Therapeutic Drug Monitoring of Beta-Lactams and Other Antibiotics in the Intensive Care Unit: Which Agents, Which Patients and Which Infections?

Muller AE, Huttner B et al. *Drugs* 2018;78:439-451

- Beta-lactam antibiotics, the cornerstone of antibacterial therapy, never traditionally belonged to this group; with only a few exceptions, they are rarely toxic, and as a class have manifested strong clinical effectiveness even with fixed-dose, empiric regimens.

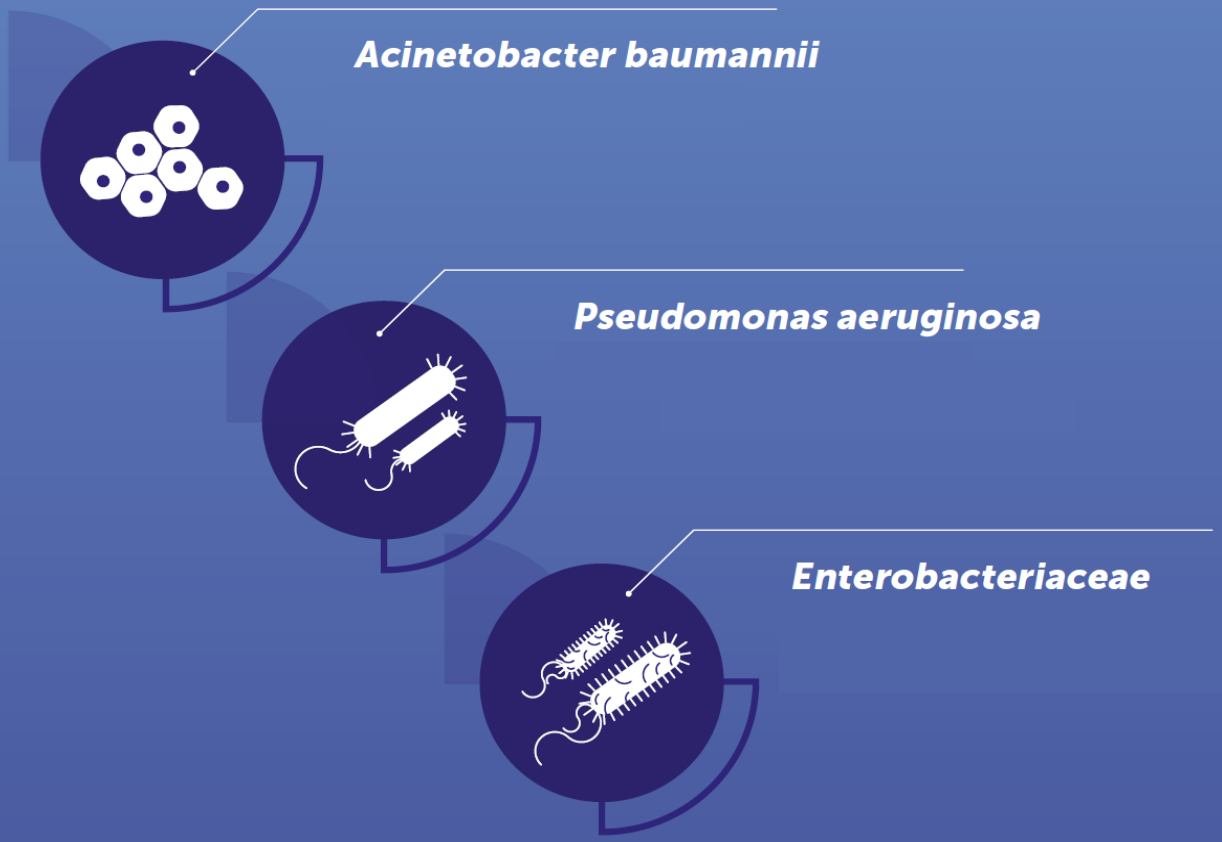
- Yet the global increases in antimicrobial resistance are slowly turning this paradigm. Minimal inhibitory concentrations (MIC)—the lowest levels of drug needed to hinder visible bacterial growth after 16–20 h of incubation—are increasing steadily, particularly for common intensive care unit (ICU) pathogens like *Pseudomonas aeruginosa* and *Acinetobacter* spp.

- Though a major focal point, less susceptible pathogens are not the only factor narrowing the beta-lactams' therapeutic range; the "average" human host has changed as well. The prevalence of both **geriatric** and "**long-term immunosuppressed**" patients is growing progressively; **obesity** rates have more than doubled in past decades; and the **critically ill** can now be maintained as a population in prolonged states of clinically important altered physiology.

