LA COMPLESSITÀ IN MALATTIE INFETTIVE:
NUOVI PARADIGMI GESTIONALI. PARTE SECONDA

L'ARMAMENTARIO TERAPEUTICO ANTI GRAM NEGATIVI DOMANI

FEDERICO PEA

DIPARTIMENTO AREA MEDICA, UNIVERSITA' DEGLI STUDI DI UDINE

ISTITUTO DI FARMACOLOGIA CLINICA, PRESIDIO OSPEDALIERO UNIVERSITARIO SM MISERICORDIA UDINE

Bologna, 17 Settembre 2019

DEFINING ADEQUATE ANTIMICROBIAL THERAPY IN SEVERE INFECTIONS

- For antimicrobial therapy to be adequate, three requirements need to be fulfilled.
- First, the antimicrobial agent(s) should be initiated as soon as possible after the onset of sepsis.
- Second, as therapy is to be initiated empirically, the antimicrobial spectrum of the agent should be broad enough to cover the potential causative microorganisms.
- Finally, appropriate antimicrobial dosing is required to:
  - maximize microbial killing,
  - minimize the development of multidrug antimicrobial resistance,
  - and avoid concentration-related adverse drug reactions.

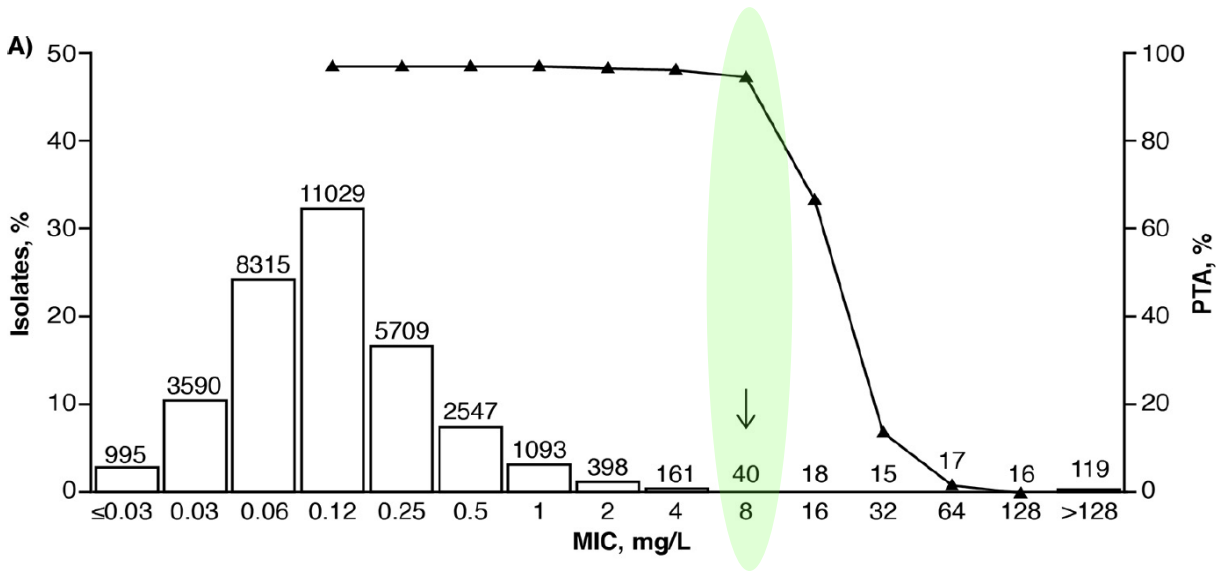
Blot S, Pea F, Lipman J. *Adv Drug Deliv Rev* 2014; 77: 3-11

