Convegno Nazionale
Terapia Antibiotica dei patogeni multiresistenti (MDRO): una sfida aperta

Ferrara, 15 giugno 2018

La farmacologia in aiuto

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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]

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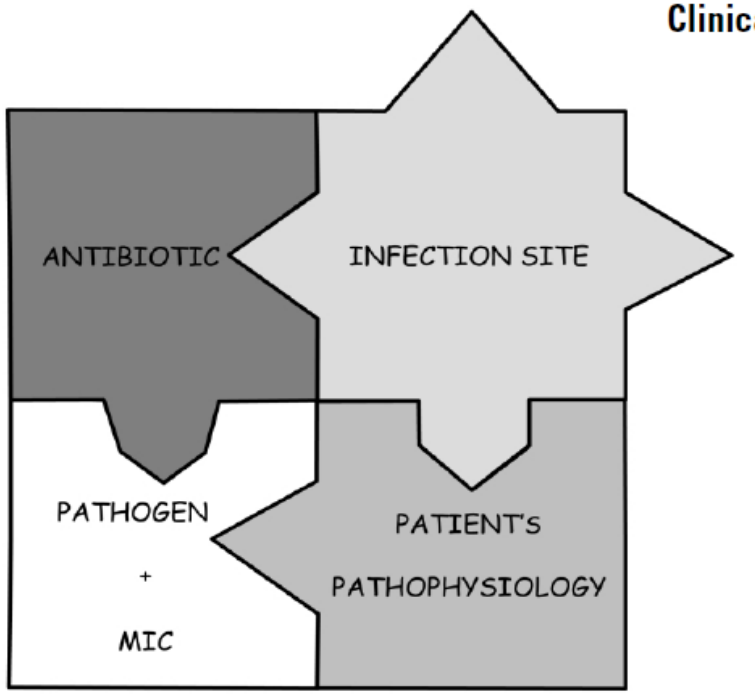
Clinical Infectious Diseases 2006; 42:1764–71



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.

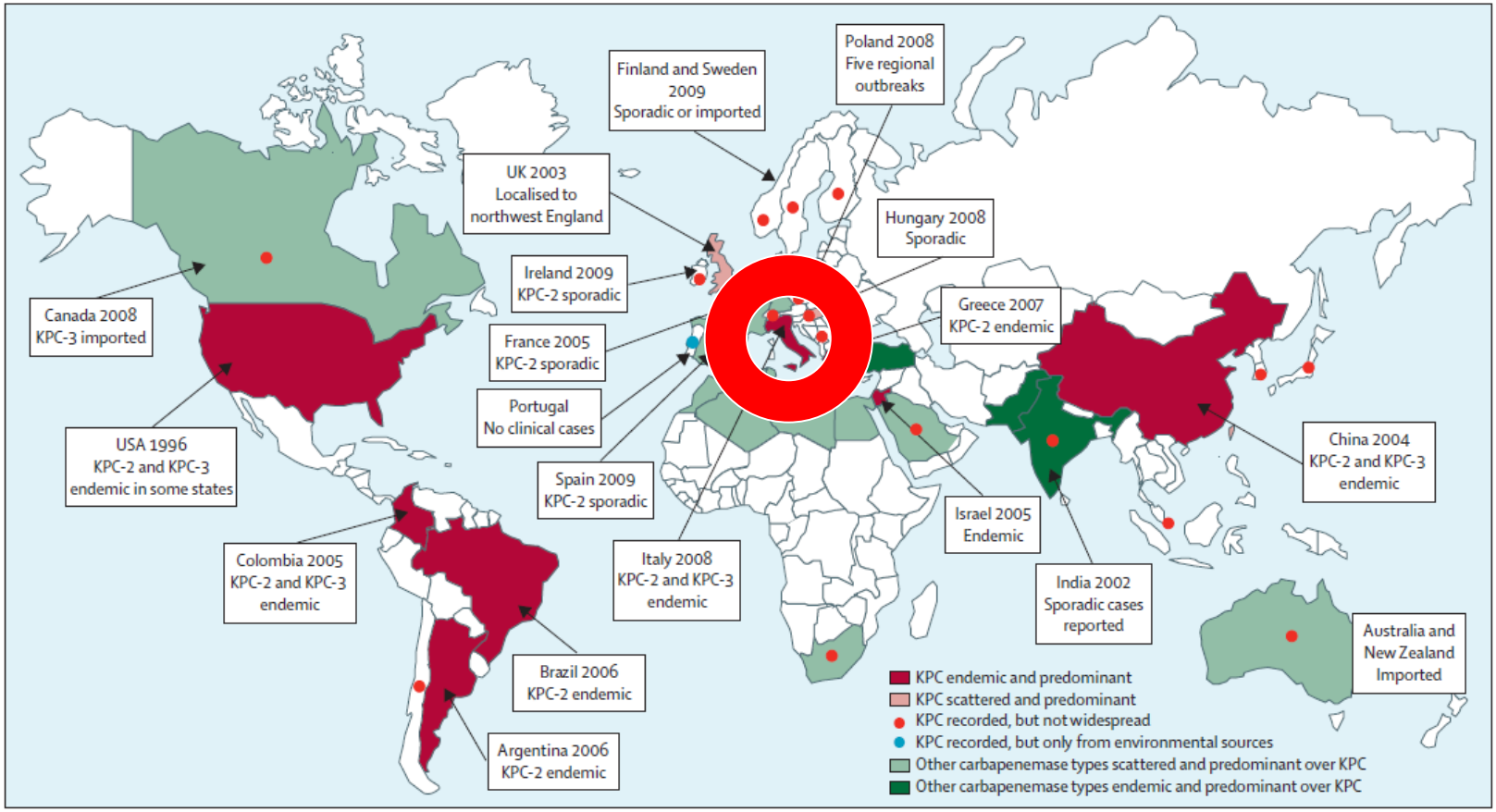
- Yet the global increases in antimicrobial resistance are slowly turning this paradigm. Minimal inhibitory concentrations (MIC)—the lowest levels of drug needed to hinder visible bacterial growth after 16–20 h of incubation—are increasing steadily, particularly for common intensive care unit (ICU) pathogens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

CLINICAL EPIDEMIOLOGY OF THE GLOBAL EXPANSION OF *Klebsiella pneumoniae* CARBAPENEMASES