World Health Organization

PRIORITIZATION OF PATHOGENS TO GUIDE RESEARCH AND DEVELOPMENT OF NEW ANTIBIOTICS

CRITICAL PRIORITY



WHO/EMP/IAU/2017.11

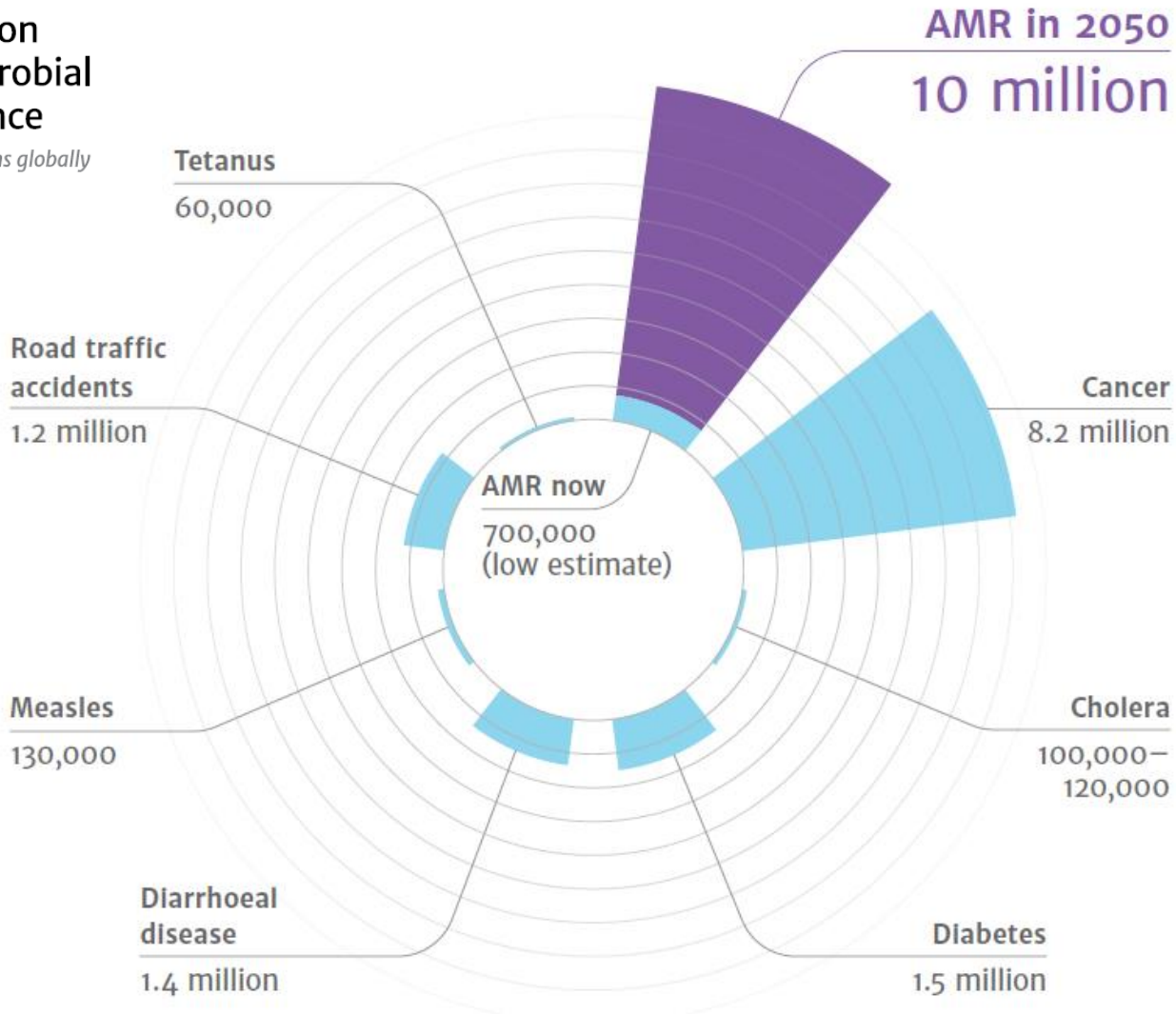
Institute of Clinical Pharmacology

AZIENDA OSPEDALIERO UNIVERSITARIA
Santa Maria della Misericordia di Udine

Deaths attributable to AMR every year

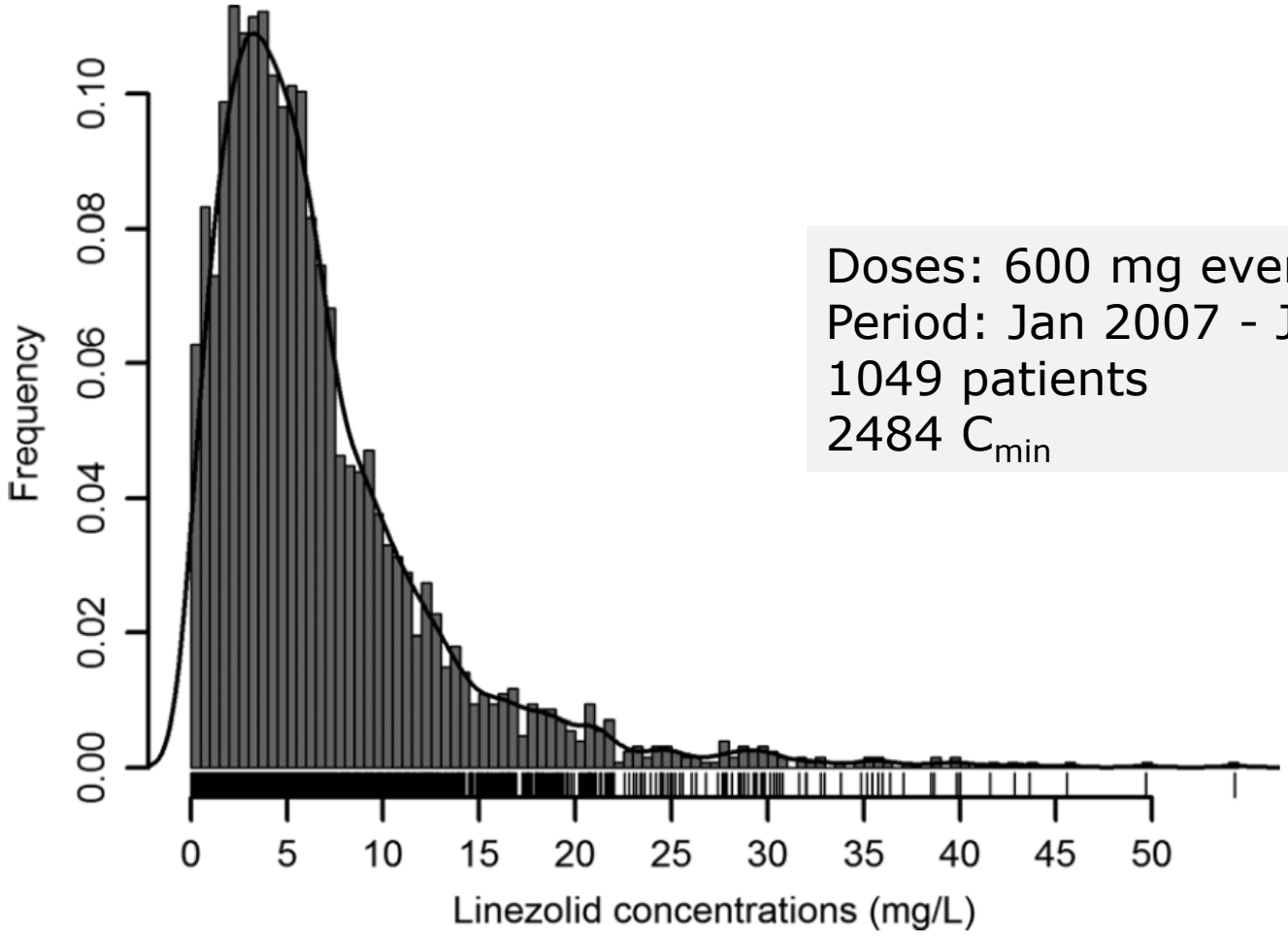
Review on Antimicrobial Resistance

Tackling drug-resistant infections globally



A 10-year experience of TDM of linezolid in a hospital-wide population of patients receiving conventional dosing: is there enough evidence for suggesting TDM in the majority of patients?

Pea F, Cojutti P, Baraldo M. *Basic Clin Pharmacol Toxicol* 2017;121(4):303-8



Doses: 600 mg every 12 hr
Period: Jan 2007 - Jun 2016
1049 patients
2484 C_{min}

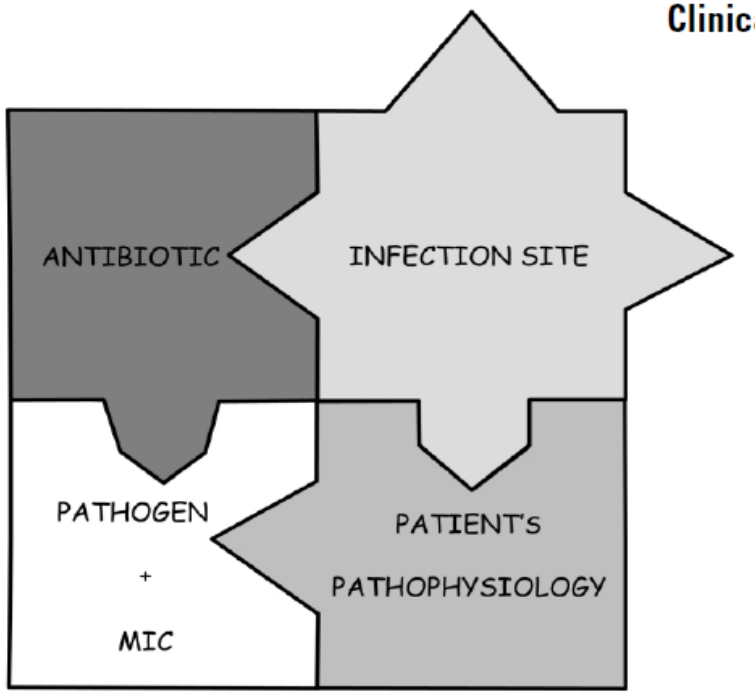
Louis D. Saravolatz, Section Editor

The Antimicrobial Therapy Puzzle: Could Pharmacokinetic-Pharmacodynamic Relationships Be Helpful in Addressing the Issue of Appropriate Pneumonia Treatment in Critically Ill Patients?

Federico Pea[1] and Pierluigi Viale[2]

[1]Institute of Clinical Pharmacology and Toxicology, Department of Experimental and Clinical Pathology and Medicine, and [2]Clinic of Infectious Diseases, Department of Medical and Morphological Research, Medical School, University of Udine, Udine, Italy

Clinical Infectious Diseases 2006; 42:1764–71



DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: Are Current β-Lactam Antibiotic Doses Sufficient for Critically Ill Patients?

Roberts JA et al. *Clin Infect Dis*. 2014;58:1072-83

Table 2. Clinical and Demographic Characteristics of Included Patients

Characteristic	All Patients (n = 361)	Patients Treated for Infection (n = 248)
Male sex, %	65	65
Age, y	61 (48–73)	60 (48–74)
Weight, kg	75 (65–85)	78 (65–86)
APACHE II score	18 (13–24)	18 (14–24)
SOFA score	5 (2–9)	6 (3–9)
Serum creatinine concentration, μmol/L	77 (53–134)	76 (53–144)
Calculated creatinine clearance, mL/min	80 (42–125)	82 (44–125)
Urinary creatinine clearance, mL/min	62 (31–107)	64 (32–103)

Table 1. Definitions Used for Pharmacokinetic/Pharmacodynamic and Clinical Endpoints

PK/PD Target	Description
50% $fT_{>MIC}$	Free drug concentration maintained above MIC of the known or suspected pathogen for at least 50% of dosing interval. This was considered to be the most conservative PK/PD target.
50% $fT_{>4\times MIC}$	Free drug concentration maintained above a concentration 4-fold higher than the MIC of the known or suspected pathogen for at least 50% of dosing interval.
100% $fT_{>MIC}$	Free drug concentration maintained above MIC of the known or suspected pathogen throughout the entire dosing interval.
100% $fT_{>4\times MIC}$	Free drug concentration maintained above a concentration 4-fold higher than the MIC of the known or suspected pathogen throughout the entire dosing interval.
Positive clinical outcome	Completion of treatment course without change or addition of antibiotic therapy, and with no additional antibiotics commenced with 48 h of cessation. De-escalation to a narrower spectrum antibiotic was permitted but excluded from the clinical outcome analysis.
Negative clinical outcome	Any clinical outcome other than positive clinical outcome.

DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: Are Current β-Lactam Antibiotic Doses Sufficient for Critically Ill Patients?

Roberts JA et al. *Clin Infect Dis*. 2014;58:1072-83

Table 4. Multivariate Regression Results of Clinical Outcome for Patients Who Did Not Receive Renal Replacement Therapy

	50% $fT_{>MIC}$			100% $fT_{>MIC}$		
Model Parameters	OR	95% CI	*P* Value	OR	95% CI	*P* Value
APACHE II score	0.94	.92–.96	<.001	0.94	.92–.96	.97
SOFA score	0.97	.94–1.00	.053	0.97	.94–1.01	.13
50% $fT_{>MIC}$	1.03	1.01–1.04	.001			
100% $fT_{>MIC}$	. . .			1.02	1.01–1.05	.040
AIC	1758.60					
BIC	1785.07					

Of the 248 patients treated for infection, 16% did not achieve 50%*f*T>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%*f*T>MIC and 100%*f* T>MIC ratios (OR, 1.02 and 1.56, respectively; P < .03), with significant interaction with sickness severity status.