DOSE SELECTION AND VALIDATION FOR CEFTAZIDIME-AVIBACTAM IN ADULTS WITH cIAIs, cUTIs, AND NP

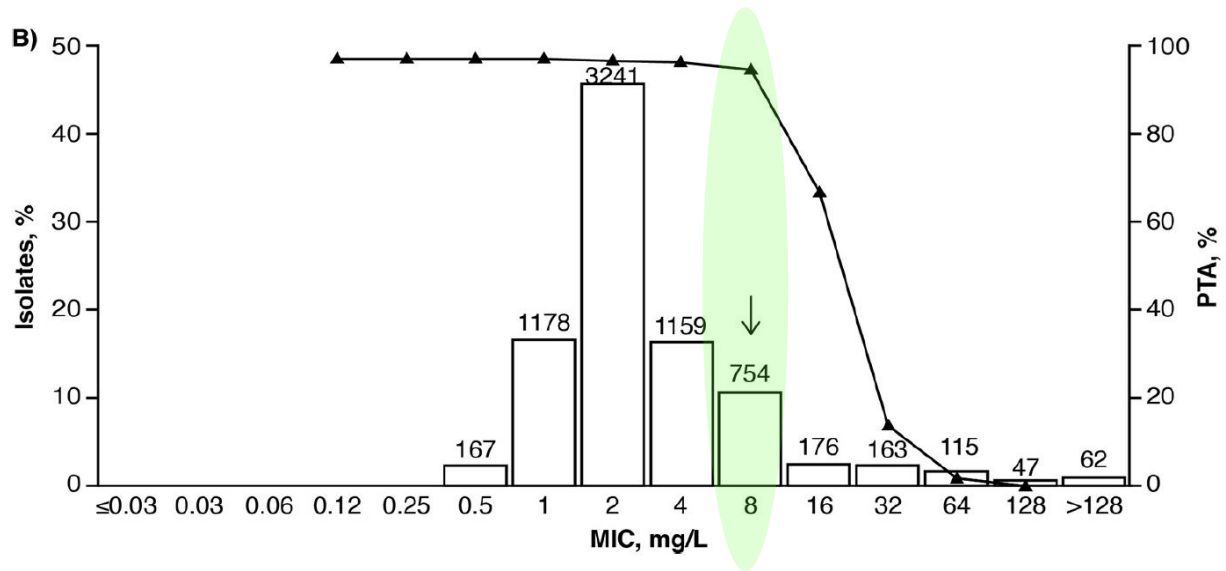
Das S et al. *Antimicrob Agents Chemother* 2019 Mar 27; 63(4). pii: e02187-18

JOINT PTA FOR PATIENTS WITH cIAI RECEIVING CEFTAZIDIME-AVIBACTAM 2000/500 MG Q8H
PLOTTED AS A FUNCTION OF CEFTAZIDIME-AVIBACTAM MIC OVERLAYING THE CEFTAZIDIME-AVIBACTAM MIC DISTRIBUTIONS FROM THE INFORM GLOBAL SURVEILLANCE STUDY (2012 TO 2014)

AGAINST Enterobacteriaceae (N = 34062)



AGAINST *P. aeruginosa* (N = 7062)



PTA = Probability of Target Attainment

PHASE 1 STUDY ASSESSING THE STEADY-STATE CONCENTRATION OF CEFTAZIDIME AND AVIBACTAM IN PLASMA AND ELF FOLLOWING TWO DOSING REGIMENS

Nicolau DP et al. *J Antimicrob Chemother* 2015; 70: 2862–2869

SUMMARY OF KEY PK PARAMETERS OF CEFTAZIDIME AND AVIBACTAM

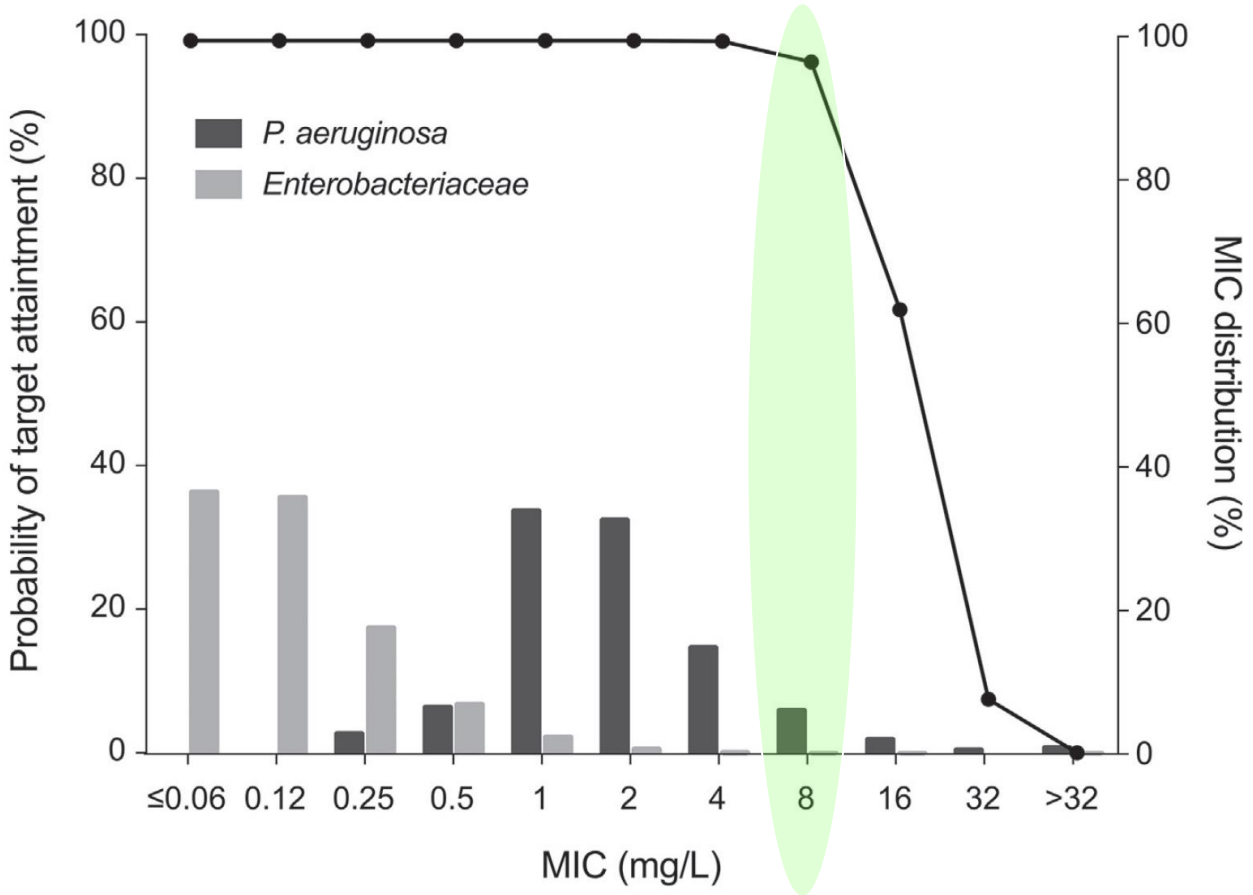
	AVI		CAZ	
Parameter, cohort	plasma	ELF, composite profile[a]	plasma	ELF, composite profile[a]
Geometric mean (CV, %) C_{max} (mg/L) 2000 mg of CAZ + 500 mg of AVI (n=22)	14.5 (9.7)	5.1	90.1 (13.3)	23.2
Geometric mean (CV, %) AUC_{τ} (mg·h/L) 2000 mg of CAZ + 500 mg of AVI (n=22)	39.2 (9.7)	13.7	295 (13.0)	92.3
Median (range) T_{max} (h) 2000 mg of CAZ + 500 mg of AVI (n=22)	2.00 (1.97–2.02)	2.0	2.00 (1.97–2.02)	2.0
Mean (SD) $t_{1/2}$ (h) 2000 mg of CAZ + 500 mg of AVI (n=22)	3.29 (0.82)	1.94	2.86 (0.294)	3.77

