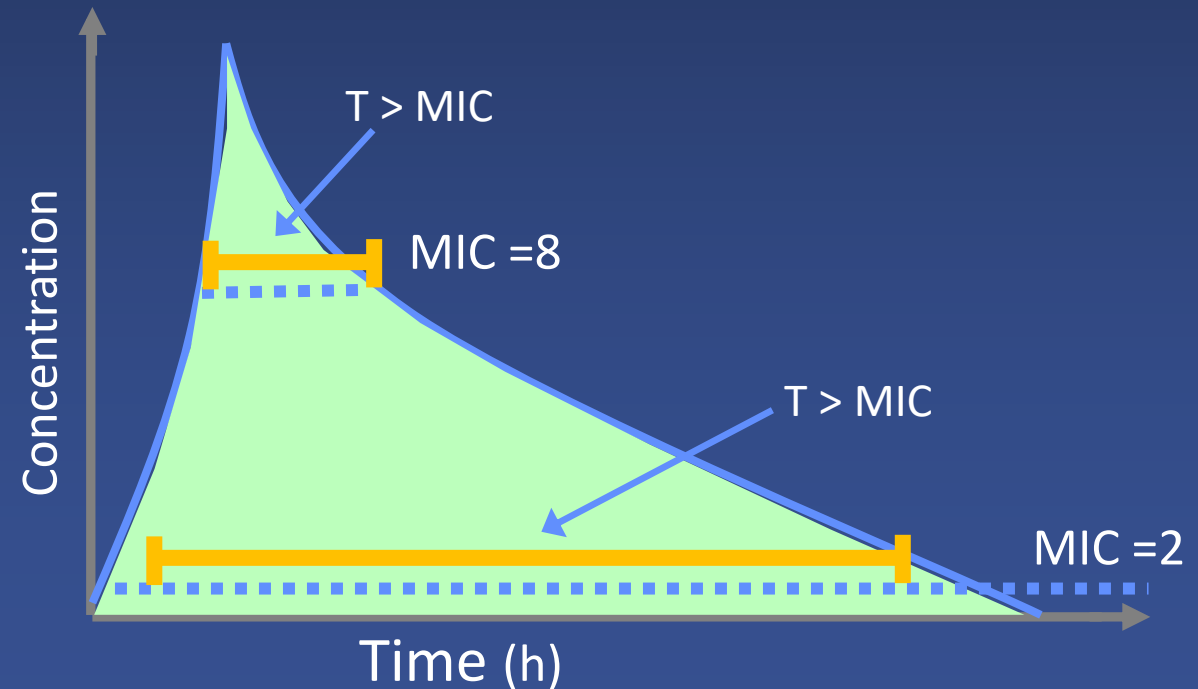
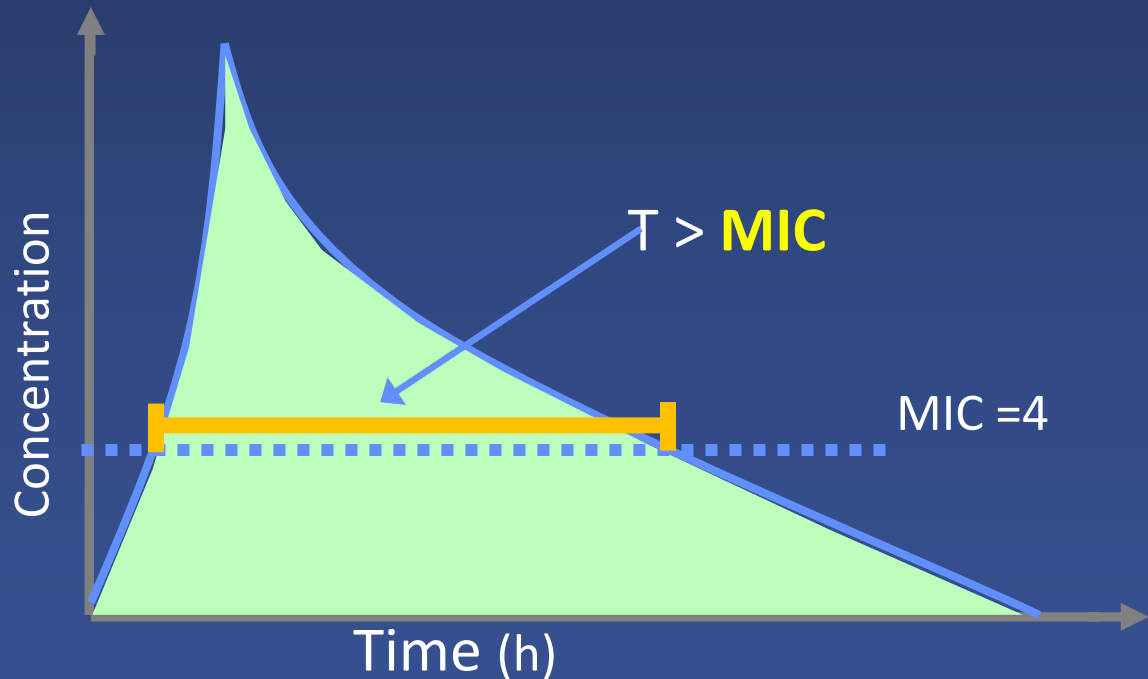


MIC

Consideration of the Denominator in the Pharmacodynamic Equation

What's the variability in the MIC determination?

2 ← 4 → 8



Clinical Pharmacodynamics of Antipseudomonal Cephalosporins in Ventilator-Associated Pneumonia (VAP): Predictors of Microbiological Success

Model parameters	Odds ratio (95% CI)	P
<i>f</i>T > MIC > 53 %	10.27 (1.1-92.3)	0.04
APACHE II	1.01 (0.9-1.1)	0.85
Combination Therapy	0.74 (0.3-2.2)	0.59

Multiple Logistic Regression; CI, confidence interval

Carbapenem Serum Exposure is Predictive of Clinical Success in Ventilator-Associated Pneumonia (VAP)

Model parameters	Odds ratio (95% CI)	<i>P</i>
<i>f</i>T>MIC > 19 %	5.8 (1.2–29.2)	0.03
ARDS on Day 1	1.6 (0.2–1.8)	0.36
Day 7 SOFA Score	1.0 (0.9–1.2)	0.92
Day 7 Mechanical Ventilation	1.6 (0.4–6.1)	0.46

***f*T>MIC = time the concentration of unbound (bioactive) drug exceeds the MIC for given patient**

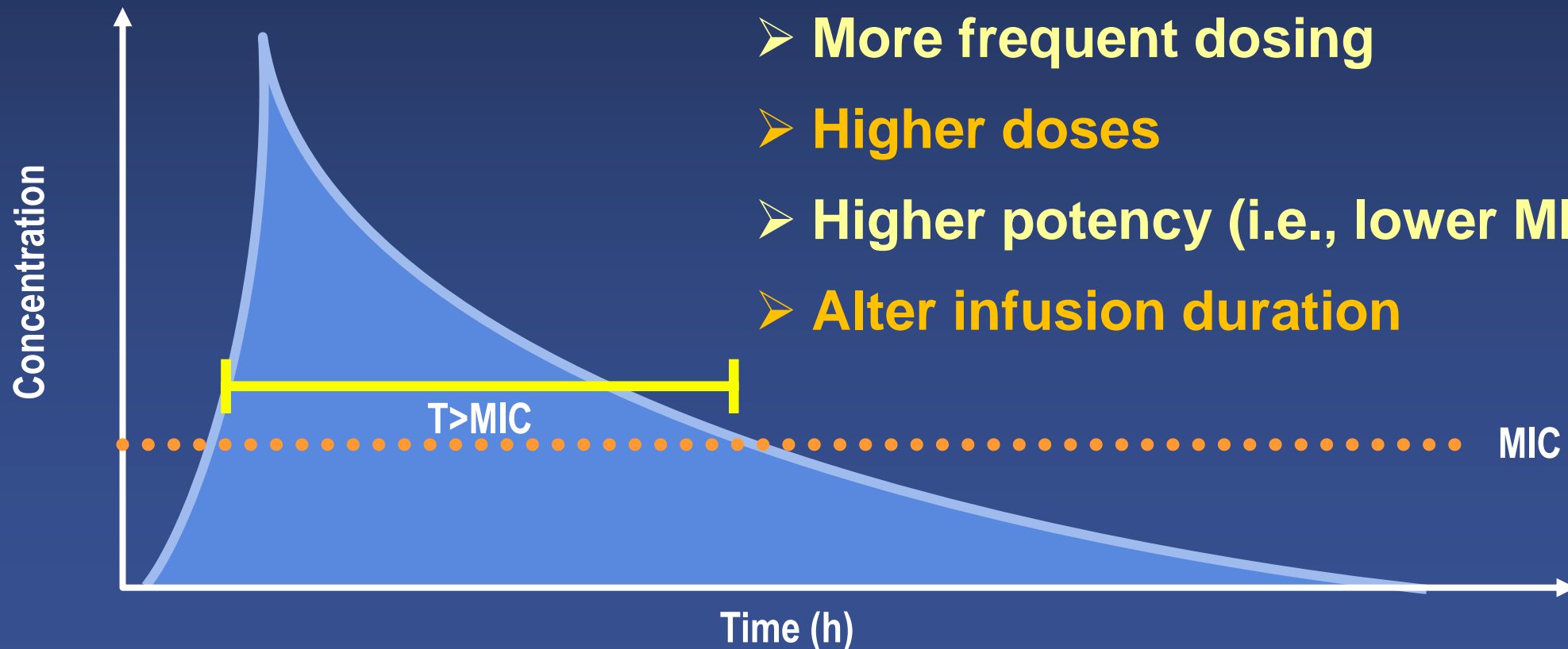
Multiple Logistic Regression; CI, confidence interval