Role of renal function in risk assessment of target non-attainment after standard dosing of meropenem in critically ill patients: a prospective observational study

Ehmann L. et al. *Critical Care* 2017;21:263

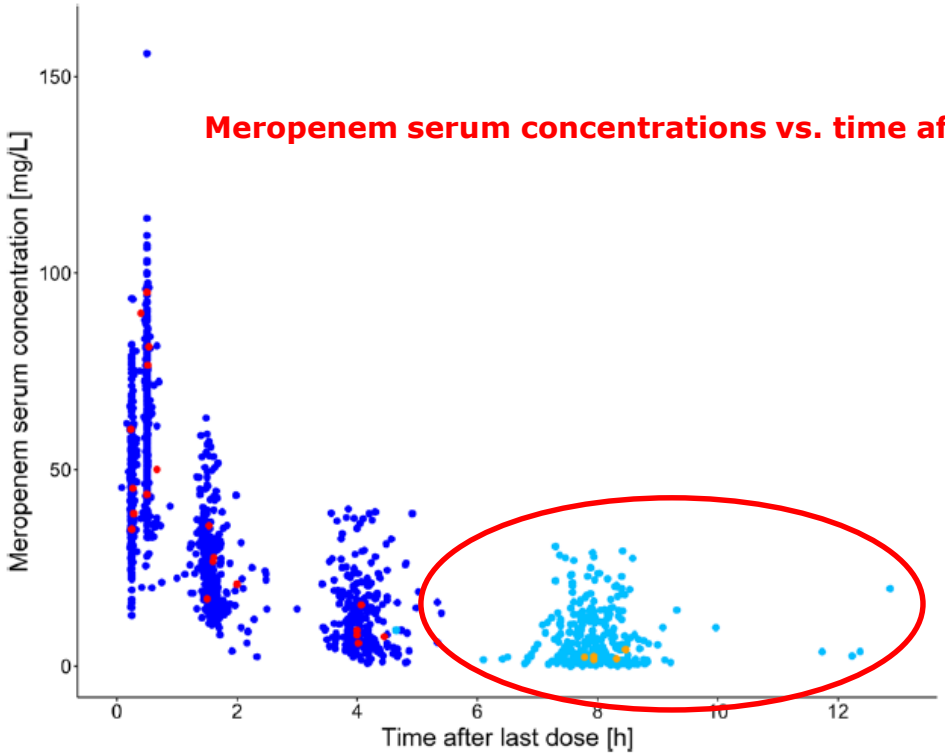
The attainment of two PK/PD targets (100%T>MIC, 50%T>4×MIC) was evaluated for MIC values of 2 mg/L and 8 mg/L and standard meropenem dosing (1000 mg, 30-minute infusion, every 8 h).

The planned sampling time points per intensively monitored dosing interval were as follows: 15 minutes, 30 minutes, 1.5 h, 4 h, and 8 h (directly before next dose; Cmin) after the start of infusion.

A total of 48 patients were included. 83.3% of patients had sepsis. CrCL was of 70.8 (34.8-160) mL/min.

Role of renal function in risk assessment of target non-attainment after standard dosing of meropenem in critically ill patients: a prospective observational study

Ehmann L. et al. *Critical Care* 2017;21:263



- Attainment of the target 100%T>MIC was merely 48.4% and 20.6%, given MIC values of 2 mg/L and 8 mg/L, respectively, and similar for the target 50%T>4×MIC.
- The investigated standard meropenem dosing regimen appeared to result in insufficient meropenem exposure in a considerable fraction of critically ill patients

CONFRONTING THE THREAT OF MULTIDRUG-RESISTANT GRAM-NEGATIVE BACTERIA IN CRITICALLY ILL PATIENTS

Cohen J. *J Antimicrob Chemother* 2013, 68(3): 490-491.

POSSIBLE STRATEGIES TO DEAL WITH THE PROBLEM OF MDR GRAM-NEGATIVE INFECTIONS IN CRITICALLY ILL PATIENTS

- Empirical combination therapy using a carbapenem with other antibiotic classes should be used first-line in critically ill patients at risk for MDR Gram-negative bacteria
- Pharmacokinetic/pharmacodynamic optimization of antibiotics with Gram-negative activity can overcome resistance associated with MDR Gram-negative bacteria
- Strategies to limit antibiotic exposure, such as shorter courses of antibiotics, attenuate the emergence of resistant Gram-negative bacteria
- Active surveillance of MDR Gram-negative bacteria with isolation should be an active component of infection control bundles to prevent the proliferation of MDR Gram-negative bacteria

The effect of pathophysiology on pharmacokinetics in the critically ill patient
Concepts appraised by the example of antimicrobial agents
Blot S, Pea F, Lipman J. *Adv Drug Deliv Rev.* 2014;77:3-11

	Concentration-dependent	Time-dependent	Concentration-dependent with time-dependence
Objective	Maximize concentrations	Maximize duration of exposure	Maximize amount of drug exposure
Optimal PK/PD index	C_{max}/MIC	T > MIC	$AUC_{0-24\ h}$ / MIC
Antimicrobials	Aminoglycosides	Carbapenems	Azithromycin
	Daptomycin	Cephalosporins	Clindamycin
	Fluoroquinolones	Erythromycin	Linezolid
	Ketolides	Linezolid	Tetracyclines
	Metronidazole	Clarithromycin	Fluoroquinolones
	Quinupristin/dalfopristin	Lincosamides	Aminoglycosides
		Penicillins	Quinupristin/dalfopristin
	ODD	MDD→ EI-CI	Tigecycline
			Vancomycin

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) **82** 900–902 900

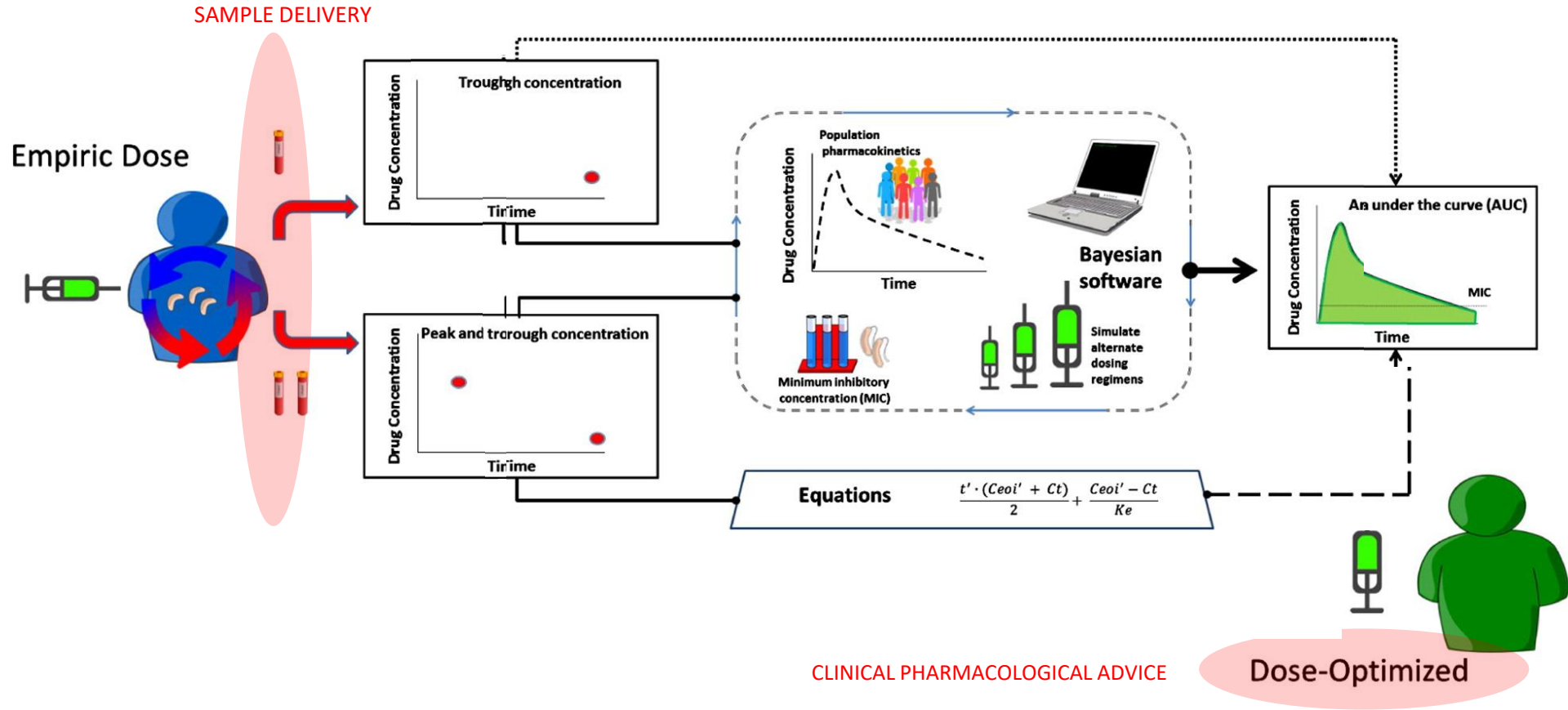
EDITORIAL

Therapeutic drug monitoring in the era of precision medicine: opportunities!

Serge Cremers[1], Nishan Guha[2] and Brian Shine[2]

- Individual patients might benefit from **dose adjustments** based on rapidly determined **drug levels** that are compared with the scarce pharmacokinetic data available.
- In a sense, laboratories would, therefore, simultaneously generate both drug development and TDM data.
- This exciting and novel application of TDM requires .....**rapid turnaround times** so that assays can be used for drug development and individual patient care.
- This new and exciting era of **precision medicine** has created never-before-seen opportunities for TDM in support of drug development and patient care

Innovative approach to optimizing antimicrobial therapy



Adapted from Pai MP et al. *Adv Drug Deliv Rev* 2014; 77: 50–57

Therapeutic Drug Monitoring of Beta-Lactams and Other Antibiotics in the Intensive Care Unit: Which Agents, Which Patients and Which Infections?