- **Ceftazidime C_{max} and AUC_t in ELF were ~ 23%–26% and 31%–32% of plasma exposure**
- **Avibactam C_{max} and AUC_t in ELF were ~ 28%–35% and 32%–35% of plasma exposure**

OPTIMIZING ANTIBIOTIC ADMINISTRATION FOR PNEUMONIA

Dimelow R et al Clin Chest Med 2018; 39: 837–852

DISTRIBUTION OF *P aeruginosa* AND Enterobacteriaceae ISOLATES FROM HABP PATIENTS IN US MEDICAL CENTERS (2011–2015) IN TERMS OF CEFTAZIDIME/AVIBACTAM MIC LEVEL AND THE PTA OF FT > MIC FOR CEFTAZIDIME/AVIBACTAM, USING 2.5 G EVERY 8 HOURS AS A 2-HOUR INFUSION



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Das S et al. *Antimicrob Agents Chemother* 2019 Mar 27; 63(4). pii: e02187-18

CEFTAZIDIME-AVIBACTAM DOSAGE ADJUSTMENTS FOR RENAL IMPAIRMENT EMPLOYED IN THE PHASE 3 TRIALS AND APPROVED MODIFICATIONS TO ORIGINAL DOSAGE ADJUSTMENTS BY RENAL FUNCTION CATEGORY

Renal function category	Original ceftazidime-avibactam dosage regimen included in protocol for phase 3 trials[b]	Modified dosage regimen[c]	Joint PTA for a target MIC of 8 mg/liter in patients with cIAI receiving approved modified dosage adjustments (%)[d]
Normal CL_{CR} >80 ml/min	2,000 + 500 mg q8h	NA	94.9
Mild renal impairment CL_{CR} 51–80 ml/min	2,000 + 500 mg q8h	NA	99.0
Moderate renal impairment CL_{CR} 31–50 ml/min	1,000 + 250 mg q12h	1,000 + 250 mg q8h	99.3
Severe renal impairment (upper range of CL_{CR}) CL_{CR} 16–30 ml/min	1,000 + 250 mg q24h	750 + 187.5 mg q12h	99.0
Severe renal impairment (lower range of CL_{CR}) CL_{CR} 6–15 ml/min	500 + 125 mg q24h	750 + 187.5 mg q24h	99.3
End-stage renal disease CL_{CR} <6 ml/min	500 + 125 mg q48h	750 + 187.5 mg q48h	99.6

PTA = Probability of Target Attainment

RECOMMENDED DOSES FOR PATIENTS WITH VARYING DEGREES OF RENAL IMPAIRMENT

Creatinine clearance, ml/min	Dosage recommendation
31–50	Ceftazidime 1 g–avibactam 0.25 g every 8 hrs over 2 h
16–30	Ceftazidime 0.75 g–avibactam 0.19 g every 12 hrs
6–15	Ceftazidime 0.75 g–avibactam 0.19 g every 24 hrs
≤ 5	Ceftazidime 0.75 g–avibactam 0.19 g every 48 hrs

Zasowski EJ et al. *Pharmacotherapy* 2015; 35(8): 755–770

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Antimicrob Agents Chemother. 2018 Apr 26;62(5). pii: e02497-17. doi: 10.1128/AAC.02497-17. Print 2018 May.