Munoz Price SL et al. *Lancet Infect Dis* 2013; 13: 785–96

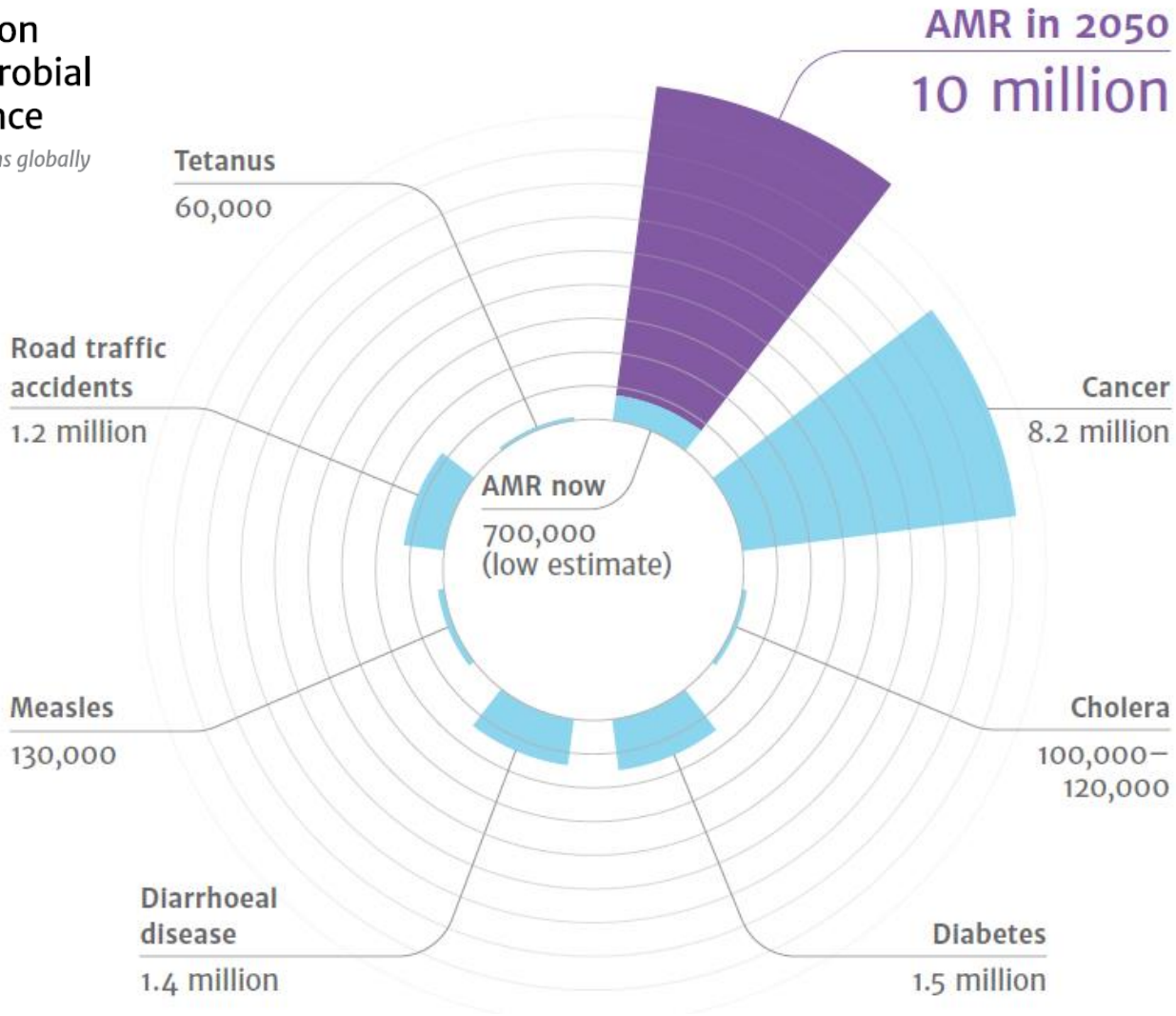
EPIDEMIOLOGICAL FEATURES OF PRODUCERS OF *K. pneumoniae* CARBAPENEMASES BY COUNTRY OF ORIGIN



Deaths attributable to AMR every year

Review on Antimicrobial Resistance

Tackling drug-resistant infections globally



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

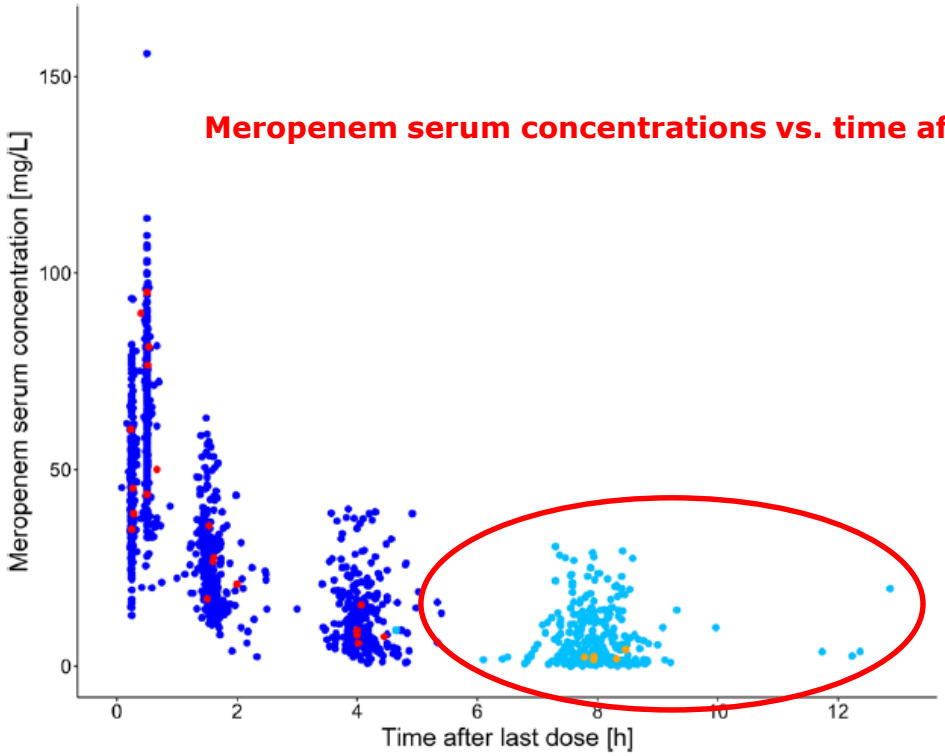
The attainment of two PK/PD targets (100%T>MIC, 50%T>4×MIC) was evaluated for MIC values of 2 mg/L and 8 mg/L and standard meropenem dosing (1000 mg, 30-minute infusion, every 8 h).