Muller AE, Huttner B et al. *Drugs* 2018;78:439-451

Indications for beta-lactam TDM	Comments, references
Patients	
Critically ill	[8, 43, 47]
Augmented renal clearance	Low serum creatinine predicts subtherapeutic plasma concentrations [8, 45]
Obesity	[63]
Renal insufficiency	Particularly haemodialysis or CRRT patients [56]
Elderly	[62]
Cystic fibrosis	[55]

CONTINUOUS vs. INTERMITTENT B-LACTAM INFUSION IN SEVERE SEPSIS

A META-ANALYSIS OF INDIVIDUAL PATIENT DATA FROM RANDOMIZED TRIALS

Roberts JA et al. *Am J Respir Crit Care Med.* 2016 Sep 15;194(6):681-91.

BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE COMBINED STUDY POPULATION

Characteristic	Continuous Infusion (*n* = 312)	Intermittent Dosing (*n* = 320)
Age, yr	61 (49–70)	63 (49–72)
Male sex	198 (63.5)	204 (63.8)
APACHE II score	21 (16–26)	20 (16–25)
Organism identified	97 (31.1)	114 (35.6)
Study antibiotic		
Piperacillin-tazobactam	203 (65.1)	221 (69.1)
Meropenem	94 (30.1)	93 (29.1)
Cefepime	11 (3.5)	2 (0.6)
Ticarcillin-clavulanate	4 (1.3)	4 (1.2)
Antibiotic 24-h dose, g		
Piperacillin-tazobactam	13.5 (13.5–18.0)	13.5 (13.5–18.0)
Meropenem	3.0 (2.0–3.0)	3.0 (1.7–3.0)
Cefepime	6.0 (6.0–6.0)	6.0
Ticarcillin-clavulanate	12.4 (12.4–13.2)	12.4
Duration from ICU admission to randomization, d	1 (0–4)	1 (1–4)
Duration of randomized treatment, d	5 (2–7)	4 (2–7)
Postrandomization length of ICU stay, d	7 (4–12)	6 (3–12)
Organ dysfunction		
Cardiovascular	214 (68.6)	217 (67.8)
Respiratory	207 (66.3)	208 (65.0)
Renal	74 (23.7)	82 (25.6)
Metabolic acidosis	71 (25.2)	73 (25.2)
Hematological	45 (14.4)	32 (10.0)
Primary infection site		
Lung	175 (56.1)	172 (53.8)
Intraabdominal	70 (22.4)	79 (24.7)
Blood	28 (9.0)	31 (9.7)
Skin or skin structure	22 (7.1)	28 (8.8)
Urinary tract	21 (6.7)	23 (7.2)
Central nervous system	4 (1.3)	7 (2.2)
Ear, nose, and throat	4 (1.3)	2 (0.6)
Indwelling vascular catheter	4 (1.3)	1 (0.3)
Pleural	2 (0.6)	3 (0.9)
Bone and joint	4 (1.3)	0 (0.0)
Cardiac	3 (1.0)	1 (0.3)
Gynecological	1 (0.3)	0 (0.0)
Others	10 (3.2)	4 (1.3)

CONTINUOUS vs. INTERMITTENT B-LACTAM INFUSION IN SEVERE SEPSIS

A META-ANALYSIS OF INDIVIDUAL PATIENT DATA FROM RANDOMIZED TRIALS

Roberts JA et al. *Am J Respir Crit Care Med.* 2016 Sep 15;194(6):681-91.

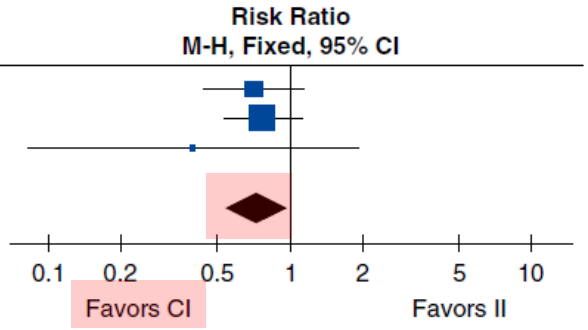
DIFFERENCES IN MORTALITY FOR CONTINUOUS INFUSION (CI) VERSUS INTERMITTENT INFUSION

A **HOSPITAL MORTALITY CENSORED AT DAY 30**

Study or Subgroup	CI Events	CI Total	II Events	II Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abdul-Aziz 2016	20	70	28	70	33.3%	0.71 [0.45, 1.14]
Dulhunty 2015	39	212	52	220	60.7%	0.78 [0.54, 1.13]
Dulhunty 2013	2	30	5	30	5.9%	0.40 [0.08, 1.90]
Total (95% CI)		**312**		**320**	**100.0%**	**0.73 [0.55, 0.98]**
Total events	61		85			

Heterogeneity: $Chi^2 = 0.69$, df = 2 (P = 0.71); $I^2 = 0\%$

Test for overall effect: Z = 2.11 (P = 0.03)

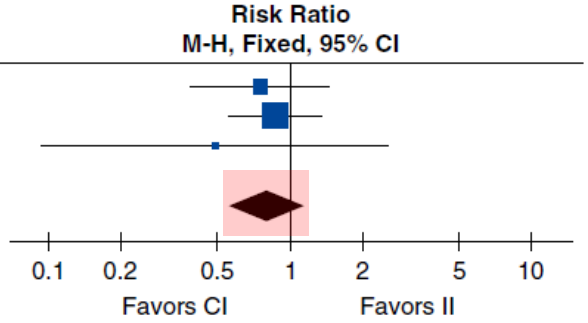


B **INTENSIVE CARE UNIT MORTALITY**

Study or Subgroup	CI Events	CI Total	II Events	II Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abdul-Aziz 2016	13	70	17	70	29.2%	0.76 [0.40, 1.45]
Dulhunty 2015	32	212	38	220	64.0%	0.87 [0.57, 1.34]
Dulhunty 2013	2	30	4	30	6.9%	0.50 [0.10, 2.53]
Total (95% CI)		**312**		**320**	**100.0%**	**0.82 [0.58, 1.16]**
Total events	47		59			

Heterogeneity: $Chi^2 = 0.49$, df = 2 (P = 0.78); $I^2 = 0\%$

Test for overall effect: Z = 1.14 (P = 0.25)



Might real-time pharmacokinetic/pharmacodynamic optimisation of high-dose continuous-infusion meropenem improve clinical cure in infections caused by KPC-producing *Klebsiella pneumoniae*?

Pea F, Cojutti P et al. Int J Antimicrob Agents. 2017;49:255-58

Univariate logistic regression analysis of variables associated with clinical cure from KPC-producing *Klebsiella pneumoniae*-related infections ($n = 30$ patients).

Variable	OR (95% CI)	*P*-value
Age	1.032 (0.969–1.100)	0.322
Male sex	1.154 (0.218–6.097)	0.866
CCI ≥ 4	0.158 (0.025–0.999)	0.050*
Length of therapy	1.091 (0.936–1.271)	0.264
Meropenem C_{ss}/MIC ratio ≥1	10.556 (1.612–69.122)	0.014*
Meropenem C_{ss}/MIC ratio ≥4	12.250 (1.268–118.361)	0.030*
Meropenem MIC	0.965 (0.930–1.003)	0.068
Site of infection		
BSI	0.143 (0.015–1.363)	0.091
No. of co-administered antimicrobials		
1 active drug	3.267 (0.334–31.914)	0.309
2 active drugs	0.952 (0.179–5.081)	0.954
3 active drugs	2.059 (0.202–20.959)	0.542
≥4 active drugs	0.167 (0.022–1.282)	0.085