Pneumonia and Renal Replacement Therapy Are Risk Factors for Ceftazidime-Avibactam Treatment Failures and Resistance among Patients with Carbapenem-Resistant Enterobacteriaceae Infections.

Shields RK[1,2], Nguyen MH[3,2], Chen L[4], Press EG[1], Kreiswirth BN[4], Clancy CJ[1,2,5].

Author information

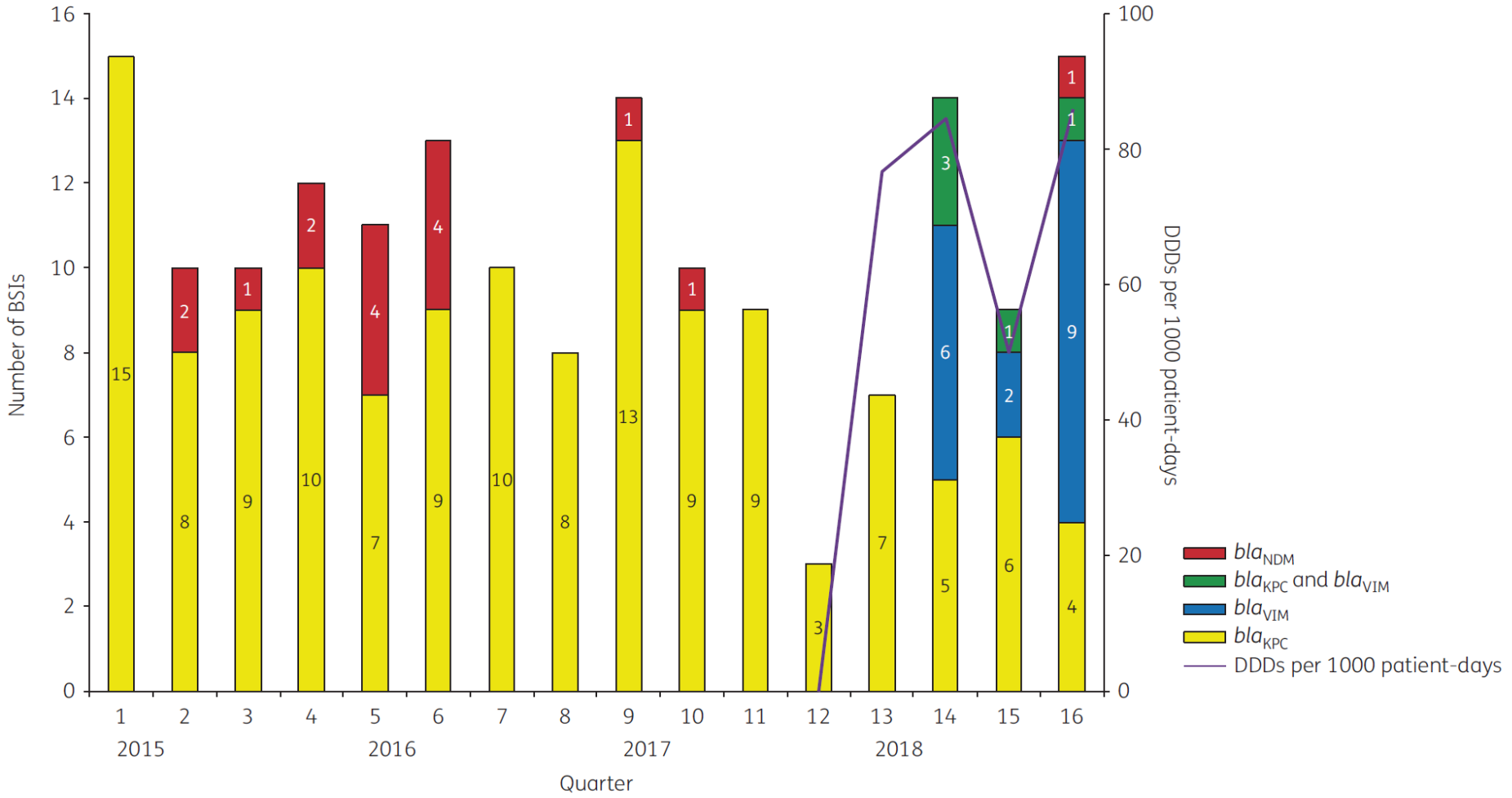
Abstract

Ceftazidime-avibactam was used to treat 77 patients with carbapenem-resistant *Enterobacteriaceae* (CRE) infections at our center. Thirty- and 90-day survival rates were 81% and 69%, respectively; these rates were higher than those predicted by SAPS II and SOFA scores at the onset of infection. Clinical success was achieved for 55% of patients but differed by the site of infection. Success rates were lowest for pneumonia (36%) and higher for bacteremia (75%) and urinary tract infections (88%). By multivariate analysis, pneumonia ($P = 0.045$) and receipt of renal replacement therapy (RRT) ($P = 0.046$) were associated with clinical failure. Microbiologic failures occurred in 32% of patients and occurred more commonly among patients infected with KPC-3-producing CRE than among those infected with KPC-2-producing CRE ($P = 0.002$). Pneumonia was an independent predictor of microbiologic failure ($P = 0.007$). Ceftazidime-avibactam resistance emerged in 10% of patients, including 14% of those infected with *Klebsiella pneumoniae* and 32% of those with microbiologic failure. RRT was an independent predictor of the development of resistance ($P = 0.009$). Resistance was identified exclusively among *K. pneumoniae* bacteria harboring variant KPC-3 enzymes. Upon phylogenetic analysis of whole-genome sequences, resistant isolates from 87.5% (7/8) of patients clustered within a previously defined sequence type 258 (ST258) clade II sublineage; resistant isolates from one patient clustered independently from other ST258 clade II isolates. In conclusion, our report offers new insights into the utility and limitations of ceftazidime-avibactam across CRE infection types. Immediate priorities are to identify ceftazidime-avibactam dosing and therapeutic regimens that improve on the poor outcomes among patients with pneumonia and those receiving RRT.