Pharmacodynamic Principles for Beta-Lactams

- The time drug concentration exceeds the MIC ($T > MIC$) is predictive of antibacterial effect

Methods to Increase % Time $>$ MIC

- More frequent dosing
- Higher doses
- Higher potency (i.e., lower MICs)
- Alter infusion duration



Hartford Hospital: VAP Pathway – EMPIRIC Therapy

1 st Line Regimen:	Dosage (CrCl ≥ 50ml/min)	Adjustment for Renal Dysfunction (CrCL in ml/min)		CRRT
		30 - 49	< 30	

Vancomycin
(Linezolid)

plus

Tobramycin

plus

High Dose β-lactam

Medical Intensive Care Unit

Meropenem

2g q 8 hr
(3 hr infusion)

Surgical and Neurosurgical Intensive Care Unit

Cefepime

2g q 8 hr
(3 hr infusion)

**Piperacillin /
Tazobactam**

4.5g q 6 hr
(3 hr infusion)

Dosing per Pharmacy Protocol (High Dose)

Dosing per Once Daily Aminoglycoside Protocol

Higher Doses & Altered Infusions

- Target entire MIC distribution → focus on MICs above the BP
- Anticipate variable PK → CI & Vd
- Maximize PD profile → $fT > MIC$

CRRT = continuous renal replacement therapy

Hartford Hospital: VAP Pathway – EMPIRIC Therapy

1st Line Regimen:

Dosage
(CrCl ≥
50ml/min)

Adjustment for Renal Dysfunction
(CrCL in ml/min)

30 - 49

< 30

CRRT

**Vancomycin
(Linezolid)
plus
Tobramycin
plus
High Dose β-lactam**

Medical Intensive Care Unit

Meropenem **2g q 8 hr
(3 hr infusion)**

**1g q 8 hr
(3 hr)**

**1g q 12 hr
(3 hr)**

Max dose

Surgical and Neurosurgical ICU

Cefepime **2g q 8 hr
(3 hr infusion)**

**2g q 12 hr
(3 hr)**

**1g q 12 hr
(3 hr)**

Max dose

**Piperacillin /
Tazobactam** **4.5g q 6 hr
(3 hr infusion)**

**4.5g q 8 hr
(3 hr)**

**4.5g q 12 hr
(3 hr)**

Max dose

CRRT = continuous renal replacement therapy

Improved Outcomes: VAP Pathway

Outcome

Historic

Pathway

P-value

n = 74

n = 94

The Pathway Statistically Decreased:**

Infection Related Mortality**

Infection Related Length of Stay**

Time to Appropriate Therapy**

Number of Super-infections**

Enhanced effectiveness of β -lactams for High MIC *P. aeruginosa*

Extended Infusion Cefepime for the Treatment of Invasive *P. aeruginosa* Infections

- Respiratory & Blood isolates
- Intermittent 1g q8 [n=51] vs. Extended 2g q8 [n =35]
 - Reduced LOS 18 vs. 12 days
 - Reduced LOS_{ICU} 18 vs. 10 days
 - Reduced Mortality_{hospital} 23 vs. 6%
 - Reduced Mortality_{14 day} 20 vs. 3%
 - Reduced Cost of Care \$53,000 vs. \$30,000 USD

Potential Role of β -Lactam TDM: Target Populations

- Discordant therapy (i.e., **inadequate** therapy low exposures due to insufficient dose and / or regimen)
 - » Increased body weight
 - » \uparrow volume of distribution (sepsis / septic shock)

Potential Role of β -Lactam TDM: Target Populations

- Discordant therapy (i.e., **inadequate** therapy low exposures due to insufficient dose and / or regimen)
 - » Increased body weight
 - » \uparrow volume of distribution (sepsis / septic shock)
 - » **Renal function**
 - Reduced
 - Optimizing dose / minimizing toxicity
 - Adequate assessment of Cl_{cr}

Renal Dosing of Antibiotics: Are We Jumping the Gun?

- Illustration of the dynamic nature of renal impairment in acutely infected patients

- Retrospective study

- 18,500 patients included with cUTI (41%), acute bacterial pneumonia (11%), SSSI (32%) or cIAI (16%)

- Total population:

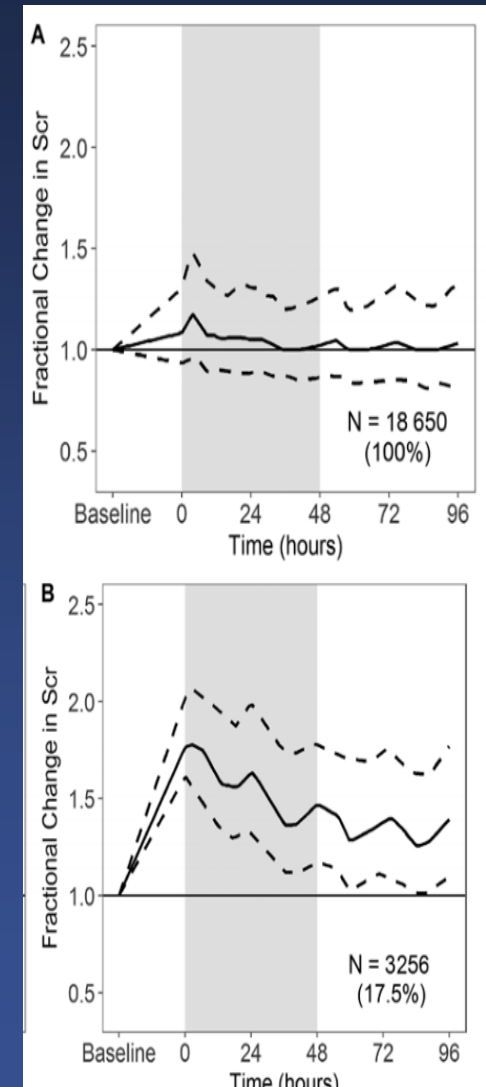
- » Rate of AKI on admission: 17.5%

- » Kidney injury resolved in 57% of patients after 48 h


- Subgroup with moderate RI (16.4%)

- » Rate of AKI on admission: 38%

- » Kidney injury resolved in 46% of patients after 48 h



Urinary Creatinine Clearance and Pharmacokinetics Studies: If We Can Measure It, Why Do We Estimate It?