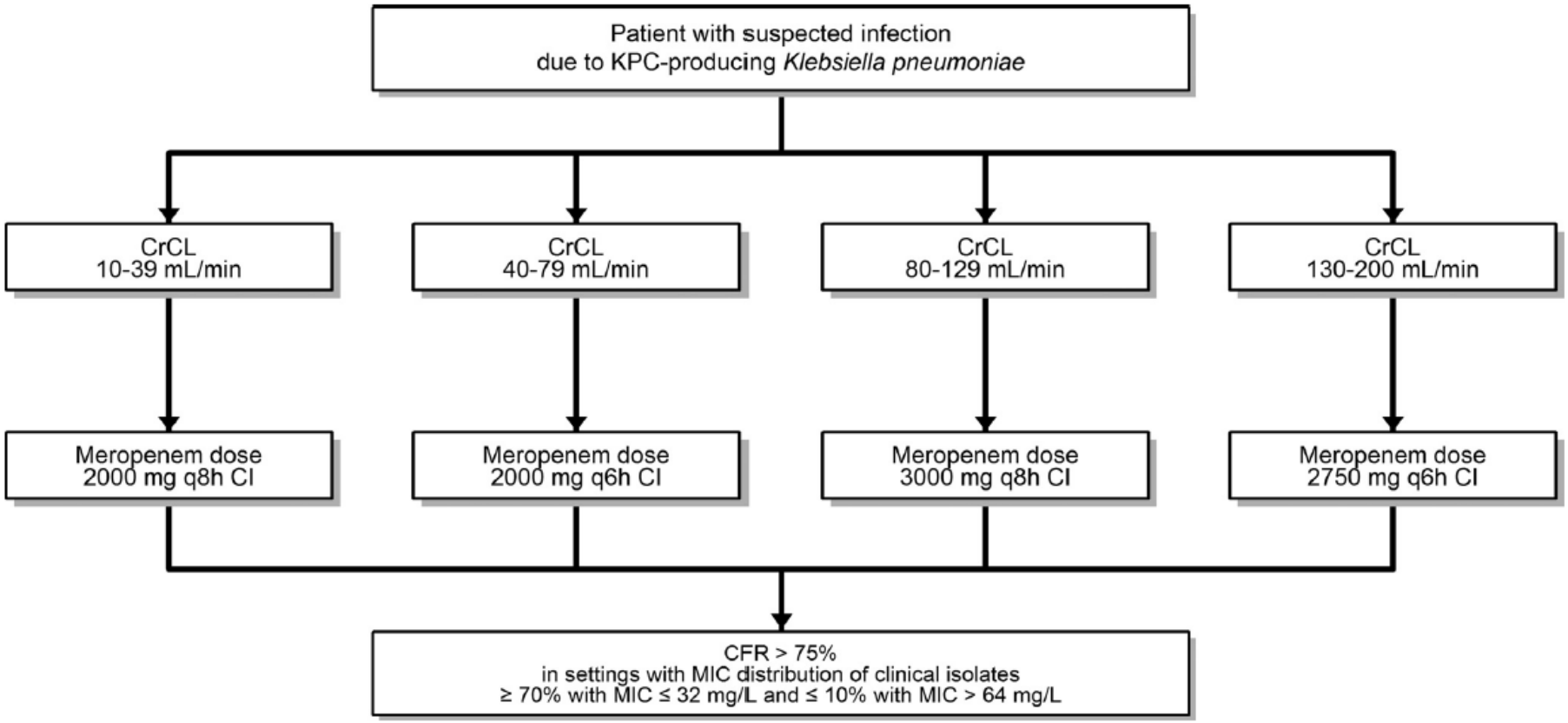
Population Pharmacokinetics of High-Dose Continuous-Infusion Meropenem and Considerations for Use in the Treatment of Infections Due to KPC-Producing *Klebsiella pneumoniae*

Cojutti P et al. *Antimicrob Agents Chemother* 2017 Sep 22; 61(10)

TABLE 2 Permissible HDCI meropenem regimens enabling acceptable PTA of the PK/PD targets in relation to different classes of renal function and to the meropenem MIC of the invading KPC-producing *Klebsiella pneumoniae* strain[a]

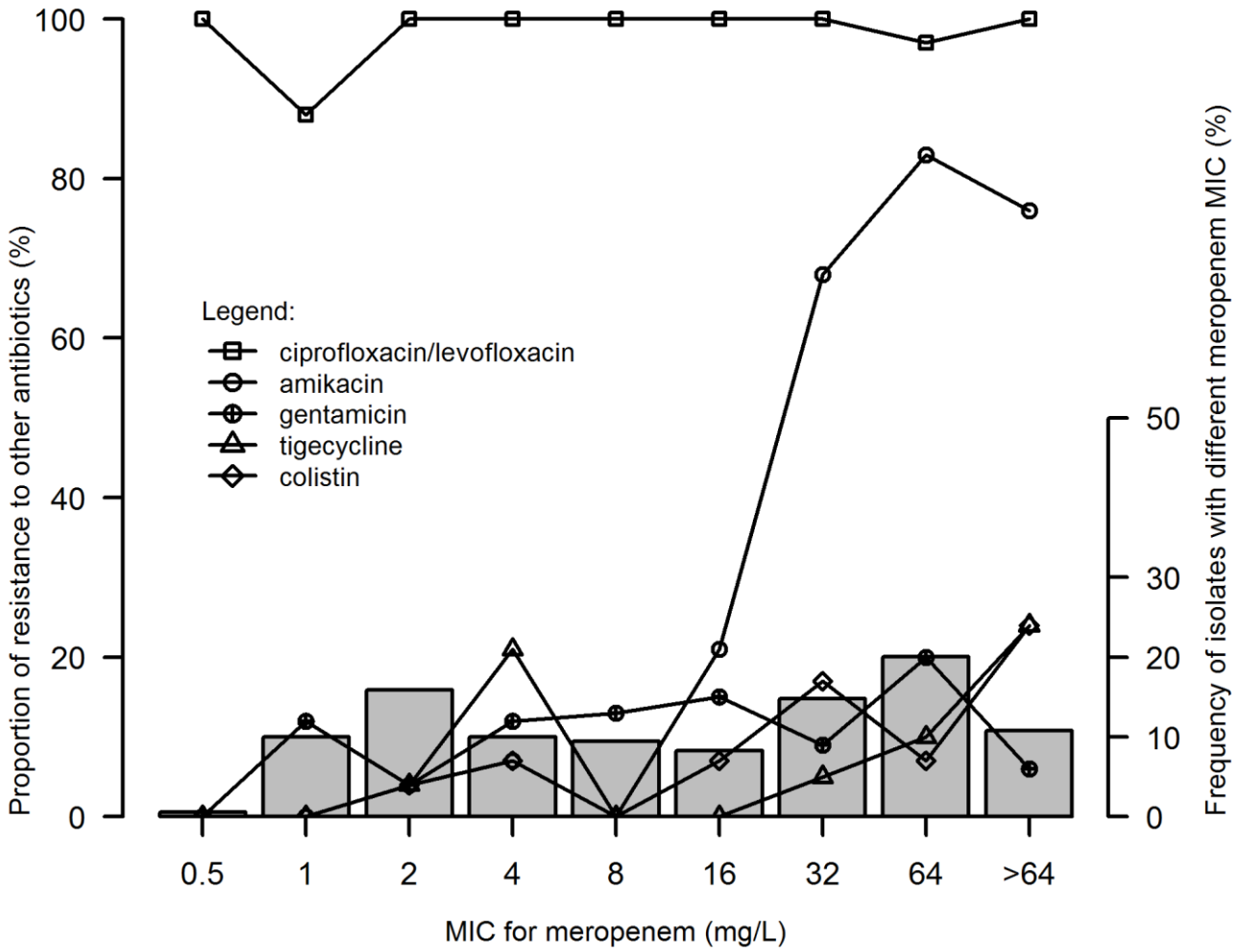
Population Pharmacokinetics of High-Dose Continuous-Infusion Meropenem and Considerations for Use in the Treatment of Infections Due to KPC-Producing *Klebsiella pneumoniae*

Cojutti P et al. *Antimicrob Agents Chemother* 2017 Sep 22; 61(10)



Is MIC increase of meropenem against *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae* correlated with the increase of resistance rates against some other antibiotics with Gram-negative activity?

Cojutti P et al. *J Glob Antimicrob Resist* 2018 May 15; e-pub ahead of print



AMINOGLYCOSIDES: HOW SHOULD WE USE THEM IN THE 21ST CENTURY ?

Jackson J et al. *Curr Opin Infect Dis* 2013 Dec; 26(6): 516-25

DOSING AND MONITORING

- C_{max}/MIC and AUC/MIC ratios are the best PK/PD predictors associated with aminoglycoside efficacy
- Increasing evidence suggests that AGAs should be administered as a once daily dose (ODD), taking advantage of their concentration-dependent bactericidal effect as well as their post-antibiotic effect
- Some evidence suggests clinical outcomes may be improved and nephrotoxicity reduced with ODD
- ODD in antibiotic courses <10 days may be particularly beneficial in delaying or preventing renal impairment

Reappraisal of contemporary pharmacokinetic and pharmacodynamic principles for informing aminoglycoside dosing

Bland C, Pai M, Lodise T. *Pharmacotherapy* 2018;38(12):1229-38

- **Support is now increasing for the area under the plasma concentration–time curve (AUC)/MIC ratio as a more accurate measure of exposure–efficacy relationships**

- Therefore, based on current literature, an AUC/MIC ratio of 30–50 for aminoglycoside therapy may provide optimal outcomes when targeting non-critically ill immunocompetent patients with low-bacterial burden gram-negative infections such as urinary tract infections, or in patients receiving additional gram-negative therapy with good source control.

- An AUC/MIC ratio target of 80–100 may be more prudent when treating patients with aminoglycoside monotherapy or in critically ill patients with high-bacterial burden infections, such as hospital-acquired pneumonia

- Software is readily available to implement the Bayesian approach at the patient's bedside. The Bayesian software requires only one or two serum concentrations to accurately calculate AUC, can support innovative dosing regimens, does not require waiting until steady state is reached to obtain the concentration sample, and can model covariates such as creatinine clearance that affect drug PK

PHARMACOTHERAPY

SPECIAL ARTICLE

International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP)†

(Pharmacotherapy 2019;39(1):10–39) doi: 10.1002/phar.2209

International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP)

Tsuji B. et al. *Pharmacotherapy* 2019;39(1):10-39

Table 1. CLSI/EUCAST Breakpoints for Colistin

	Colistin MIC, mg/L		
Organism	Susceptible	Intermediate	Resistant
CLSI[a]			
Acinetobacter sp	≤ 2	–	≥ 4
Pseudomonas aeruginosa	≤ 2	–	≥ 4
EUCAST			
Acinetobacter sp	≤ 2		> 2
P. aeruginosa	≤ 2		> 2
Enterobacteriaceae	≤ 2		> 2

Is There a Recommended PK/PD Therapeutic Target for Maximization of Efficacy for Colistin and Polymyxin B?