REVERSAL OF CARBAPENEMASE-PRODUCING *K. pneumoniae* EPIDEMIOLOGY FROM bla_{KPC}- TO bla_{VIM}-HARBOURING ISOLATES IN A GREEK ICU AFTER INTRODUCTION OF CEFTAZIDIME/AVIBACTAM

Papadimitriou-Olivgeris M et al. *J Antimicrob Chemother* 2019 Jul; 74: 2051-2054

QUARTERLY DISTRIBUTION OF CARBAPENEMASE GENES AMONG CP-KP BSIs AND CEFTAZIDIME/AVIBACTAM CONSUMPTION (DDDS PER 1000 PATIENT-DAYS)



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Papadimitriou-Olivgeris M et al. *J Antimicrob Chemother* 2019 Jul; 74: 2051-2054

UNIVARIATE ANALYSIS OF RISK FACTORS FOR CEFTAZIDIME/AVIBACTAM RESISTANT BSI

Characteristic	CZA-S BSI (*n* = 18)	CZA-R BSI (*n* = 27)	*P*
Days at risk[a]	45.8 ± 64.6	53.5 ± 70.7	0.372
Demographics			
age (years)	60.2 ± 15.5	50.4 ± 14.6	0.041
male gender	14 (77.8)	21 (77.8)	1.000
Chronic diseases			
diabetes mellitus	2 (11.1)	2 (11.1)	1.000
COPD	0 (0.0)	4 (14.8)	0.138
chronic heart failure	0 (0.0)	1 (3.7)	1.000
chronic renal failure	0 (0.0)	3 (11.1)	0.264
malignancy	1 (5.6)	1 (3.7)	1.000
immunosuppression	0 (0.0)	1 (3.7)	1.000
obesity (BMI ≥30 kg/m^2)	7 (38.9)	8 (29.6)	0.538
Charlson Comorbidity Index	2.6 ± 1.8	2.6 ± 3.3	0.368
Admission data			
APACHE II score upon admission	19.3 ± 5.3	16.2 ± 5.4	0.128
prior surgery	6 (33.3)	8 (29.6)	1.000

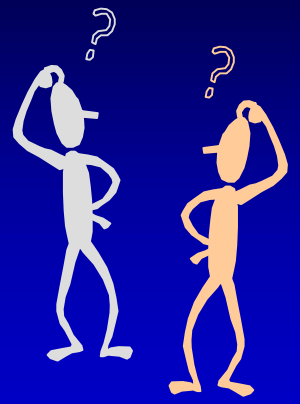
Characteristic	CZA-S BSI (*n* = 18)	CZA-R BSI (*n* = 27)	*P*
Prior antibiotic administration[b]			
penicillin/β-lactamase inhibitors	11 (61.1)	24 (88.9)	0.064
third- and fourth-generation cephalosporins	4 (22.2)	13 (48.1)	0.118
ceftazidime/avibactam	1 (5.6)	13 (48.1)	0.003
carbapenems	13 (72.2)	19 (70.4)	1.000
quinolones	3 (16.7)	10 (37.0)	0.188
colistin	12 (66.7)	20 (74.1)	0.739
aminoglycosides	6 (33.3)	5 (18.5)	0.304
fosfomycin	2 (11.1)	2 (7.4)	1.000
tigecycline	11 (61.1)	17 (63.0)	1.000
glycopeptides	15 (83.3)	20 (74.1)	0.716
linezolid	10 (55.6)	20 (74.1)	0.218
daptomycin	4 (22.2)	10 (37.0)	0.343
number of antibiotics administered	5.3 ± 2.9	6.6 ± 2.8	0.136
antifungal administration	11 (61.1)	21 (77.8)	0.317