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

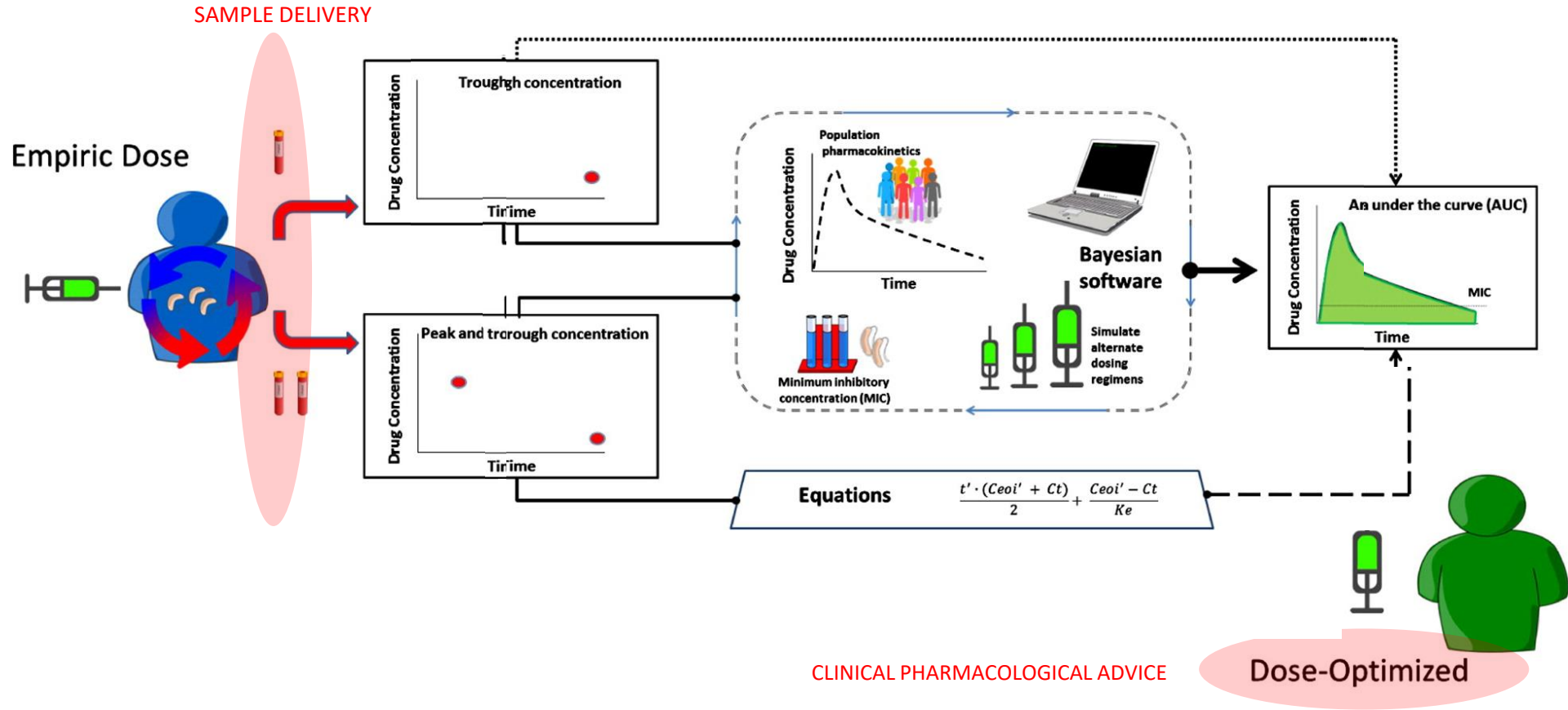
EDITORIAL

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

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

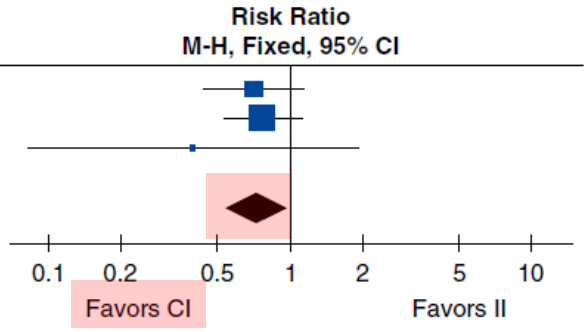
DIFFERENCES IN MORTALITY FOR CONTINUOUS INFUSION (CI) VERSUS INTERMITTENT INFUSION

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)

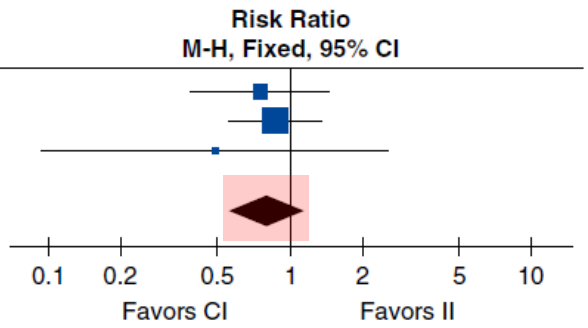


B **INTENSIVE CARE UNIT MORTALITY**

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

Pharmacokinetic/pharmacodynamic analysis of continuous-infusion meropenem (MER) therapy optimised by means of clinical pharmacological advice in patients with KPC-producing *Klebsiella pneumoniae* infections ($n = 30$).