Recommendations. R2: We recommend that for colistin, an area under the plasma concentration-time curve across 24 hours at steady state (AUCss,24 hr) of ~50 mgh/L is required that equates to a target average steady-state plasma concentration (Css,avg) of ~2 mg/L for total drug.

Although this target might be suboptimal for lower respiratory tract infections, it is noted that this should be considered as a maximum tolerable exposure. Concentrations higher than this were shown to increase both the incidence and severity of AKI.

Clinical Infectious Diseases

MAJOR ARTICLE

Dosing Guidance for Intravenous Colistin in Critically Ill Patients

Roger L. Nation,[1] Samira M. Garonzik,[3] Visanu Thamlikitkul,[5] Evangelos J. Giamarellos-Bourboulis,[6] Alan Forrest,[3] David L. Paterson,[2] Jian Li,[1] and Fernanda P. Silveira[4]

Table 3. "Look-up" Table of Daily Doses of Colistimethate for a Desired Target colistin $C_{ss,avg}$ of 2 mg/L for Narrow Windows of Creatinine Clearance

Creatinine clearance, mL/min	Dose of Colistimethate for $C_{ss,avg}$ of 2 mg/L[a]	
	CBA, mg/d	Million IU/d
0	130	3.95
5 to <10	145	4.40
10 to <20	160	4.85
20 to <30	175	5.30
30 to <40	195	5.90
40 to <50	220	6.65
50 to <60	245	7.40
60 to <70	275	8.35
70 to <80	300	9.00
80 to <90	340	10.3
≥90	360	10.9

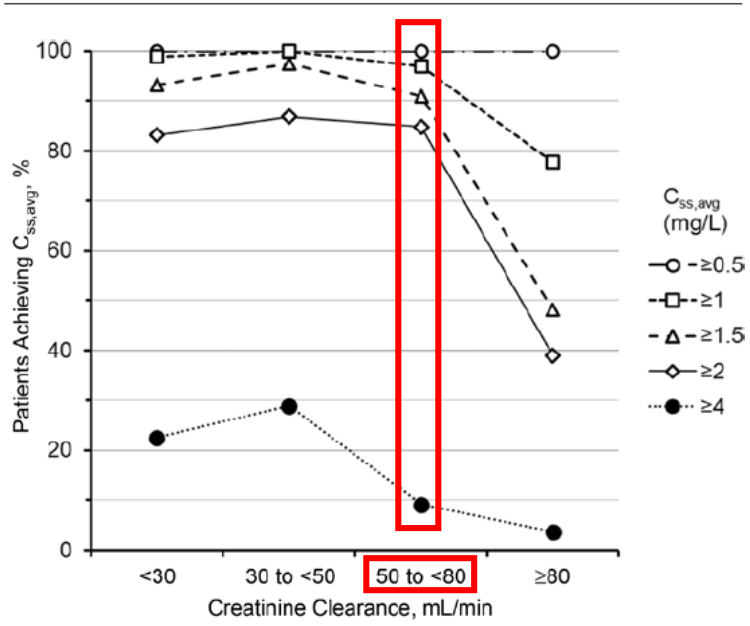


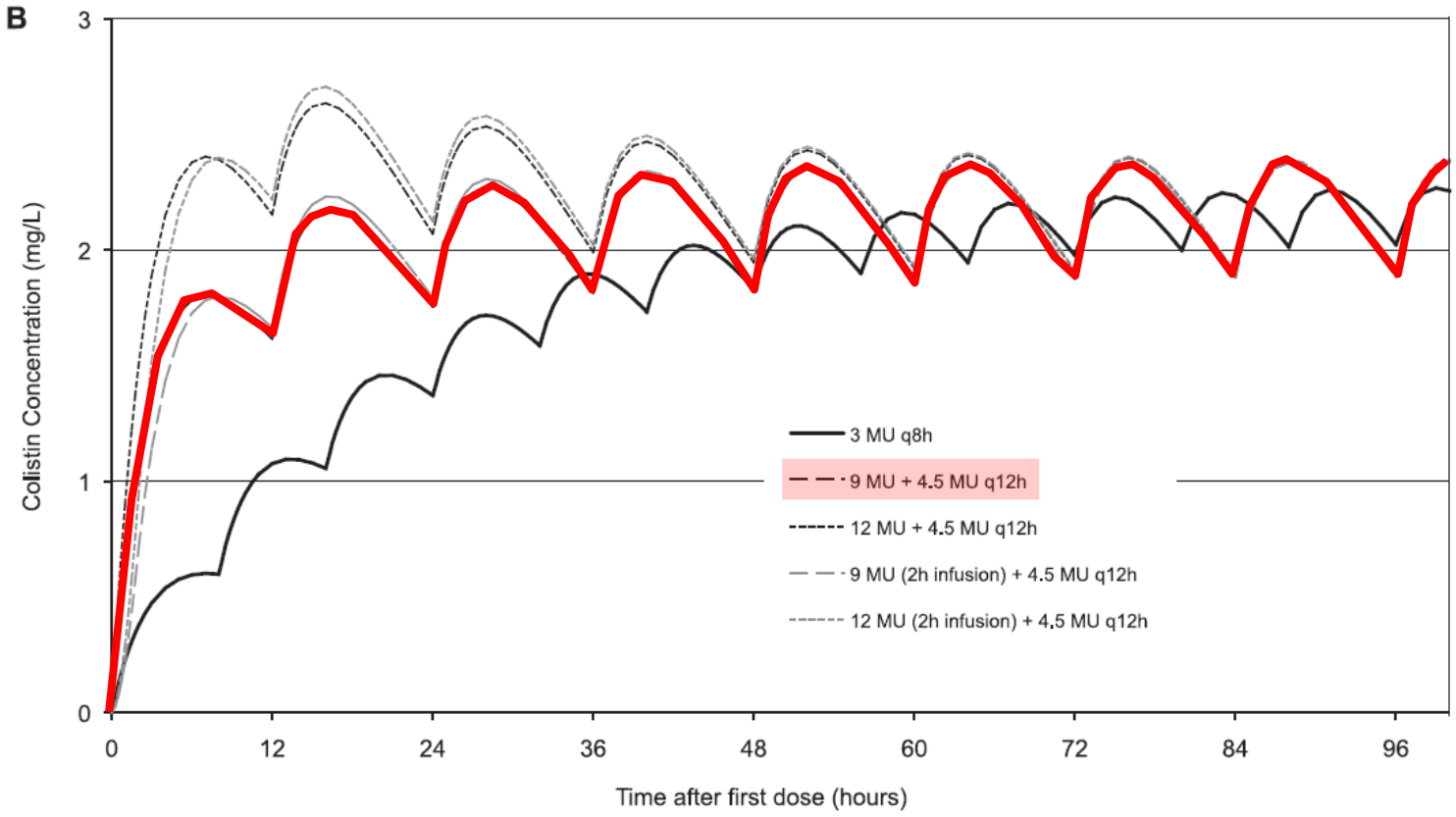
Figure 3. Percentage of patients in each creatinine clearance cluster achieving average steady-state plasma concentrations of colistin ($C_{ss,avg}$) of ≥0.5, ≥1, ≥1.5, ≥2, and ≥4 mg/L using the daily dose of colistimethate in Table 3 relevant to the actual creatinine clearance of each patient.

Daily dose administered in 2 divided doses 12 h apart

POP PK ANALYSIS OF COLISTIN METHANESULFONATE AND COLISTIN AFTER IV ADMINISTRATION IN CRITICALLY ILL PATIENTS WITH INFECTIONS CAUSED BY GRAM-NEGATIVE BACTERIA

Plachouras D et al. *Antimicrob Agents Chemother* 2009; 53: 3430–3436

PREDICTED COLISTIN PLASMA LEVELS



International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP)

Tsuji B. et al. *Pharmacotherapy* 2019;39(1):10-39

Should I Preferentially Use One Polymyxin Over the Other?

R6: We recommend polymyxin B as the preferred agent for routine systemic use in invasive infections. The rationale for this recommendation is that polymyxin B has superior PK characteristics in humans as well as a decreased potential to cause nephrotoxicity.
R7: We recommend colistin as the preferred polymyxin for the treatment of lower urinary tract infections given renal clearance of the prodrug CMS that then converts to the active moiety colistin in the urinary tract.

Colistin: IHD and CRRT

IHD: On a nondialysis day, administer a CMS dose of 130 mg CBA/day (~3.95 million IU/day). On a dialysis day, administer a supplemental dose of CMS 40 mg CBA (~1.2 million IU) or 50 mg CBA (~1.6 million IU) for a 3- or 4-hour IHD session, respectively.
If possible, the supplement to the baseline (nondialysis) daily dose should be administered with the next regular dose, after the dialysis session has ended.
CRRT: for a plasma colistin Css,avg of 2 mg/L, to administer CBA 440 mg/day (~13.3 million IU/day). This equates to 220 mg CBA every 12 hours (~6.65 million IU every 12 hours).