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^aServiço de Medicina Intensiva, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

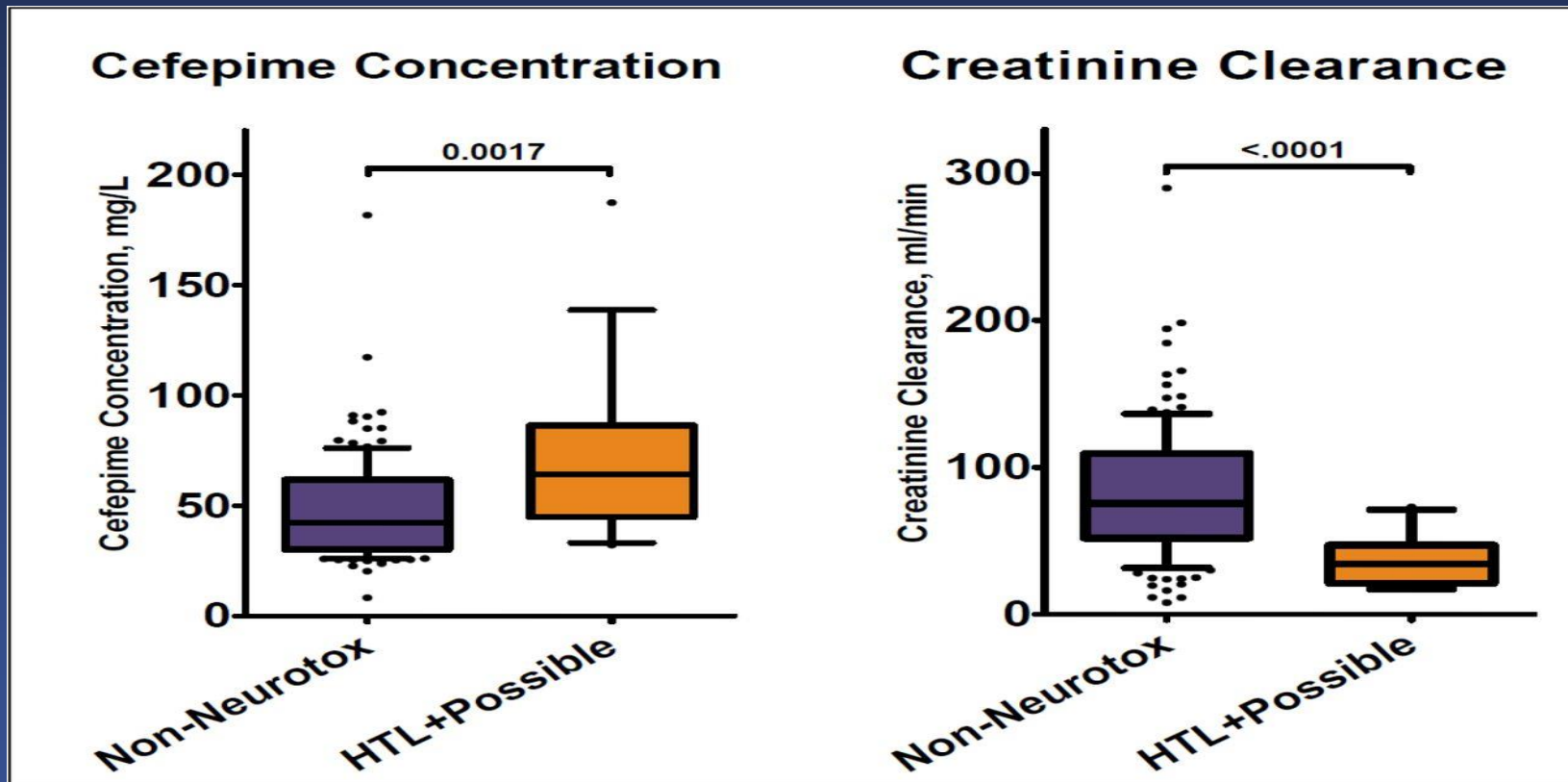
^bAustralian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia

^cDepartment of Intensive Care and Hyperbaric Medicine, The Alfred, Melbourne, Victoria, Australia

- Urinary creatinine clearance (CR_{CL}) is frequently used at the bedside as a surrogate of the glomerular filtration rate (GFR)
- Mathematical estimates have been shown to significantly underestimate measured CR_{CL} in critically ill patients
- CR_{CL} is neither a perfect nor a gold standard method for evaluating renal function in acutely critically ill patients, we argue that it offers an inexpensive, reproducible, and more biologically accurate surrogate than mathematical estimates.

Cefepime Induced Neurotoxicity (CIN)

- Evaluating the primary outcomes of the study, the mean cefepime trough concentrations in those with CIN were significantly greater than those without neurotoxicity (74.2 mg/L \pm 41.1 vs. 46.6 mg/L \pm 23, $p=0.015$).
- Lower renal function (CrCl < 30 ml/min), greater time to TDM (≥ 72 hours), and each 1 mg/mL incremental rise in cefepime trough were independently associated with increased risk of CIN in the adjusted regression analysis.





Prospective assessment of breakthrough infections and neurotoxicity and their association with cefepime trough concentrations in patients with febrile neutropenia

Matthias Gijzen ^{a, b} , Britt Bekkers ^b, Johan Maertens ^{c, d}, Katrien Lagrou ^{d, e}, Stefanie Desmet ^{d, e}, Erwin Dreesen ^a, Willy E. Peetermans ^{d, f}, Yves Debaveye ^g, Isabel Spriet ^{a, b}

- Routine TDM may not be needed in FN patients with preserved renal function
- No breakthrough infections were observed in patients with febrile neutropenia
- Few patients with preserved renal function showed neurotoxicity
- There was a significant trend for higher cefepime trough concentrations with neurotoxicity

Potential Role of β -Lactam TDM: Target Populations

- Discordant therapy (i.e., **inadequate** therapy low exposures due to insufficient dose and / or regimen)
 - » Increased body weight
 - » \uparrow volume of distribution (sepsis / septic shock)
 - » **Renal function**
 - Reduced
 - Adequate assessment of Cl_{cr}
 - Optimizing dose / minimizing toxicity
 - Augmented

Augmented renal clearance (ARC)

Defined as a CrCl > 130 ml/min/1.73 m²

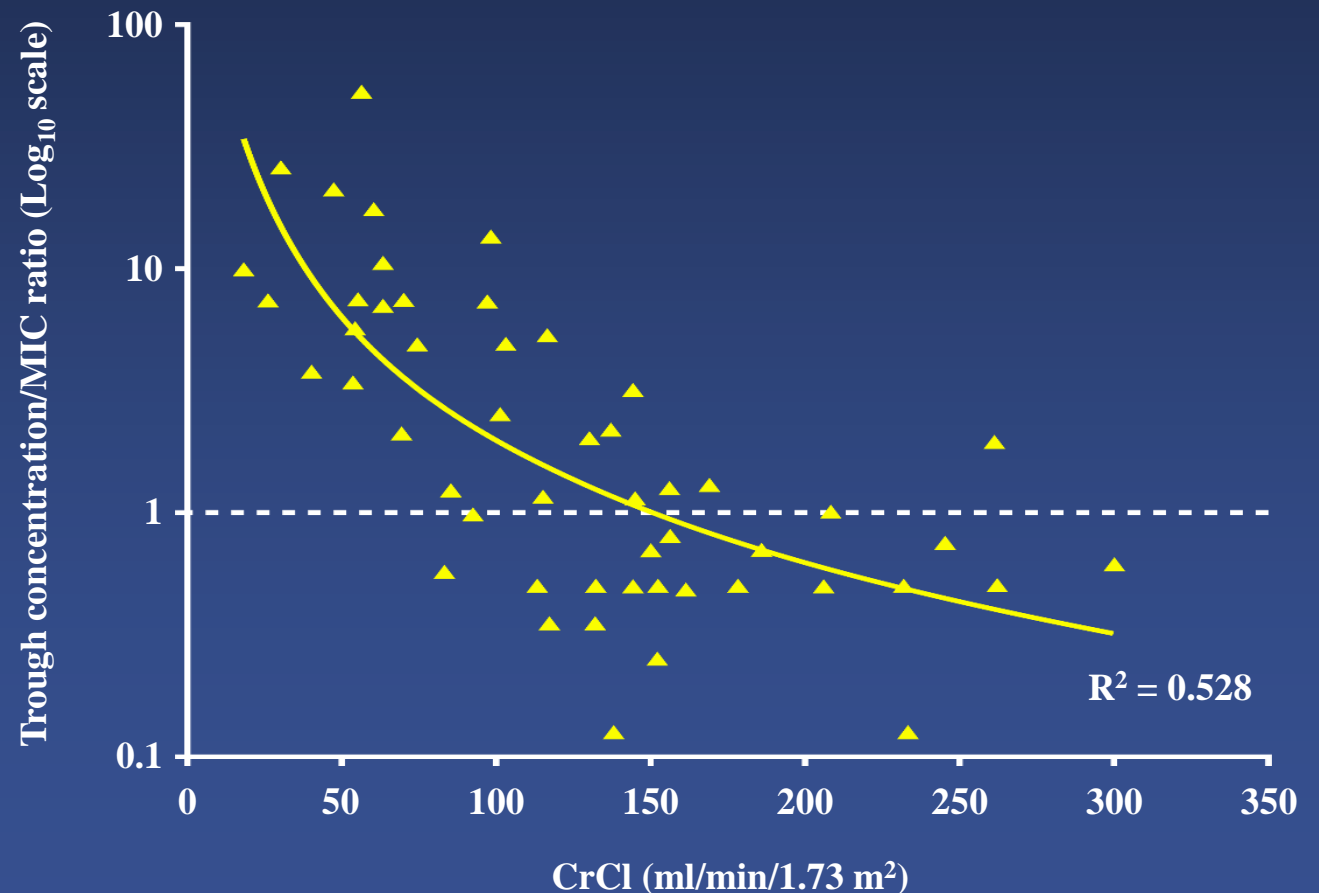
At-risk population includes:

- younger patients
- surgical patients
- patients with sepsis (SIRS + infection)

Best measured by 8 hour urine CrCl

Patients with ARC are likely to have:

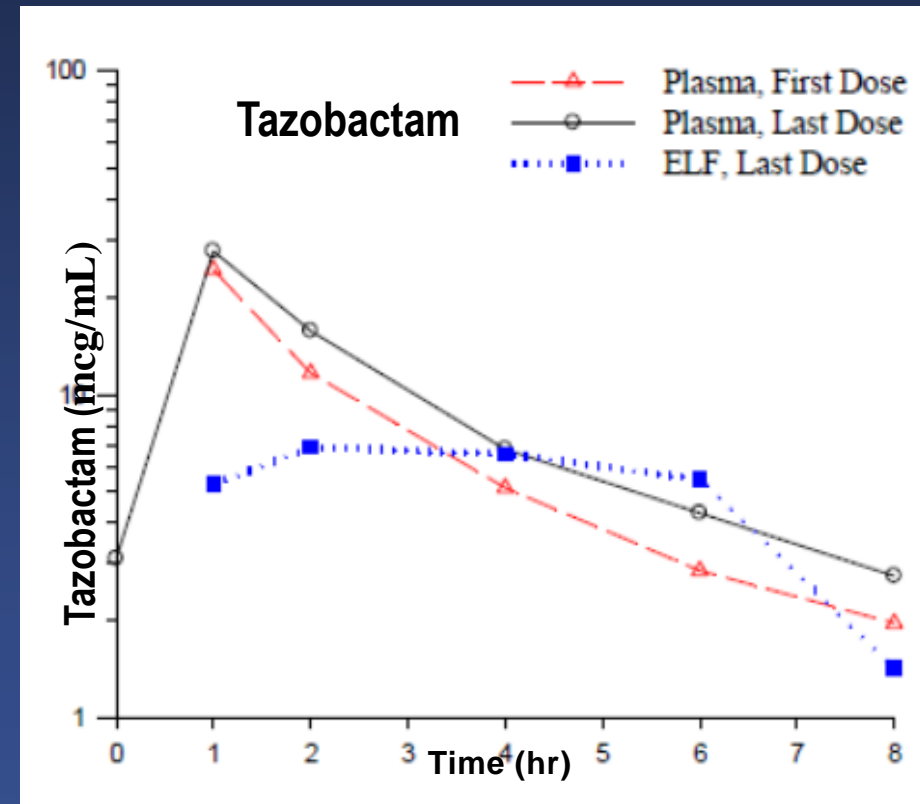
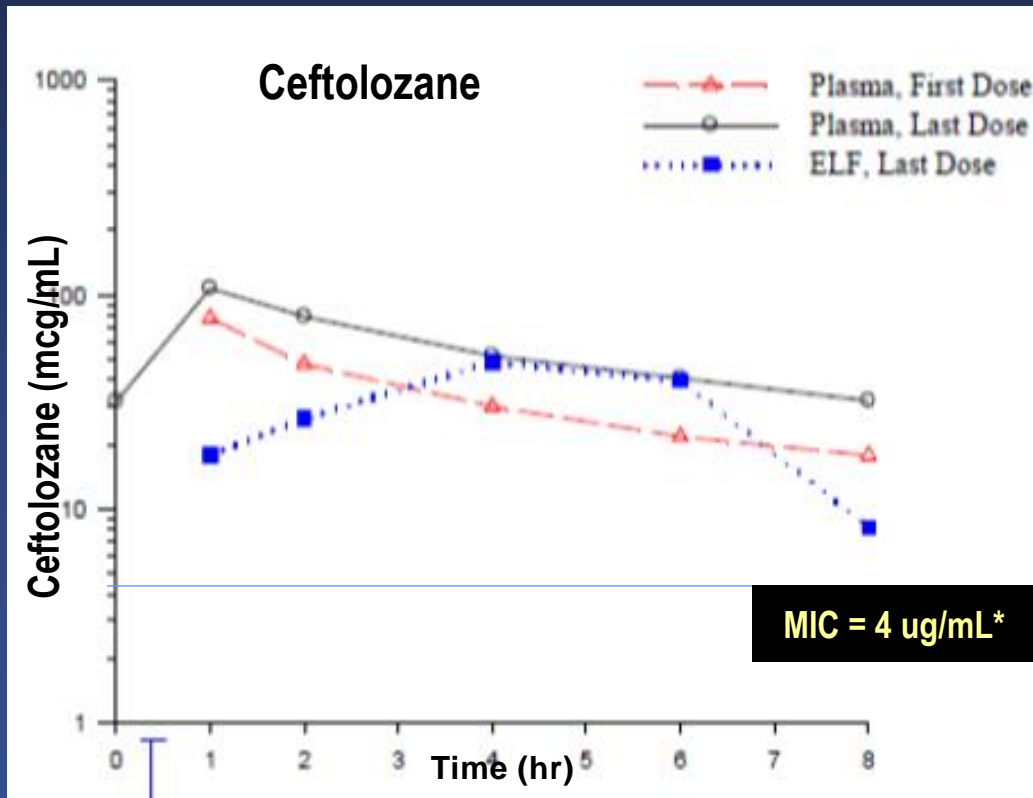
- **Substantially higher drug clearance**
- Lower concentrations for agents predominantly eliminated via glomerular filtration (vancomycin, aminoglycosides, beta-lactams, fluoroquinolones)



Ceftolozane/Tazobactam ELF Penetration in the Critically ILL

Phase 1 PK Study of Ceftolozane/Tazobactam 3 g in Critically Ill

- Mean ceftolozane ELF concentrations remained $>4 \mu\text{g/mL}$ and $>8 \mu\text{g/mL}$ for 100% of the dosing interval, and mean tazobactam ELF concentrations were $>1 \mu\text{g/mL}$ for 100% of the dosing interval

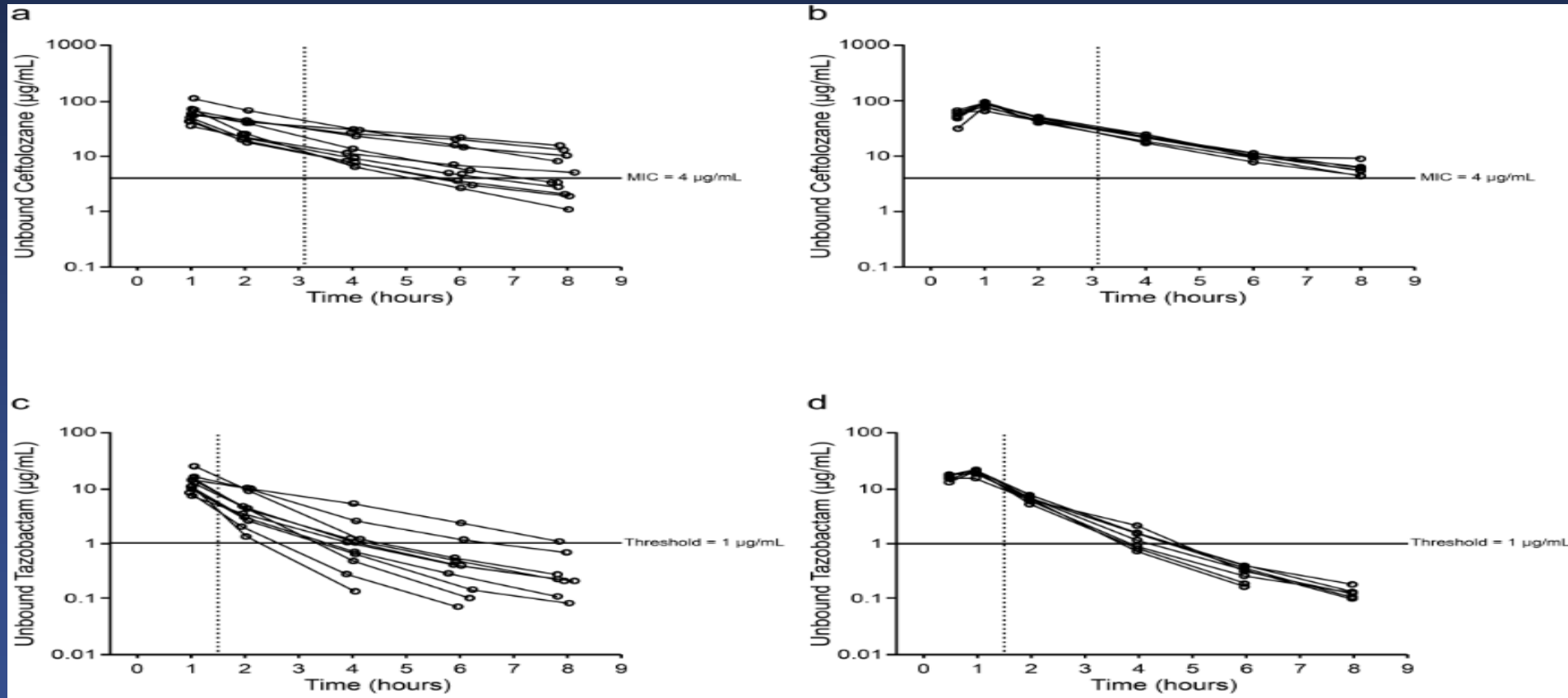


Mean (\pm SD) total concentration-time profiles in plasma (first dose [N=25 patients] and last dose [N=24 patients]) and ELF (last dose; N=22 patients) for (a) ceftolozane and (b) tazobactam.