Patient ID	Site of infection	CCI	MER MIC (mg/L)	Daily MER dose (g/daily)	$CL_{Cr,C-G}$ (mL/min)	$C_{ss,mean}$ (mg/L)	$C_{ss,mean}$/MIC ratio	Combination therapy	Length of treatment (days)	Outcome
1	BSI	3	0.5	5.2 ± 1.1	123.0 ± 27.8	15.6	31.2	AMK+CIP	9	Cured
2	Cholangitis	0	1	3.4 ± 1.1	91.2 ± 5.8	21.3	21.3	TIG+COL	21	Cured
3	UTI	0	1	5.2 ± 3.2	79.0 ± 5.5	53.5	53.5	AMK	7	Cured
4	IAI	2	2	4.7 ± 2.3	53.4	28.6	14.3	GEN	8	Cured
5	UTI	2	2	5.0 ± 2.0	77.9 ± 92.1	62.2	31.1	GEN	9	Cured
6	BSI	3	2	3.0 ± 0.8	62.6 ± 22.0	107.2	53.6	TIG+COL	15	Cured
7	BSI	3	4	4.0	122.3	23.3	5.8	TIG+COL	14	Cured
8	BSI	2	4	3.5 ± 0.6	113.8 ± 27.1	32.0	8.0	TIG+GEN	15	Cured
9	Sepsis	5	4	1.8 ± 0.3	46.1 ± 1.0	37.0	9.2	GEN+FOS+COL	20	Cured
10	UTI	0	4	4.5 ± 1.9	58.2 ± 5.8	48.5	12.1	GEN	14	Cured
11	Septic shock	4	4	7.5	33.2	143.0	35.8	TIG+GEN	8	Cured
12	UTI	3	8	4.5	81.2 ± 2.3	33.0	4.1	GEN	7	Cured
13	BSI	2	8	4.8 ± 1.5	80.1 ± 7.6	47.0	5.9	COL	14	Cured
14	Cholecystitis	2	8	3.7 ± 0.5	38.1 ± 9.1	51.0	6.4	TIG+COL	13	Cured
15	BSI	0	32	8.9 ± 1.6	254.7 ± 62.3	46.0	1.4	TIG+ERT+FOS+SXT	69	Cured
16	UTI	1	32	5.3 ± 1.2	54.3 ± 2.5	61.1	1.9	GEN	8	Cured
17	IAI	4	64	4.3 ± 0.5	30.9 ± 6.1	41.6	0.7	TIG+COL+RIF	15	Cured
18	BSI	2	64	2.8 ± 1.0	68.9 ± 4.2	45.3	0.7	TIG+COL	24	Cured
19	BSI	2	64	7.0 ± 1.2	141.2 ± 18.4	59.2	0.9	TIG+COL+RIF	16	Cured
20	BSI	2	64	13.2 ± 1.0	143.4 ± 6.0	85.3	1.3	GEN+ERT+RIF	27	Cured
21	BSI	2	64	11.1 ± 3.6	107.4 ± 29.9	87.4	1.4	TIG+COL+RIF+ERT	22	Cured
22	BSI	2	64	10.6 ± 1.9	127.4 ± 24.0	94.5	1.5	TIG+COL+RIF	16	Cured
23	BSI	5	16	5.0 ± 0.9	44.4 ± 13.1	77.7	4.9	TIG+COL+RIF+AMK	19	Failed
24	BSI	6	32	1.7 ± 0.6	114.8 ± 41.6	18.6	0.6	TIG+COL	6	Failed
25	BSI	2	64	6.4 ± 3.6	91.4 ± 15.3	29.8	0.5	TIG+COL+RIF	14	Failed
26	Pneumonia	5	64	4.8 ± 1.1	86.1 ± 48.7	91.0	1.4	TIG+COL	13	Failed
27	BSI	3	64	5.7 ± 0.8	32.0 ± 8.5	133.7	2.1	TIG+COL+RIF+GEN	21	Failed
28	BSI	2	>64	4.0	85.8	23.2	<0.4	AMK	7	Failed
29	BSI	2	>64	4.0	257.6	24.0	<0.4	TIG+COL+RIF+AMK+FOS	8	Failed
30	BSI	6	>64	6.0	42.2	69.4	<0.5	TIG+COL	6	Failed

73.3 %

BSI, bloodstream infection; UTI, urinary tract infection; IAI, intra-abdominal infection; CCI, Charlson co-morbidity index; MIC, minimum inhibitory concentration; $CL_{Cr,C-G}$, creatinine clearance estimated by means of the Cockcroft–Gault formula; $C_{ss,mean}$, mean steady-state concentration; AMK, amikacin; CIP, ciprofloxacin; TIG, tigecycline; COL, colistin; GEN, gentamicin; FOS, fosfomycin; ERT, ertapenem; SXT, trimethoprim/sulfamethoxazole; RIF, rifampicin.

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

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

KEY POINTS

- Our study seem to suggest that high dose continuous infusion meropenem optimized by means of rapid regimen adjustment **based on real-time TDM may be helpful in improving clinical outcome** when dealing with the treatment of infections caused by KPC-Kp with an MIC for meropenem of ≤ 64 mg/L
- Consistently, **knowledge of local prevalence data of KPC-Kp epidemiology** should be considered **mandatory** nowadays, since the proportion of strains with an MIC > 64 mg/L for meropenem may vary greatly from hospital to hospital. It's worth noting that it was only of 10% in our case-series

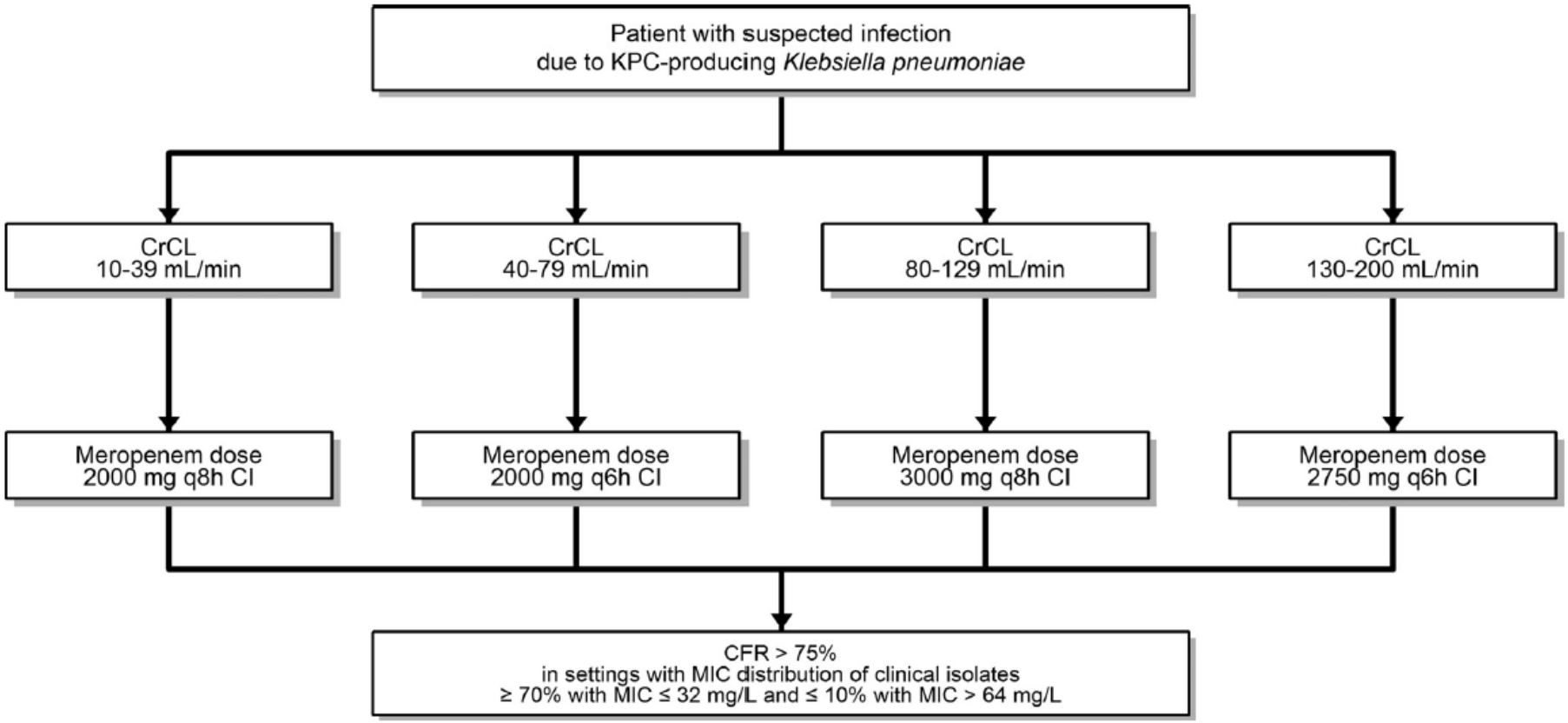
Population Pharmacokinetics of High-Dose Continuous-Infusion Meropenem and Considerations for Use in the Treatment of Infections Due to KPC-Producing *Klebsiella pneumoniae*