Polymyxin B: IHD and CRRT

We recommend that neither the loading dose nor maintenance dose be adjusted in patients receiving renal replacement therapy.
Recommendation. R16: We recommend that for patients with severe infections, a polymyxin B dose of 1.25–1.5 mg/kg (equivalent to 12,500–15,000 IU/kg TBW) every 12 hours is infused over 1 hour.

Is there a role for TDM of Colistin or Polymyxin B?

Recommendation. R19: We recommend that TDM and adaptive feedback control (AFC) be used wherever possible for both colistin and polymyxin B.

WHAT IS THE RELEVANCE OF FOSFOMYCIN PK IN THE TREATMENT OF SERIOUS INFECTIONS IN CRITICALLY ILL PATIENTS?

Parker S et al. *Int J Antimicrob Agents* 2013; 42: 289-293

KEYPOINTS FOR OPTIMAL DOSAGE OF FOSFOMYCIN IN THE CRITICALLY ILL

- Fosfomycin is hydrophilic → ↑ Vd plus ↑ CL_R are expected in septic patients
- PD → time-dependent activity
- T1/2 → ~ 2h in presence of normal renal clearance (NRC) or < 2h in ARC
- Dosage of fosfomycin disodium → up to 16-18 g/day
  - in 4 refracted doses (**NRC**) → up to 3-4g q6h
  - in 6 refracted doses (**ARC**) → up to 2-3 g q 4h ?
  - ↓ dose amount but maintain dosing interval in IRC
- <u>WARNING:</u>
  - → 330 mg Na^+ per gram of fosfomycin disodium
  - → avoid use in patients with heart failure (Reffert J et al. *Pharmacotherapy* 2014;34:845-57)

Population Pharmacokinetics and Pharmacodynamics of Levofloxacin in Acutely Hospitalized Older Patients with Various Degrees of Renal Function

Cojutti P et al. *Antimicrob Agents Chemother.* 2017;61(2):e-02134–16

Characteristic	Value
Patient demographic	
Age (yr [mean ± SD])	81.2 ± 7.8
Gender (male/female) [*n* (%)]	103/65 (61.3/38.7)
Body wt (kg) [median (IQR)]	70 (65–80)
$CrCL_{CKD\text{-}EPI}$ (ml/min/1.73 m^2)[a] [median (IQR)]	30.2 (18.2–50.2)
Indication for levofloxacin use [*n* (%)]	
Community-acquired pneumonia	77 (45.8)
Urinary tract infections	22 (13.1)
Chronic obstructive pulmonary disease	19 (11.3)
Fever of unknown origin	12 (7.1)
Sepsis of unknown origin	13 (7.7)
Intra-abdominal infections	11 (6.6)
Skin and soft tissue infections	8 (4.8)
Bone and joint infections	6 (3.6)
Patients with identified microbiological isolates [*n* (%)]	49 (29.2)
Levofloxacin treatment	
Duration of therapy (days) [median (IQR)]	10 (7–14)
Route of administration (oral/i.v.) [*n* (%)]	145/23 (86.3/13.7)
Clinical outcome [*n* (%)]	
Cured	95 (56.5)
Improved	28 (16.7)
Failed	26 (15.5)
Dead/modified antibiotic therapy	19 (11.3)

[a]At first TDM.

MIC (mg/liter)	Dosing regimen (mg) for class of renal function (ml/min/1.73 m^2):				
	0–19	20–39	40–59	60–79	>80
0.125	125 every 48 h	500 every 48 h	500 every 48 h	500 every 48 h	750 every 48 h
0.25	250 every 48 h	500 every 48 h	500 every 48 h	750 every 48 h	750 every 24 h
0.5	500 every 48 h	750 every 48 h	500 every 24 h	750 every 24 h	500 every 12 h

Population Pharmacokinetics and Pharmacodynamics of Levofloxacin in Acutely Hospitalized Older Patients with Various Degrees of Renal Function

Cojutti P et al. *Antimicrob Agents Chemother.* 2017;61(2):e-02134–16

CFR of the permissible doses of levofloxacin against the invading pathogens more frequently yielded in the study population according to their EUCAST MIC distributions

Class of renal function (ml/min/1.73 m²)	Levofloxacin dose (mg)	CFR			
		S. aureus	*H. influenzae*	*E. coli*	*P. aeruginosa*
0–19	125 every 48 h	59.89	99.66	82.06	16.48
	250 every 48 h	77.03	99.78	85.07	40.36
	500 every 48 h	81.59	99.85	87.34	62.24
20–39	500 every 48 h	79.22	99.79	85.80	47.07
	750 every 48 h	81.26	99.84	87.12	59.63
	500 every 24 h	81.49	99.85	87.43	63.08
40–59	500 every 48 h	71.28	99.73	83.45	25.81
	750 every 48 h	77.73	99.78	85.26	42.03
	500 every 24 h	79.42	99.81	86.16	50.72
	750 every 24 h	81.13	99.84	87.28	61.63
60–79	500 every 48 h	57.19	99.65	81.57	14.41
	750 every 48 h	70.61	99.73	83.52	26.68
	500 every 24 h	74.86	99.76	84.55	36.08
	750 every 24 h	79.16	99.81	86.20	51.22
>80	750 every 48 h	60.72	99.67	82.12	18.21
	500 every 24 h	67.91	99.71	83.27	25.50
	750 every 24 h	75.51	99.77	84.90	39.43
	500 every 12 h	81.67	99.85	87.52	63.81

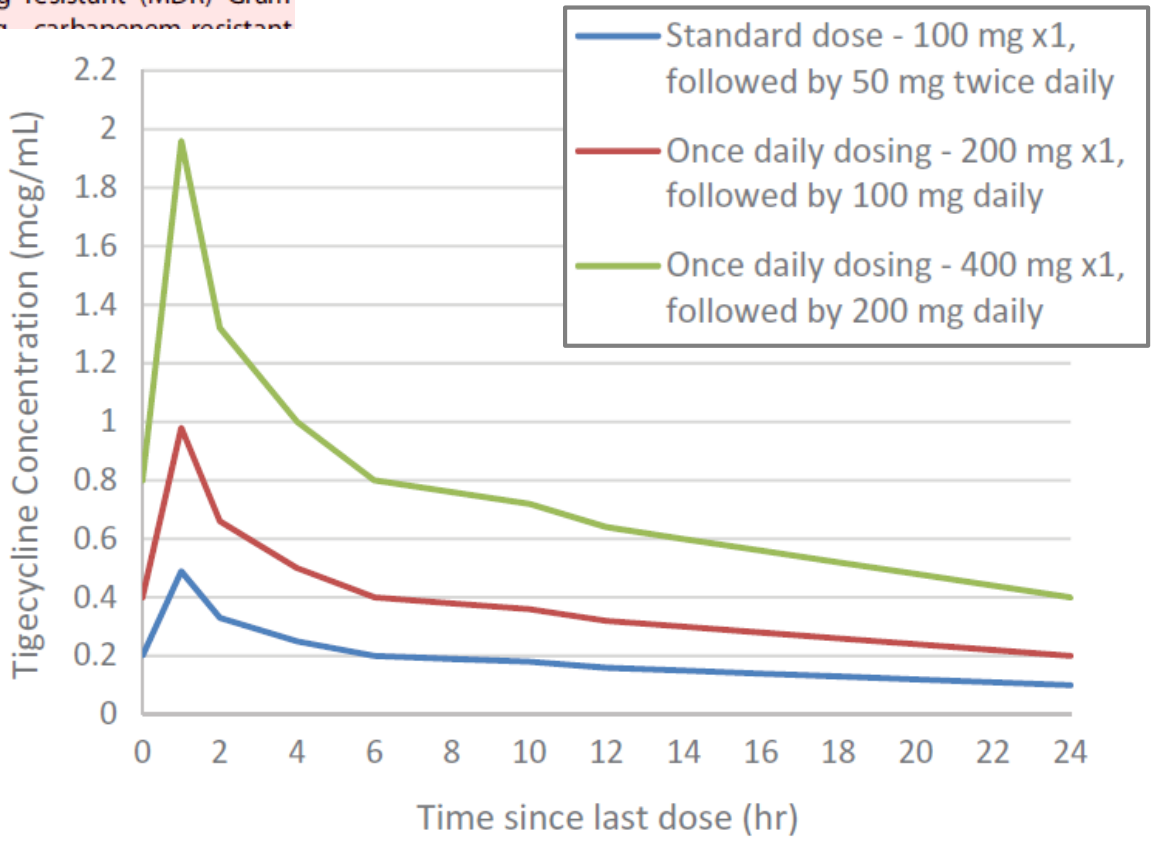
Once daily high dose tigecycline – pharmacokinetic/pharmacodynamic based dosing for optimal clinical effectiveness: dosing matters, revisited

Cunha BA et al. *Expert Rev Anti Infect Ther* 2017;15:257-67

Key issues

- Tigecycline is a minocycline derivative highly active against all Gram-positive, nearly all Gram negative and all anaerobic pathogens
- Due to its broad spectrum of activity, tigecycline has emerged as first line therapy for serous systemic infections including those due to multi-drug resistant (MDR) Gram negative bacilli (GNB) includi carbapenem resistant Enterobacteriacae (CRE).
- Tigecycline has no activity ag Proteus sp., and some Providen
- In serous systemic infections efficacy is dependent on opti MDR GNB pathogens.
- Once daily SDT has been used cSSSIs, and CAP.
- Standard dose tigecycline (SDT) concentrations could result in c resistance, especially in treating
- Tigecycline has a long serum permits once daily is dosing a dependent killing.
- Pharmacokinetic/pharmacodyna of tigecycline using higher dose concentrations and prolonged e
- Clinically, high dose tigecyclin effective treatment for severe sy
- Once daily HDT is the optimal systemic infections particularly GNB infections.