*MIC of 4 $\mu\text{g/mL}$ is the target unbound MIC for Ceftolozane

Ceftolozane/Tazobactam Exposures in Critically ill Patients With Augmented Renal Clearance (ARC)

Individual unbound plasma concentration–time profiles of ceftolozane^a in (a) patients with ARC and (b) healthy subjects; tazobactam^b in (c) patients with ARC, and (d) healthy subjects after the administration of a 3 g dose of ceftolozane/tazobactam. Vertical hashed line indicates the pharmacodynamic threshold.



In patients with ARC, a 3 g C/T dose met respective pharmacodynamic targets for ceftolozane and tazobactam

Ceftazidime–Avibactam: Dosage and Method of Administration

Recommended intravenous dose for patients with estimated CrCL ≥ 51 mL/min*

Type of infection	Dose ceftazidime–avibactam	Frequency	Infusion time	Duration of treatment
Complicated IAI ^{†‡}	2 g/0.5 g	Every 8 hours	2 hours	5–14 days
Complicated UTI & Hospital-acquired pneumonia, including VAP [‡]	2 g/0.5 g	Every 8 hours	2 hours	7–14 days
Infections due to aerobic Gram-negative organisms in patients with limited treatment options ^{†‡}	2 g/0.5 g	Every 8 hours	2 hours	Guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress [¶]

*CrCL estimated using the Cockcroft-Gault formula.

†To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process.

‡To be used in combination with an antibacterial agent active against Gram-positive pathogens when these are known or suspected to be contributing to the infectious process.

§The total duration shown may include intravenous ceftazidime–avibactam followed by appropriate oral therapy.

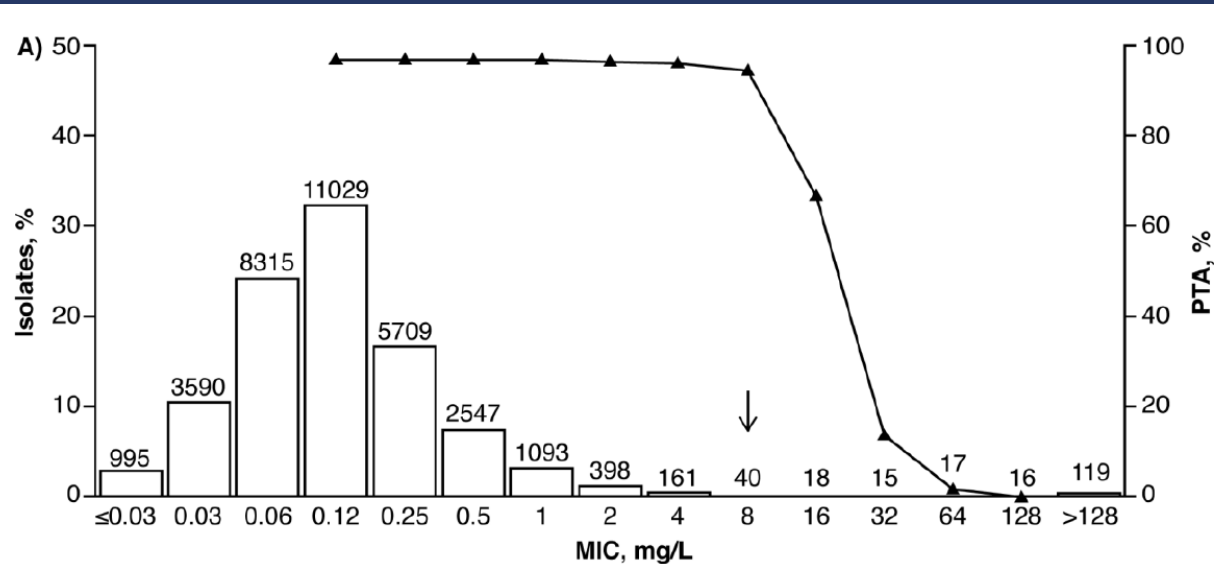
¶There is very limited experience with the use of ceftazidime–avibactam for more than 14 days.

CrCL, creatinine clearance; IAI, intra-abdominal infection; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

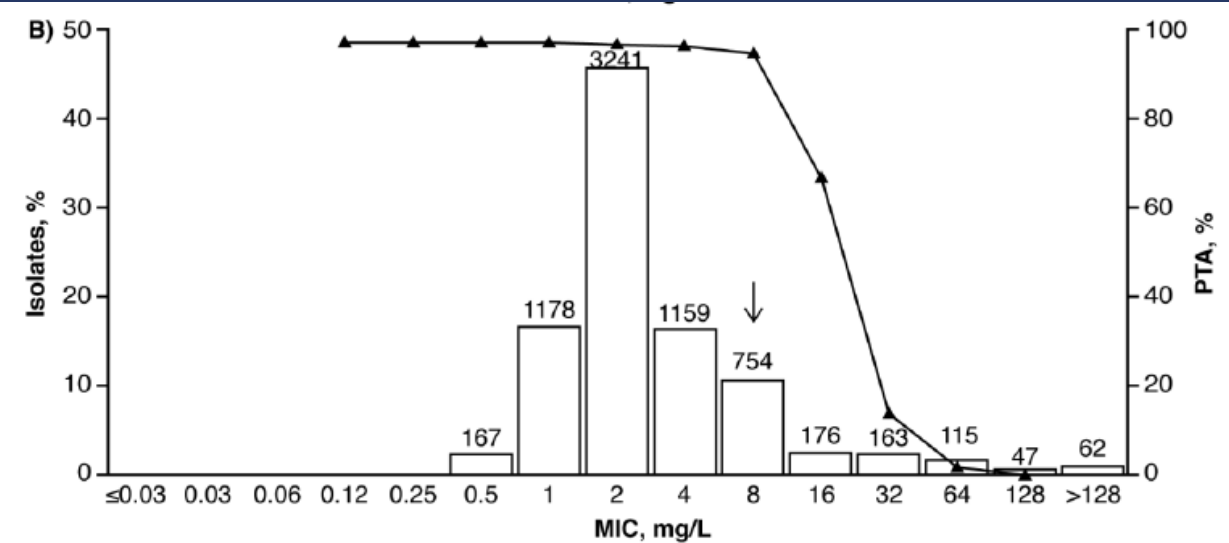
Ceftazidime–Avibactam Pharmacodynamic Profiling Enterobacteriaceae and *P. aeruginosa*

Joint PTA for patients with cIAI receiving ceftazidime–avibactam 2,000 + 500 mg q8h plotted as a function of ceftazidime–avibactam MIC overlaying the ceftazidime–avibactam MIC distributions against (A) *Enterobacteriaceae* (n=34,062) and (B) *Pseudomonas aeruginosa* (n=7,062) from the INFORM global surveillance study (2012–2014)

Enterobacteriaceae



Pseudomonas aeruginosa



Defined as simultaneous attainment of 50% fT>MIC of ceftazidime–avibactam for ceftazidime and 50% fT>CT of 1 mg/l for avibactam, with both targets having to be achieved for a simulated patient to be categorized as achieving the joint target. Joint PTA calculated using iteration 4 of the population PK models. Ceftazidime–avibactam MIC distributions were obtained from the INFORM 2012–2014 global surveillance study. Values above the bars are the numbers of isolates tested at each MIC. The arrows show the position of the approved ceftazidime–avibactam susceptible clinical breakpoint of MIC ≤8 mg/l.

cIAI, complicated intra-abdominal infection; MIC, minimum inhibitory concentration; PTA, probability of target attainment.