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]

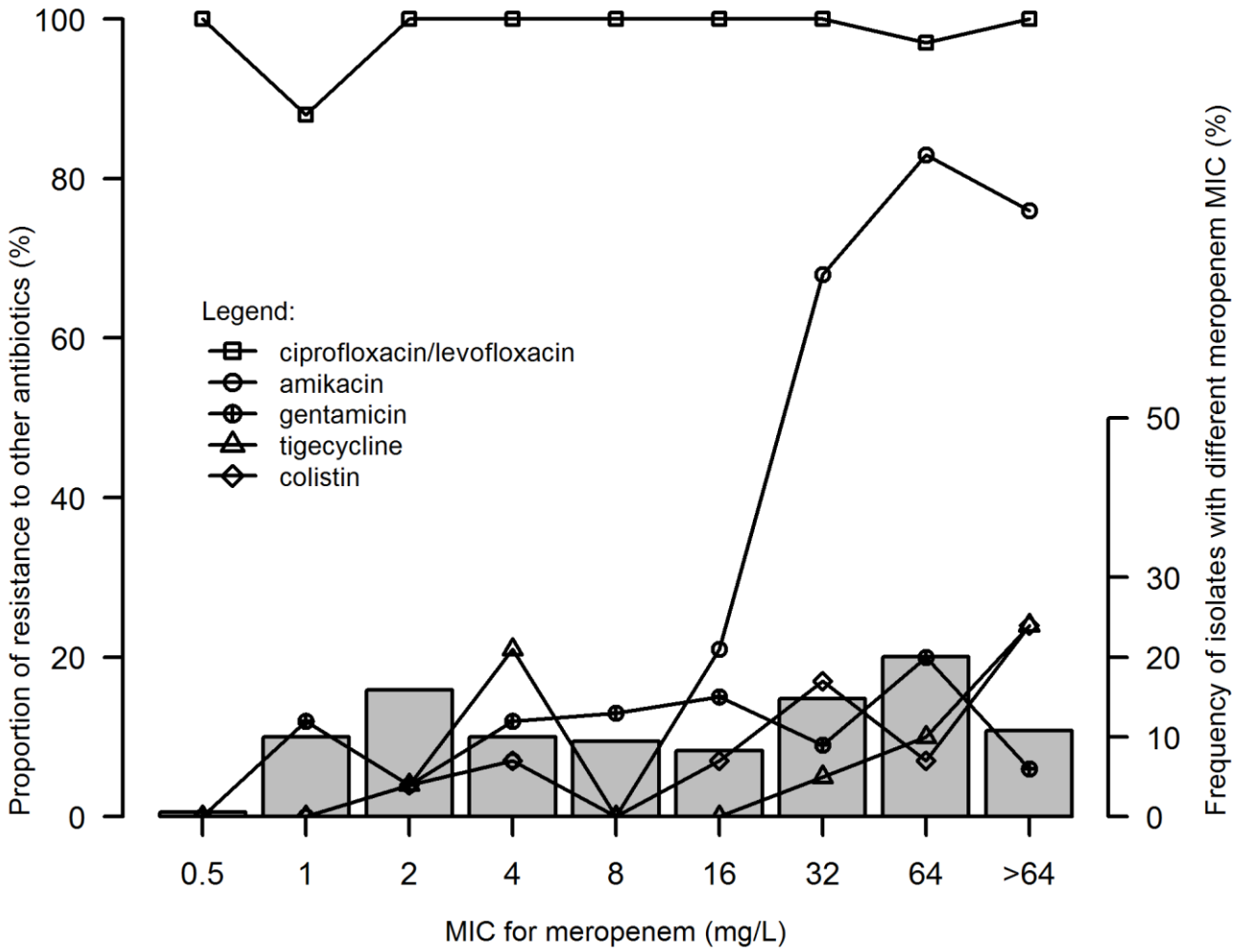
Population Pharmacokinetics of High-Dose Continuous-Infusion Meropenem and Considerations for Use in the Treatment of Infections Due to KPC-Producing *Klebsiella pneumoniae*

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



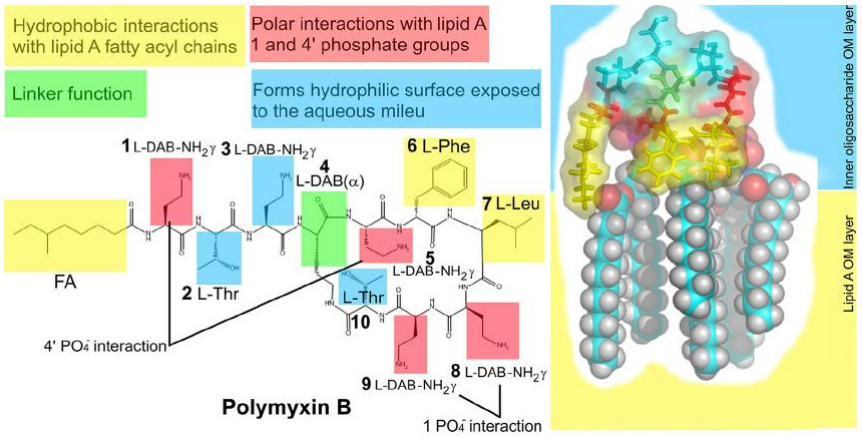
AMINOGLYCOSIDES: HOW SHOULD WE USE THEM IN THE 21ST CENTURY ?