Susceptibility breakpoints for CRE: resistance implications	
FDA	EUCAST
• Susceptible: MIC ≤ 2 mcg/ml	• Susceptible: MIC ≤ 1 mcg/ml
• Resistant: MIC ≥ 8 mcg/ml	• Resistant: MIC > 2 mcg/ml



Once daily high dose tigecycline – pharmacokinetic/pharmacodynamic based dosing for optimal clinical effectiveness: dosing matters, revisited

Cunha BA et al. *Expert Rev Anti Infect Ther* 2017;15:257-67

High-dose tigecycline (HDT) optimizes clinical effectiveness.

Tigecycline: suggested infusion regimens[b]		
Tigecycline dose[a] (mg)	Infusion volume (ml)	Infusion time (min)
100	100	30
200[c]	250	60
400[d]	500	120

[a]Maintenance dose is half the loading dose.
[b]To minimize/eliminate nausea/vomiting.
[c]For serious systemic infections.
[d]For serious systemic infections or UTIs due to MDR gram-negative pathogens.
Adapted from: Cunha CB, Cunha BA. Antibiotic Essentials (15th Ed.) JayPee Medical Publishers, New Delhi, 2017; pp. 700–701.

Posologia. Per via e.v 100 mg come dose di carico, poi 100 mg in 2 somministrazioni giornaliere. Nelle infezioni più gravi e dove una MIC ≥ 1 aumentare la dose a 200 mg come dose di carico e 200 mg in 2 somministrazioni giornaliere.

Infections Caused by Carbapenem-Resistant *Enterobacteriaceae*: An Update on Therapeutic Options

Sheu C et al. F*ront Microbiol.* 2019 Jan 30;10:80

Classification and characteristics of major carbapenemases in *Enterobacteriaceae:*

Carbapenemase	KPC	MBLs (NDM, VIM, IMP)	OXA-48
Ambler molecular class	A	B	D
Substrates of hydrolysis	All β-lactams	All β-lactams except for aztreonam	Penicillins and carbapenems
Inhibited by classic β-lactamase inhibitors	Minimally	No	No
Inhibited by avibactam	Yes	No	Yes
Inhibited by vaborbactam	Yes	No	No
Inhibited by relebactam	Yes	No	No
Common species in *Enterobacteriaceae*	*K. pneumoniae, E. coli, Enterobacter* spp.	NDM: *K. pneumoniae, E. coli* VIM: *K. pneumoniae* IMP: *K. pneumoniae*	*K. pneumoniae*

KPC, Klebsiella pneumoniae carbapenemase; MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; VIM, Verona integrin-encoded metallo-β-lactamase; IMP, imipenemase; OXA, oxacillinase.

ANTIMICROBIAL SPECTRUM OF NEW ANTIBIOTICS:

Antibiotic	ESBL-producing Enterobacteriaceae	KPC-producing *Klebsiella pneumoniae*	MBL-producing Enterobacteriaceae	AmpC-producing Enterobacteriaceae	*Pseudomonas aeruginosa* (including MDR strains)	*Acinetobacter baumannii* (including carbapenem-resistant strains)	Anaerobes
Ceftolozane/tazobactam	✓	×	×	✓	✓	×	Limited[a]
Ceftazidime/avibactam	✓	Limited[b]	×	✓	✓	×	Limited[c]
Aztreonam/avibactam	✓	✓	✓	✓	×	×	N/D
Imipenem/relebactam	✓	✓	×	✓	✓	N/D	✓
Meropenem/RPX7009	✓	✓	×	✓	×	×	✓
Eravacycline	✓	✓	✓	N/D	×	✓	✓
Plazomicin	✓	✓	×	✓	✓	✓	×
S-649266	✓	✓	✓	N/D	✓	✓	×

[a] Active only against *Bacteroides fragilis*, *Prevotella* spp. and *Fusobacterium* spp., but not other *Bacteroides* spp. or other anaerobic pathogens.

Syue LS et al. *Int J Antimicrob Agents* 2016; 47: 250–258

PHARMACOKINETIC CHARACTERISTICS OF CEFTOLOZANE/TAZOBACTAM

	Ceftolozane/tazobactam
FDA indications	cIAI (with metronidazole), cUTI (including pyelonephritis)
Dosing	
CL_{Cr} >50 mL/min	1.5 g i.v. q8h
CL_{Cr} 30–50 mL/min[a]	750 mg i.v. q8h
CL_{Cr} 15–29 mL/min[b]	375 mg i.v. q8h
CL_{Cr} 6–15 mL/min	N/A
CL_{Cr} ≤5 mL/min	N/A
ESRD on HD	Load 750 mg i.v. × 1, then 150 mg i.v. q8h
Infusion time	1 h
Ratio of cephalosporin to BLI	2:1 ceftolozane:tazobactam
Hepatic dosage adjustment	No
Drug interactions	No clinically significant CYP450 interactions. No other enzymatic interactions anticipated

Liscio JL et al. *Int J Antimicrob Agents* 2015 Sep; 46 (3): 266-71

RECOMMENDED DOSES OF CEFTAZIDIME/AVIBACTAM FOR PATIENTS WITH VARYING DEGREES OF RENAL IMPAIRMENT

- **CLCR 31–50 mL/min → 1.25 g IV every 8 h**
- **CLCR 16–30 mL/min → 0.94 g IV every 12 h**
- **CLCR 6–15 mL/min → 0.94 g IV every 24 h**
- **CLCR ≤ 5 mL/min → 0.94 g IV every 48 h**

Falcone M and Patterson D. *J Antimicrob Chemother* 2016 on line published July 17

Treatment of Infections Due to MDR Gram-Negative Bacteria

Bassetti et al. *Front Med.* 2019;6:74

CRE

- Ceftazidime/avibactam (as preferred empirical choice when both KPC and OXA carbapenemases are reported locally) or meropenem/vaborbactam
- Although in the lack of high-level evidence, for both empirical and targeted treatment a combination with old (colistin, polymyxin B, tigecycline, old aminoglycosides, fosfomycin) or novel agents (plazomicin, eravacycline, double BL-BLI combinations) could be considered in the attempt of delaying emergence of resistance, after having carefully balanced potential additional toxicity on a case-by-case basis (expert opinion)
- In case of resistance to novel BL-BLI, consider polymyxins-based or aminoglycosides-based combinations with carbapenems and/or (tigecycline or eravacycline) and/or fosfomycin
- Consider concomitant administration of inhaled polymyxins/aminoglycosides when they are used intravenously for VAP

CRPA

- Ceftolozane/tazobactam (as preferred empirical choice in absence of concomitant risk of CRE) or ceftazidime/avibactam
- For empirical therapy, administer a second anti-pseudomonal agent (an aminoglycoside or a polymyxin or fosfomycin)
- Although in the lack of high-level evidence, for targeted therapy combination with old (colistin, polymyxin B, old aminoglycosides, fosfomycin) or novel agents (plazomicin, double BL-BLI combinations) could be considered in the attempt of delaying emergence of resistance, after having carefully balanced potential additional toxicity on a case-by-case basis (expert opinion)
- In case of resistance to novel BL-BLI, consider polymyxins-based or aminoglycosides-based combinations with carbapenems and/or fosfomycin and/or rifampin
- Consider concomitant administration of inhaled polymyxins/aminoglycosides when they are used intravenously for VAP

CRAB

- Administer a polymyxin as the backbone agent
- Consider combination with old (carbapenems, old aminoglycosides, tigecycline, fosfomycin, rifampin) or novel agents (plazomicin, eravacycline)
- Consider concomitant administration of inhaled polymyxins/aminoglycosides when they are used intravenously for VAP

Ceftazidime/Avibactam, Meropenem/Vaborbactam, or Both? Clinical and Formulary Considerations

Pogue J et al. *Clin Infect Dis.* 2019;68:519-24

Organism	Resistance Present	Ceftazidime/ Avibactam	Meropenem/ Vaborbactam
Enterobacteriaceae			
	ESBL	+++	+++
	AmpC	+++	+++
	KPC	+++	+++
	MBL	–	*
	OXA-48–like	+++	*
Acinetobacter baumannii			
	Carbapenem- resistant	–	–
Pseudomonas aeruginosa			
	Carbapenem-resistant	++	–
	Pan-β-lactam resistant	+	–
Stenotrophomonas maltophilia			
	Ceftazidime-resistant	–	–

- The enhanced in vitro potency of meropenem/vaborbactam ($MIC_{50/90}$ of 0.06/1 compared to 1/4) against KPC producers, as well as data suggesting that emergence of resistance is less likely to occur, makes **meropenem/vaborbactam the preferred agent for treatment of KPC-producing CRE**.

- Due to avibactam's unique inhibitory profile against OXA-48–like enzymes and ceftazidime's stability to hydrolysis by this enzyme, **ceftazidime/avibactam is the preferred agent for treatment of OXA-48–producing CRE**. Furthermore, avibactam's broad inhibitory profile also makes it an ideal agent to combine with aztreonam for the management of MBLs.