Das S, et al. Antimicrob Agents Chemother 2019 Jan 22. pii: AAC.02187-18. doi: 10.1128/AAC.02187-18.

Ceftazidime–Avibactam in ICU Patients

- Ceftazidime–avibactam, infused over 2 h, in 10 ICU patients
- Two patients with ARC, 6 patients with normal RF, two patients with moderate RI

TABLE 3. POPULATION PHARMACOKINETIC PARAMETERS FOR CEFTAZIDIME AND AVIBACTAM IN ADULT INTENSIVE CARE UNIT PATIENTS

Pharmacokinetic parameter	Mean (SD)
Ceftazidime	
Model derived parameters	
V_d	34.78 (10.49)
CL_i	1.15 (0.63)
CL_s	0.043 (0.016)
Calculated parameters	
CL	6.14 (3.80)
$t_{1/2}$	4.84 (2.15)
Avibactam	
Model derived parameters	
V_d	50.81 (14.32)
CL_i	0.89 (0.58)
CL_s	0.10 (0.03)
Calculated parameters	
CL	11.09 (6.78)
$t_{1/2}$	4.09 (2.13)

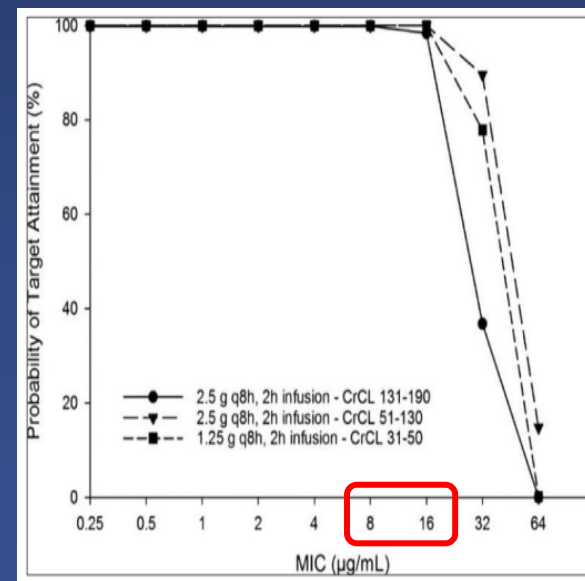
V_d = volume of distribution; CL_i = clearance intercept term; CL_s = clearance slope term; CL = total body clearance, where $CL = CL_i + (CL_s * CrCL)$; $t_{1/2}$ = half-life.

Higher V_d
and
Longer $t_{1/2}$

TABLE 2. BASELINE CHARACTERISTICS OF STUDY PARTICIPANTS (n = 10)

Characteristic	Mean (range)
Age (y)	55 (37– 86)
Weight (kg)	75 (50–131)
BMI (kg/m ²)	25 (17– 39)
APACHE II (score)	21 (11– 33)
Creatinine clearance (mL/min)	103 (47–190)

BMI = body mass index; APACHE = Acute Physiology and Chronic Health Evaluation.

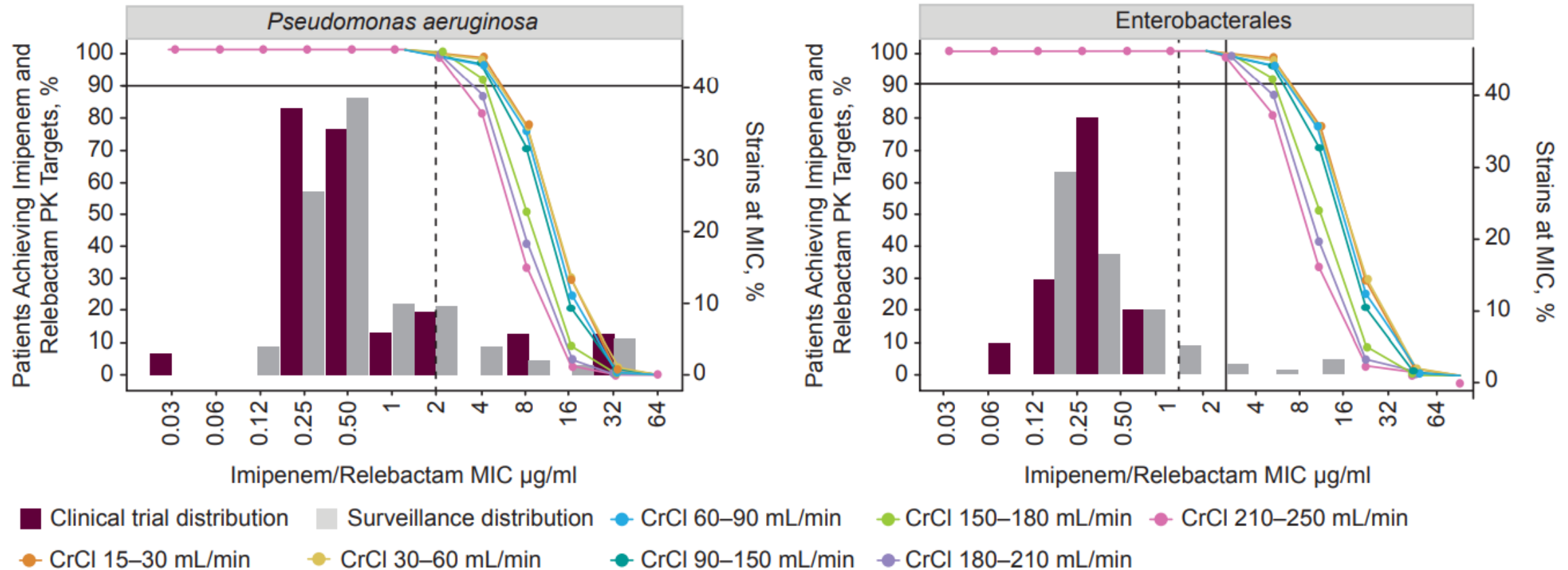


Imipenem/Relebactam PK/PD using Imipenem/Cilastatin/Relebactam 1.25g every 6 hours (500mg/500mg/250mg) or equivalent based on renal adjustment

Sufficient PTA(>90%) achieved at:

- Imipenem 40% $fT > MIC$
- Relebactam $fAUC/MIC \geq 8$

At susceptibility breakpoint ($MIC \leq 2 \mu g/mL$), PTA >98% at all CrCL categories including patients with Augmented Renal Clearance (ARC)



Imipenem-Cilastatin-Relebactam (I/R) Pharmacokinetics (PK) in Critically Ill Patients with Augmented Renal Clearance (ARC)

- Five patients completed the study
- Mean (SD) were
 - Age: 43 (14) years age,
 - Weight: 90 (15) kg weight, 16 (6)
 - APACHE-II, CrCl 160.6 ± 47.0 mL/min (range: 135-244mL/min)
- IMI and REL plasma concentrations fit 2-compartment model well

All 5 patients met PD targets:

- 40% $fT > MIC$ for IMI
- $fAUC:MIC$ 8 for REL up to MIC 2 mg/L

Table 1. Patient demographics and baseline information

Demographics	Sex	Age	Weight (kg)	APACHE II	Urine CrCL (mL/min)	Albumin (g/dL)
Patient 1	F	45	84	23	243.9	3.8
Patient 2	F	50	106	14	134.9	2.9
Patient 3	M	45	68	19	151.0	2.3
Patient 4	F	19	61	10	134.9	3.2
Patient 5	M	54	100	10	138.4	3.3

Table 2. IMI and REL pharmacokinetic parameters

PK Parameter		V_{cc} (L)	CL (L/hr)	K12 (1/h)	K21 (1/h)	Beta HL (h)
Mean (SD)	IMI	15.6 (11.2)	17.9 (8.7)	1.54 (1.28)	1.45 (0.50)	1.45 (0.52)
	REL	17.0 (11.3)	11.9 (7.5)	1.24 (1.36)	1.23 (0.75)	2.84 (2.22)