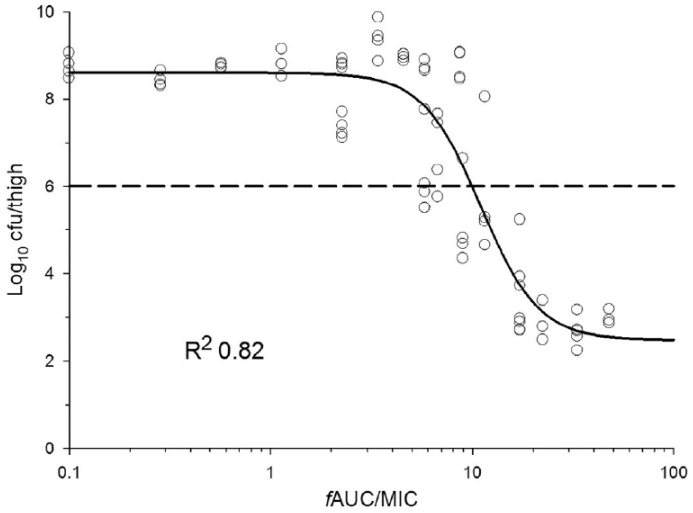
Jackson J et al. *Curr Opin Infect Dis* 2013 Dec; 26(6): 516-25

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

Colistin (Polimyxin E)





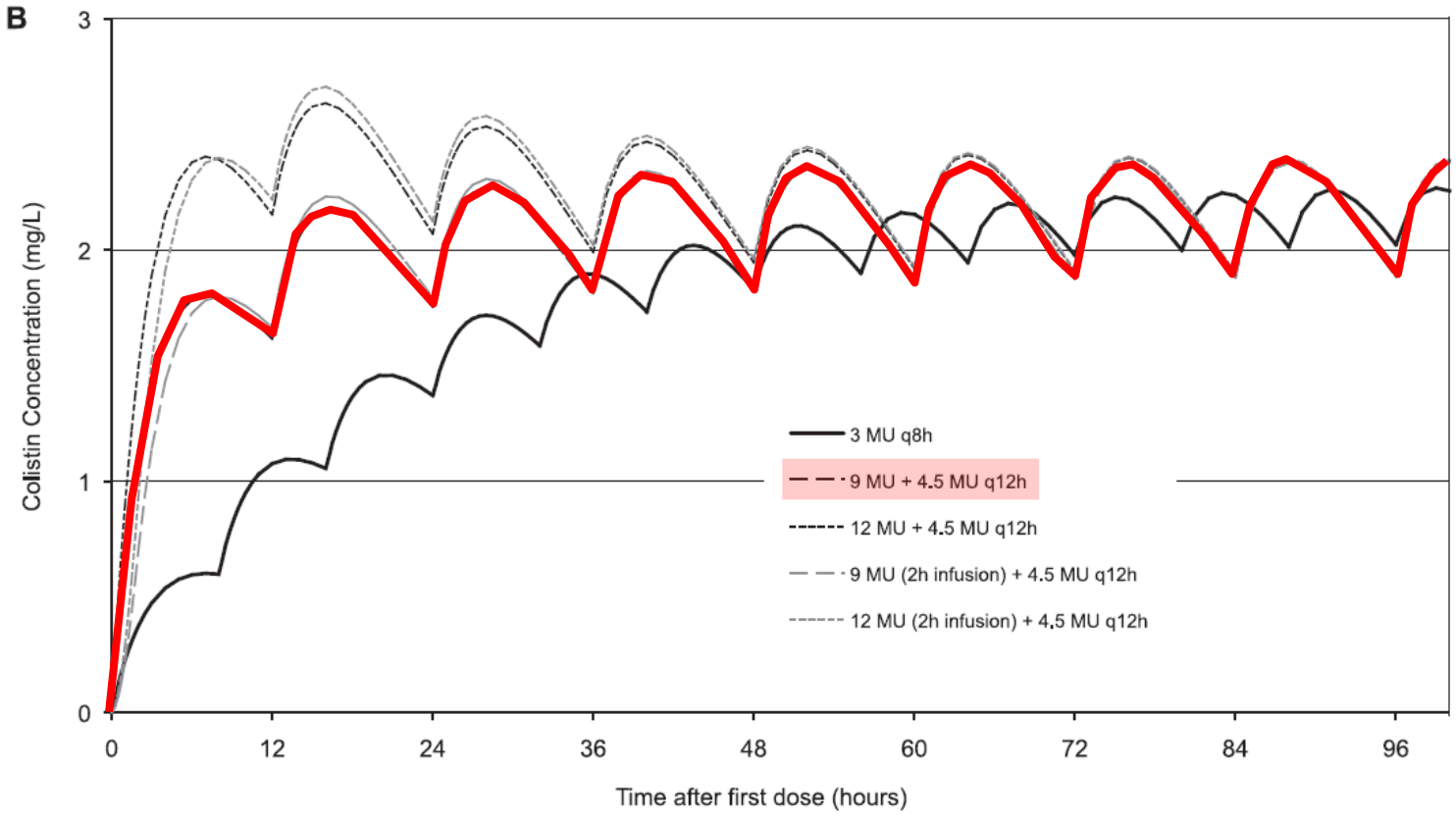
Source	Dosing recommendations for patients with normal renal function	Daily dose for a 70-kg patient with Cl_{cr} of 70 ml/min (expressed in mg CBA)
Colomycin package insert[1]	≤ 60 kg: 50,000 IU/kg/day in 3 divided doses (maximum daily dose 75,000 IU/kg) > 60 kg: 1–2 million IU (MU) 3 times/day (maximum daily dose 6 MU)	90–180 mg/day CBA in 3 divided doses
Coly-Mycin M Parenteral package insert[2]	2.5–5 mg CBA/kg/day in 2–4 divided doses (maximum daily dose 300 mg CBA)	175–350 mg/day CBA in 2–4 divided doses
Plachouras et al[4]	Loading dose: 9–12 million IU Maintenance dose: 4.5 million IU every 12 hrs	270–360 mg CBA loading dose + 135 mg CBA every 12 h
Garonzik et al[5]	Loading dose: colistin $C_{ss,avg}$ target × 2.0 × ideal body weight (kg)[a] (maximum dose 300 mg CBA) Maintenance dose: colistin $C_{ss,avg}$ target × ([1.50 × Cl_{cr}] + 30) in 2–3 divided doses[b]	If $C_{ss,avg}$ = 2.5 μg/ml: 300 mg CBA loading dose + 340 mg/day CBA in 3 divided doses

Cheah SE et al. *J Antimicrob Chemother* 2015;70:3291–7
Velkov T et al. *J Med Chem* 2010;53:1898–916.
Ortwine JK et al. *Pharmacotherapy* 2015;35(1):11–16