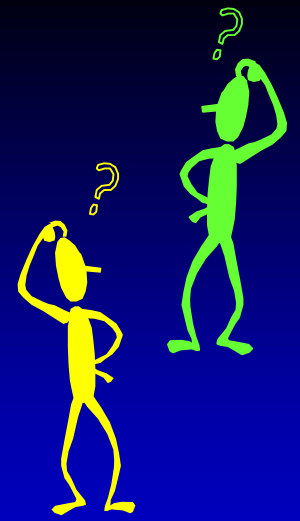
Characteristic	CZA-S BSI (*n* = 18)	CZA-R BSI (*n* = 27)	*P*
ICU procedures			
corticosteroid administration	12 (66.7)	17 (63.0)	1.000
parenteral nutrition	10 (55.6)	12 (44.4)	0.550
enteral nutrition	12 (66.7)	22 (81.5)	0.304
Microbiological data			
resistance of bacteraemic isolate			
meropenem	18 (100)	27 (100)	–
colistin	12 (66.7)	8 (29.6)	0.031
tigecycline	4 (22.2)	9 (33.3)	0.514
gentamicin	18 (100)	25 (92.6)	0.509
fosfomycin	8 (44.4)	11 (40.7)	1.000
primary bacteraemia	7 (38.9)	16 (59.3)	0.231

Data are *n* (%) of patients or mean ± SD.

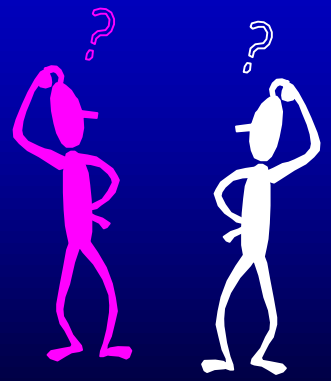
a Length of stay until BSI development.

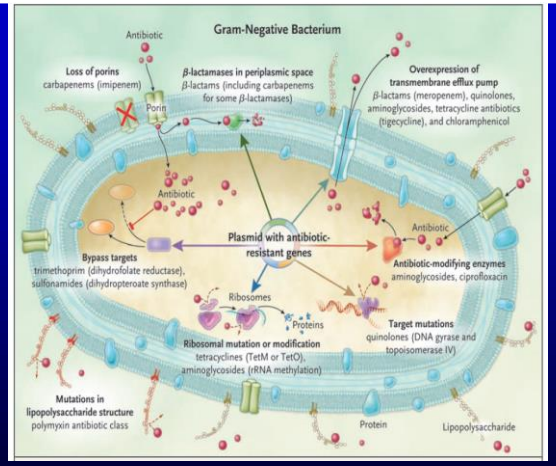
b Administration on the last 30 days prior to BSI onset.

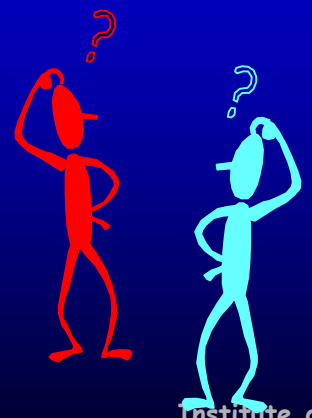




HOW TO MINIMIZE THE EMERGENCE OF RESISTANCE ?







DETERMINING B-LACTAM EXPOSURE THRESHOLD TO SUPPRESS RESISTANCE DEVELOPMENT IN GRAM-NEGATIVE BACTERIA

Tam V et al. *J Antimicrob Chemother* 2017; 72: 1421–1428

STUDY DESIGN

- Two strains of *Klebsiella pneumoniae* and two strains of *Pseudomonas aeruginosa* were examined
- Various dosing exposures of cefepime, ceftazidime and meropenem were simulated in the hollow-fibre infection model
- Serial samples were obtained to ascertain the pharmacokinetic simulations and viable bacterial burden for up to 120 h
- Resistance development was detected by quantitative culture on drug-supplemented media plates
- The Cmin/MIC breakpoint threshold to prevent bacterial regrowth was identified by classification and regression tree (CART) analysis