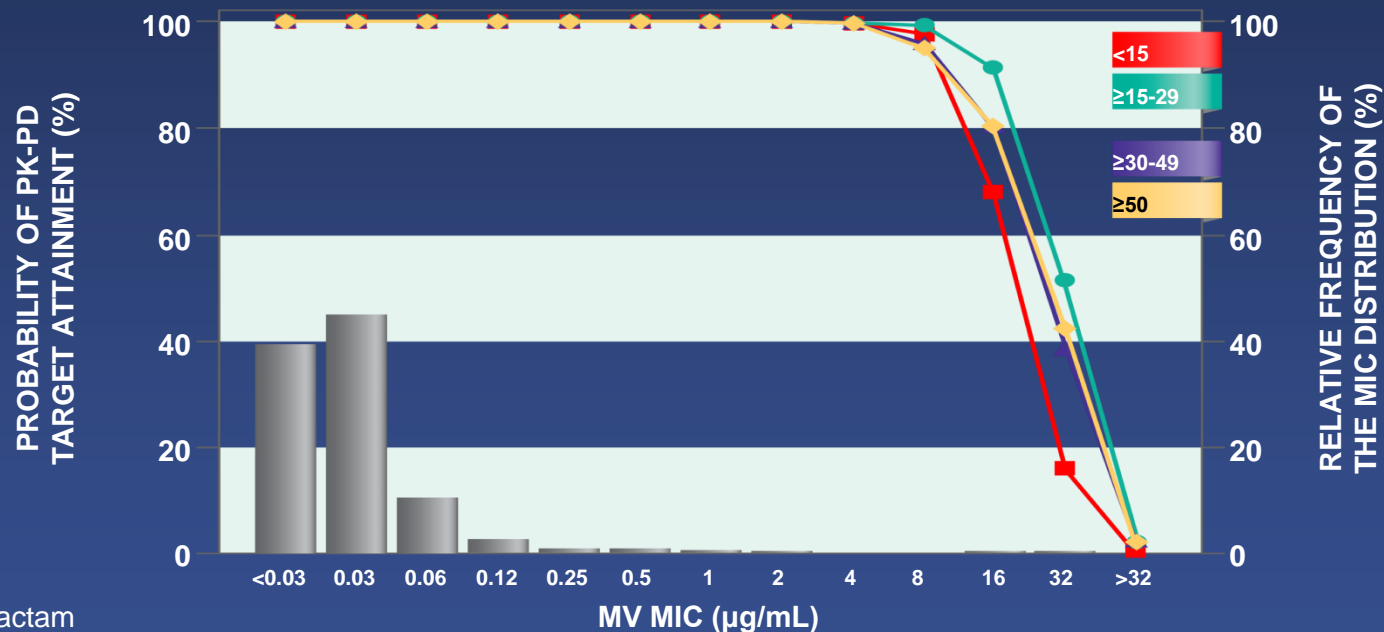
Table 3. Pharmacodynamic exposures for IMI and REL in each patient by MIC

MIC ($\mu\text{g/mL}$)		0.25	0.5	1	2	4
Patient 1	IMI (% $fT > MIC$)	100	80	58	40	28
	REL ($fAUC_{0-24}/MIC$)	259.0	129.5	64.8	32.4	16.2
Patient 2	IMI (% $fT > MIC$)	100	100	100	90	53
	REL ($fAUC_{0-24}/MIC$)	336.4	168.2	84.1	42.1	21.0
Patient 3	IMI (% $fT > MIC$)	100	100	100	80	53
	REL ($fAUC_{0-24}/MIC$)	472.2	236.1	118.1	59.0	29.5
Patient 4	IMI (% $fT > MIC$)	85	70	55	42	25
	REL ($fAUC_{0-24}/MIC$)	181.1	90.5	45.3	22.6	11.3
Patient 5	IMI (% $fT > MIC$)	100	95	75	53	33
	REL ($fAUC_{0-24}/MIC$)	311.6	155.8	77.9	39.0	19.5

Meropenem / Vaborbactam Optimized Dosing for Increased Time Above MIC

- Combined with vaborbactam (2 g), a high dose of meropenem administered as a prolonged infusion (2 g over 3 hours, every 8 hours) provides optimized PK/PD exposures leading to enhanced bacterial killing¹⁻³

REGARDLESS OF RENAL COMPROMISE, HIGH PROBABILITY OF PK-PD TARGET ATTAINMENT



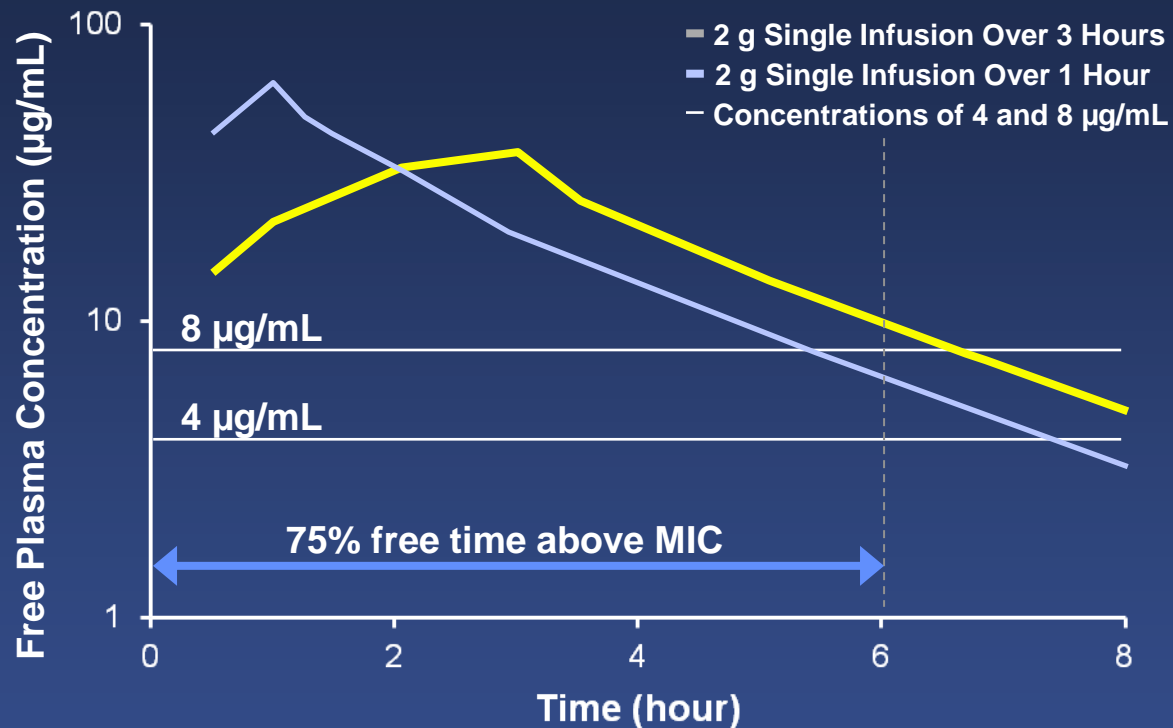
*Based upon meropenem-vaborbactam MIC distribution for 11,559 Enterobacteriaceae isolates. In vitro activity does not necessarily correlate with clinical efficacy.

MIC=minimum inhibitory concentration; PD=pharmacodynamics.

1. Grupper M, et al. *Clin Microbiol Rev.* 2016;29(4):759-772.
2. Kuti JL, et al. *J Clin Pharmacol.* 2003;43(10):1116-1123.
3. Lee LS, et al. *Diagn Microbiol Infect Dis.* 2010;68(3):251-258.
4. Bhavnani SM, et al. ID Week 2017. Poster 1852.

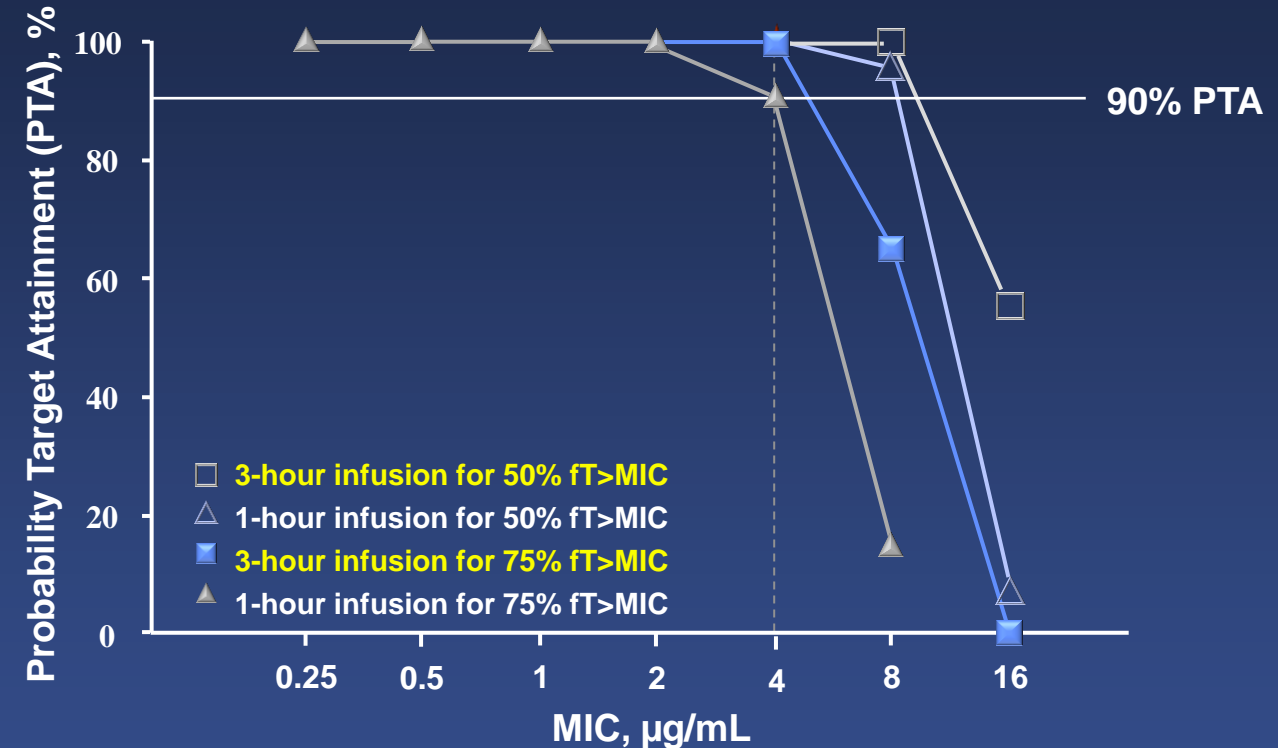
Cefiderocol Pharmacodynamic Dose Optimization