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



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 2. Suggested Loading and Daily Doses of Colistimethate for a Desired Target colistin $C_{ss,avg}$ of 2 mg/L in Various Categories of Critically ill Patients

Dose	Category of Critically Ill Patient	Dosing Suggestions[a]
Loading dose	All patient categories	Equation 1: Loading dose of CBA (mg) = $C_{ss,avg}$ target (mg/L) × 2.0 × ideal body weight (kg) To achieve a $C_{ss,avg}$ of 2 mg/L in a patient with an ideal body weight of 75 kg, the loading dose would be 300 mg CBA (9 million IU), the suggested maximum loading dose. The 1st regular daily dose should be administered 12 h later.
Daily dose[b]	Not receiving RRT	Equation 2[c]: Daily dose of CBA (mg) = $C_{ss,avg}$ target (mg/L) × $10^{(0.0048 \times CrCl + 1.825)}$ See Table 3 ("look-up" table) for the daily dose to target a plasma colistin $C_{ss,avg}$ of 2 mg/L, depending on the patient's creatinine clearance.
	Receiving RRT	The baseline daily dose of colistimethate for a $C_{ss,avg}$ of 2 mg/L in a patient with creatinine clearance of 0 mL/min is 130 mg/d of CBA (3.95 million IU/d) (see Table 3)[d]; the supplement to the baseline daily dose needed during receipt of RRT is 10% of the baseline dose per 1 h of RRT.
	Intermittent hemodialysis	Nondialysis day: CBA dose of 130 mg/d (3.95 million IU/d), ie, baseline dosing for a $C_{ss,avg}$ of 2 mg/L; dialysis day supplement: add 30% or 40% to baseline daily dose after a 3- or 4-h session, respectively.[e] The dialysis session should occur toward the end of a colistimethate dosing interval, and the supplement to the baseline (nondialysis) daily dose should be administered with next regular dose, after the dialysis session has ended.
	SLED	During SLED: add 10% per 1 h of SLED replacement to baseline daily dose for a $C_{ss,avg}$ of 2 mg/L[f]; for a patient receiving a 10-h nocturnal SLED session each day and receiving colistimethate every 12 h, the dose would be (baseline CBA dose of 130 mg/d for a patient with creatinine clearance of 0 mL/min + supplemental dose comprising 10% of the baseline dose per h × 10 h); ie, for this case the CBA dose would be 260 mg/d (7.9 million IU/d). It is suggested that the SLED session begin 1–2 h after the afternoon/evening dose; in such a case, it may be most convenient and safe to administer 130 mg CBA (3.95 million IU) every 12 h.
	CRRT	During CRRT: add 10% per 1 h of CRRT to the baseline daily dose for a $C_{ss,avg}$ of 2 mg/L[g]; the suggested CBA dose is 440 mg/d (~13 million IU/d).

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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

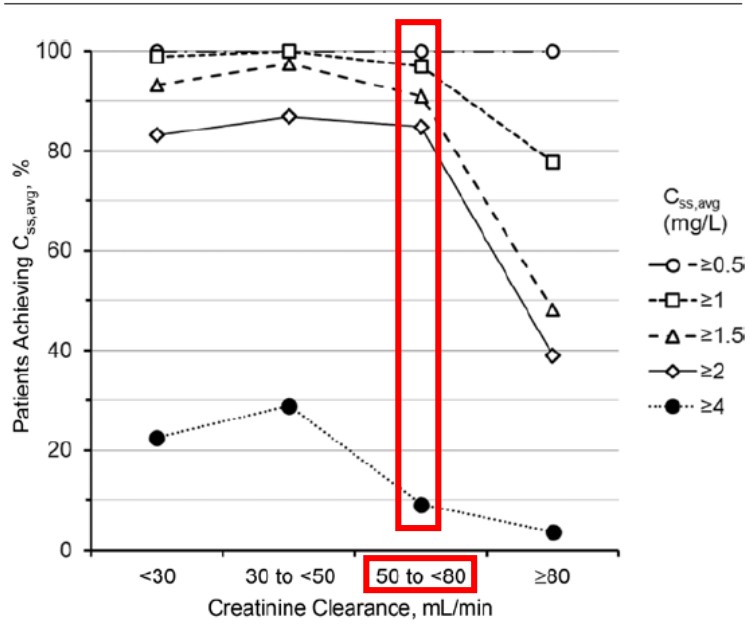


Figure 3. Percentage of patients in each creatinine clearance cluster achieving average steady-state plasma concentrations of colistin ($C_{ss,avg}$) of ≥0.5, ≥1, ≥1.5, ≥2, and ≥4 mg/L using the daily dose of colistimethate in Table 3 relevant to the actual creatinine clearance of each patient.

Daily dose administered in 2 divided doses 12 h apart

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

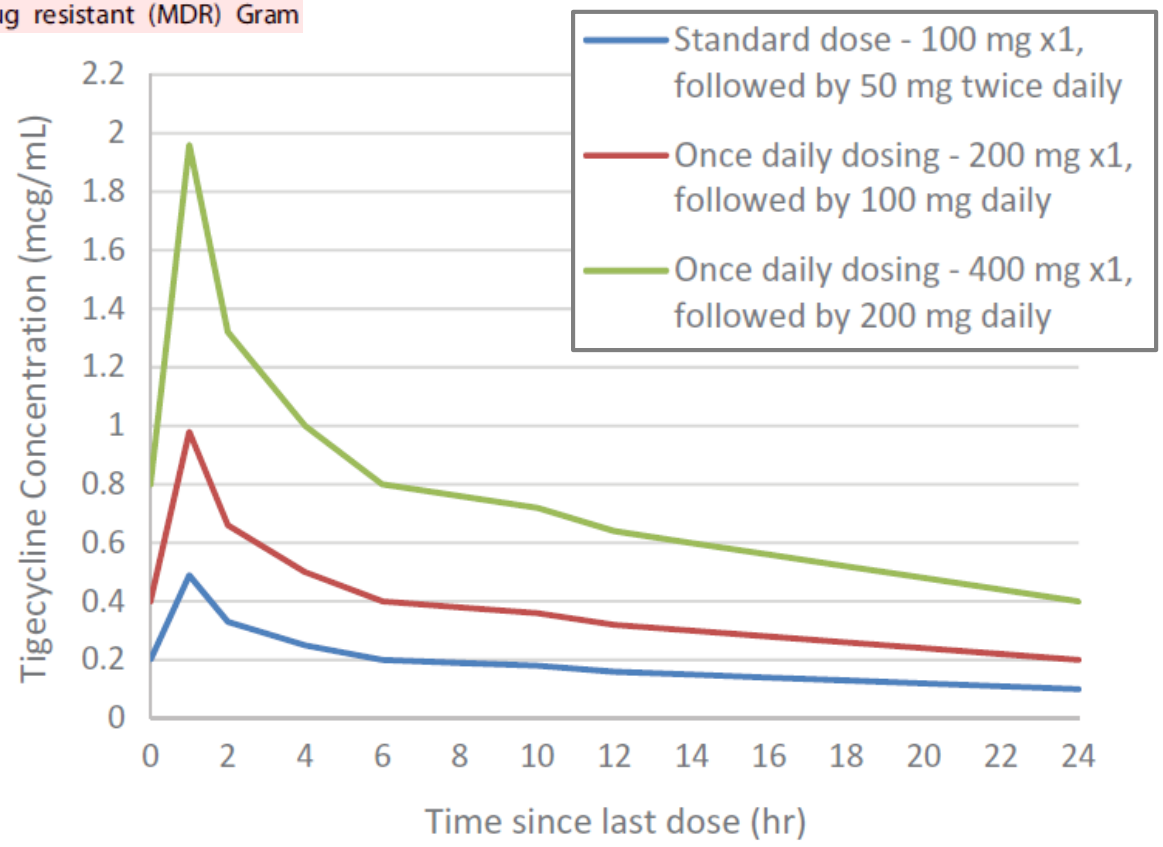
Cunha BA et al. *Expert Rev Anti Infect Ther* 2017;15:257-67