DETERMINING B-LACTAM EXPOSURE THRESHOLD TO SUPPRESS RESISTANCE DEVELOPMENT IN GRAM-NEGATIVE BACTERIA

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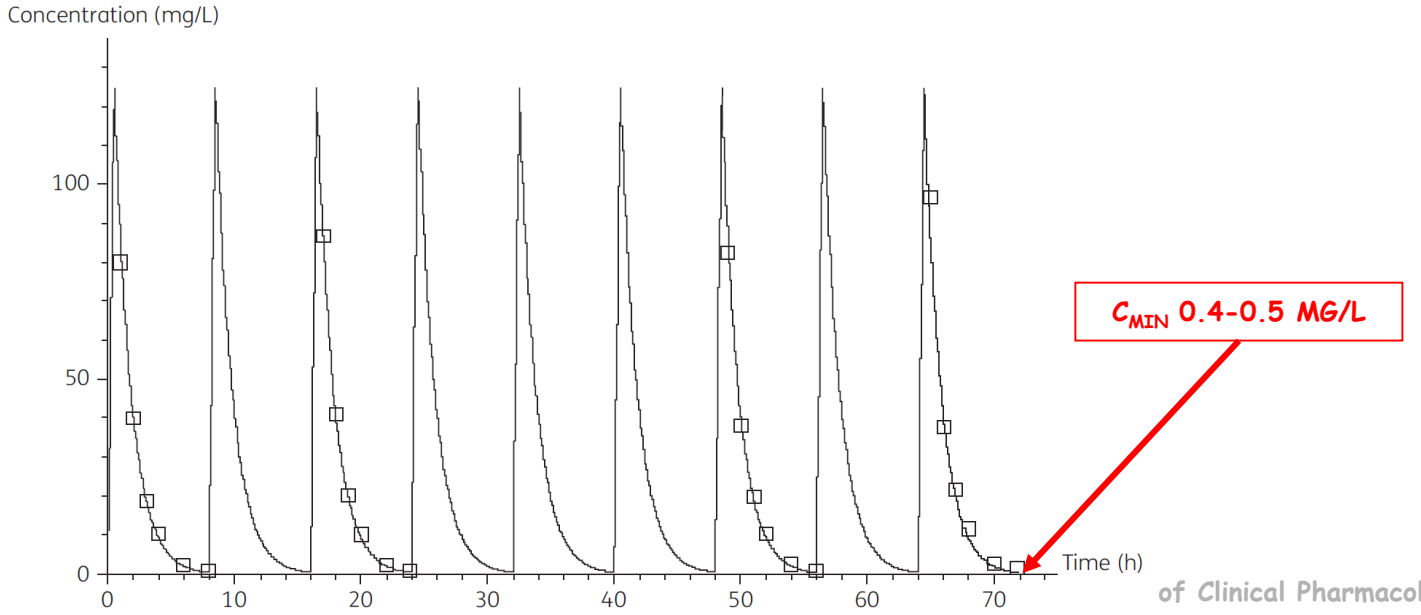
SUSCEPTIBILITY AND RESISTANCE MECHANISMS OF THE CLINICAL STRAINS USED

Bacteria	Cefepime	Ceftazidime	Meropenem	MLST (ST)	Resistance mechanism
K. pneumoniae (Kp1)	0.25	0.5	0.06	ST678	WT
K. pneumoniae (Kp2)	**16**	**64**	0.06	ST16	CTX-M-15
P. aeruginosa (Pa1)	0.5	1	0.13	ST319	WT
P. aeruginosa (Pa2)	**16**	**64**	0.25	ST175	AmpC overexpression

Bold font indicates resistant phenotype according to EUCAST breakpoints.