Free Plasma Concentration Profiles With 1-Hour and 3-Hour Infusions in Healthy Subjects¹



- ▶ Compared to a 1-hour infusion, a **3-hour infusion** increased the percent time of dosing interval that unbound plasma concentrations of cefiderocol exceed the MIC²

PTA for 50% or 75% $fT > MIC$ in Patients With Normal Renal Function for 2 g q8h Dose³



- ▶ With administration of 2 g q8h with 1- or 3-hr infusion, **>90% PTA** was achieved for 75% $fT > MIC$ at MIC of 4 µg/mL³

$fT > MIC$ = The percentage of a 24-h time period that the unbound drug concentration exceeds the MIC; MIC = minimum inhibitory concentration; q8h = every 8 hours.

1. Shionogi Inc. Presentations for the October 16, 2019 Meeting of the Antimicrobial Drugs Advisory Committee. U.S. Food and Drug Administration. <https://www.fda.gov/advisory-committees/advisorycommitteecalendar/october-16-2019-antimicrobial-drugsadvisory-committeemeeting-announcement-10162019-10162019>. Published October 28, 2019. Accessed February 29, 2020. 2. Fetroja [prescribing information]. Florham Park, NJ: Shionogi Inc. 3. Katsube T et al. *Antimicrob Agents Chemother.* 2017;61(1):e01381-16.

Cefiderocol: Dose Optimization

- Siderophore antimicrobial – Trojan Horse

- » Broad potency against Gram-negatives including Enterobacteriaceae, Pseudomonas and Acinetobacter

- » Potent against MDR phenotypes

- » **Exposure optimized dosing regimens:**

- CrCl > 60 ml/ml → 2g q 8 h 3 hr infusion

- CrCl < 60-30 ml/ml → 1.5g q 8 h 3 hr infusion

- CrCl < 30-15 ml/ml → 1g q 8 h 3 hr infusion

- » **Augmented function:**

- CrCl > 120 ml/ml → 2g q 6 h 3 hr infusion

When “S” ≠ Success ?

- Discordant therapy (i.e., **inadequate** therapy low exposures due to insufficient dose and / or regimen)
 - » **Therapeutic interventions (i.e., CRRT, ECMO)**
- Mini-BAL culture was collected that grew **pan-susceptible** culture positive for *Pseudomonas aeruginosa*
- Day 9 (cefepime 1000mg q8 / levofloxacin 250 qd day 3): vasopressor support was resumed with norepinephrine, and a repeat tracheal aspirate culture grew *P. aeruginosa* that had developed resistance to cefepime and piperacillin/tazobactam
- Day 9: Changed to meropenem 500mg every 6h, continued to respond poorly with a persistently elevated WBC (15.1 to 19.4x10³/μL) and serum lactate (3.4 to 5.9 mmol/L).
- Day 14 (meropenem day 6): tracheal aspirate **MDR *P. aeruginosa*** [R→Mero, Ceftaz, Pip/tazo, Cefepime, FQ]

When “S” ≠ Success ?

- Discordant therapy (i.e., **inadequate** therapy low exposures due to insufficient dose and / or regimen)

- » **Therapeutic interventions** → Continuous Renal Replacement Therapy (CRRT)

- **Ceftazidime-avibactam** - Pneumonia and **CRRT** are risk factors for treatment failures & resistance among patients with carbapenem-resistant Enterobacteriaceae infections¹
 - Patients often given reduced dose → **requires 2.5g q8**
- **Ceftolozane-tazobactam** - Significantly lower success rates were observed in patients with sepsis or **CRRT**
 - Patients often given lower dose (1.5g q8) → **requires 3g q8 dose**

¹Shields RK, et al. Antimicrob Agents Chemother. 2018 Mar 5. pii: AAC.02497-17

²Bassetti M, et al. Int J Antimicrob Agents 2019 Apr;53(4):408-415.

Cefiderocol Pharmacokinetics in a Patient Receiving Continuous Venovenous Hemodiafiltration

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ELSEVIER



Optimised cefiderocol exposures in a successfully treated critically ill patient with polymicrobial *Stenotrophomonas maltophilia* bacteraemia and pneumonia receiving continuous venovenous haemodiafiltration

Andrew J. Fratoni, Joseph L. Kuti, David P. Nicolau  

Table 2 Recommended Dosage of FETROJA for Patients Receiving CRRT

Effluent Flow Rate ^a	Recommended Dosage of FETROJA
2 L/hr or less	1.5 grams every 12 hours
2.1 to 3 L/hr	2 grams every 12 hours
3.1 to 4 L/hr	1.5 grams every 8 hours
4.1 L/hr or greater	2 grams every 8 hours

CRRT = continuous renal replacement therapy.

^a Ultrafiltrate flow rate for CVVH, dialysis flow rate for CVVHD, ultrafiltrate flow rate plus dialysis flow rate for CVVHDF.

Dosing regimens may need to be tailored based on residual renal function and patient's clinical status

TDM for β -Lactams: Unmet Medical Need?

Older antimicrobials:

- Poorly defined PD profiling during development of dosing regimens
- Variable doses in package insert, often low
- Variable “short” infusion times
- **Dosing regimens in practice often not consistent with contemporary PD optimized regimens**

➤ **Many patients likely to receive LOW, INEFFECTIVE EXPOSURES for targeted pathogens with contemporary MIC profiles**

➤ **Toxicity most often presents in the setting of severely reduced renal function in the absence of dosing regimen adjustment**

TDM for β -Lactams: Unmet Medical Need?

Recently developed therapies:

- Pharmacodynamic profiling has been “baked” into the clinically approved dosing regimens
 - Plazomicin
 - BL / BLIs
 - Cefiderocol
- Renal dosing substantiated → but driven by Cl_{cr} assessments
- Understand implications of CRRT, ECMO, etc. on dose requirements

CONFERENCE REPORT AND EXPERT PANEL

Antimicrobial therapeutic drug monitoring in critically ill adult patients: a Position Paper#



Mohd H. Abdul-Aziz¹, Jan-Willem C. Alffenaar^{2,3,4}, Matteo Bassetti⁵, Hendrik Bracht⁶, George Dimopoulos⁷, Deborah Marriott⁸, Michael N. Neely^{9,10}, Jose-Artur Paiva^{11,12}, Federico Pea¹³, Fredrik Sjoval¹⁴, Jean F. Timsit^{15,16}, Andrew A. Udy^{17,18}, Sebastian G. Wicha¹⁹, Markus Zeitlinger²⁰, Jan J. De Waele²¹, Jason A. Roberts^{1,22,23,24*} on behalf of the Infection Section of European Society of Intensive Care Medicine (ESICM), Pharmacokinetic/pharmacodynamic and Critically Ill Patient Study Groups of European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Group of International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) and Infections in the ICU and Sepsis Working Group of International Society of Antimicrobial Chemotherapy (ISAC)

- The Panel Members recommend routine TDM to be performed for aminoglycosides, **β-lactams**, linezolid, teicoplanin, vancomycin and voriconazole in **critically ill patients**.
- Although TDM should be the standard of care for most antimicrobials in every ICU, important barriers need to be addressed before routine TDM can be widely employed worldwide.