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) includ 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.

Recently approved antibiotics and drugs in development

	Drug name	Drug class	Potential indications
Recently approved	Ceftazidine/ Avibactam	Cephalosporin/ β-Lactamase inhibitor	cIAI, cUTI, HAP/VAP
	Ceftaroline	Extended spectrum cephalosporin	Pneumonia, skin infections
	Solithromycin	Macrolide (fluoroketolide)	CAP
	Tedizolid	Oxazolidinone	HAP/VAP, skin infections
	Ceftolozane/ Tazobactam	Cephalosporin/ β-Lactamase inhibitor	HAP/VAP, cIAI, cUTI
In development	Aztreonam/ Avibactam	Monobactam/ β-Lactamase inhibitor	cIAI
	Cadazolid	Quinolonyl-oxazolidinone	*C. difficile* infection
	Ceftaroline/ Avibactam	Cephalosporin/ β-Lactamase inhibitor	Bacterial infections
	Delafloxacin	Fluoroquinolone	Skin infections, CAP, cUTI
	Eravacycline	Tetracycline	cIAI, cUTI
	Finafloxacin11	Fluoroquinolone	cUTI, cIAI, skin infections
	Iclaprim	Dihydrofolate reductase inhibitor	Skin infections, HAP/VAP
	Imipenem/ Relebactam	Carbapenem/ β-Lactamase inhibitor	cUTI, cIAI, HAP/VAP
	Meropenem/ Vaborbactam	Meropenem/boronic β-Lactamase inhibitor	cUTI, cIAI, HAP/VAP, BSI
	Nemonoxacin8	Quinolone	CAP, skin infections
	Omadacycline	Tetracycline	CAP, skin infections, cUTI
	Plazomicin	Aminoglycoside	cUTI, BSI, HAP/VAP, cIAI
	S-649266	Siderophore cephalosporin	BSI, HAP/VAP, cUTI
	Zabofloxacin	Fluoroquinolone	CAP

cIAI complicated intra-abdominal infection, *cUTI* complicated urinary tract infection, *HAP/VAP* hospital-acquired pneumonia/ventilator-associated pneumonia, *CAP* community-acquired pneumonia, *BSI* bloodstream infection

Kollef MH. et al. *Int Care Med.* 2017 Feb 4. e-pub.

ANTIMICROBIAL SPECTRUM OF NEW ANTIBIOTICS IN DEVELOPMENT

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

CEFTOLOZANE PLASMA PHARMACOKINETIC PARAMETERS IN HEALTHY ADULT PARTICIPANTS AFTER 1000-MG DOSE ADMINISTERED AS A 1-HOUR IV INFUSION EVERY 8 HOURS FOR 10 DAYS

Agent	n	C_{max} (µg/mL)[a]	AUC (µg h/mL)[a]	Clearance (L/h)[a]	V_{ss} (L)[a]	$t_{1/2}$ (hours)[a]
Day 1						
C	6[b]	52.8 ± 12.5	148.6 ± 27[c]	6.73 ± 1.22	17.8 ± 3.8	2.38 ± 0.36
C	5[d]	68.8 ± 11.7	168 ± 28.6[e]	6.01 ± 0.84	14.1 ± 2.6	2.30 ± 0.39
C + T	10[d]	69.1 ± 7.8	172 ± 23.7[e]	5.86 ± 0.80	14.6 ± 2.3	2.77 ± 0.83
Day 10						
C	6[b]	58.0 ± 6.0	143.3 ± 22.1[c]	6.98 ± 1.07	17.1 ± 2.3	2.69 ± 0.65
C	5[d]	73.4 ± 11.2	195 ± 30[e]	5.54 ± 0.74	13.4 ± 2.4	2.73 ± 0.66
C + T	10[d]	74.4 ± 10.1	197 ± 33[e]	5.58 ± 0.70	14.2 ± 2.4	3.12 ± 0.68

Abbreviations: AUC, area under the plasma concentration-time curve; C, ceftolozane; C + T, ceftolozane with 500 mg tazobactam; n, number of participants; C_{max}, maximum plasma concentration; IV, intravenous; $t_{1/2}$, elimination half-life; V_{ss}, volume of distribution at steady state.

[a]Data reported as mean ± SD after first dose (day 1) and after multiple doses (day 10).

[b]Ge et al.[24]

[c]$AUC_{0-\infty}$.

[d]Miller et al.[11]

[e]AUC_{0-last}.

Sucker AJ et al. *Ann Pharmacother.* 2015 Sep;49(9):1046-56

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

ANTIMICROBIAL SPECTRUM OF NEW ANTIBIOTICS IN DEVELOPMENT

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

SUMMARY OF PHARMACOKINETIC PARAMETERS OF CEFTAZIDIME AND AVIBACTAM

Parameter	Ceftazidime, 2 g every 8 h	Avibactam, 500 mg every 8 h
C_{max}, mg/L	90.4	14.6
$t_{1/2}$, h	2.7	2.7
V, L	17	22.2
AUC_{0-tau}, mg·h/L	291	38.2
Protein binding, %	21	8
Elimination (urine), %	83	>97

C_{max}, peak serum concentration; $t_{1/2}$, half-life; *V*, volume of distribution; AUC_{0-tau}, area under the curve over the dosing interval.

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

RECOMMENDED DOSES 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