TYPICAL SIMULATED PHARMACOKINETIC PROFILE OF 2 G MEROPENEM Q8H OVER 30 MIN



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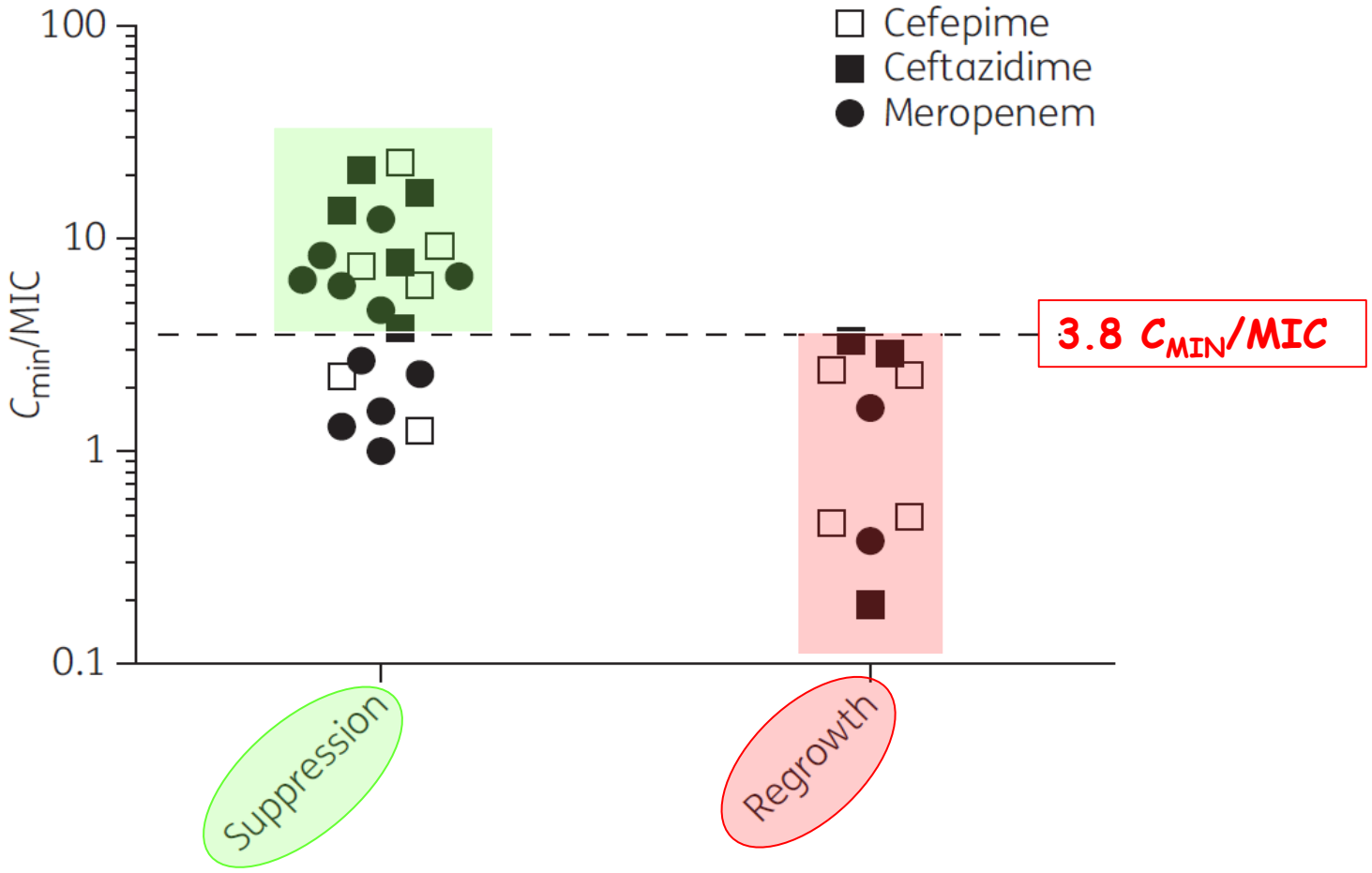
DRUG EXPOSURES (C_{MIN}/MIC) STRATIFIED BY OUTCOMES



COLISTIN DOES NOT POTENTIATE CEFTAZIDIME-AVIBACTAM KILLING OF CRE *in vitro* OR SUPPRESS EMERGENCE OF CEFTAZIDIME-AVIBACTAM RESISTANCE

Shields RK et al. *Antimicrob Agents Chemother* 2018 Jul 27;62(8). pii: e01018-18

MOLECULAR CHARACTERISTICS, DRUG MICS, AND TIME-KILL RESULTS OF 24 CRE ISOLATES

Isolate	bla_{KPC} WT or variant (*ompK36* genotype)[a]	MIC (μg/ml)[b]	
		C-A	COL
Kp-347	KPC-2 (WT)	0.5	0.25
Kp-142	KPC-2 (WT)	0.5	0.25
Kp-465	KPC-2 (WT)	1	0.5
Kp-669	KPC-2 (AA134-135)	0.5	0.25
Kp-115	KPC-2 (AA134-135)	1	0.125
Kp-436	KPC-2 (AA134-135)	1	0.25
Kp-155	KPC-2 (AA134-135)	2	0.25
Kp-873	KPC-2 (IS*5*)	1	0.25
Kp-937	KPC-2 (IS*5*)	2	0.25
Kp-306	KPC-3 (WT)	0.5	0.5
Kp-779	KPC-3 (WT)	1	0.25
Kp-929	KPC-3 (WT)	1	0.125
Kp-928	KPC-3 (WT)	2	0.5
Kp-930	KPC-3 (WT)	4	0.06
Kp-913	KPC-3 (IS*5*)	0.5	0.25
Kp-380	No KPC (IS*5*)	4	0.5
En-102	KPC-2	0.5	0.06
En-24	KPC-2	1	0.06
En-150	KPC-3	2	0.125
En-6	KPC-3	4	0.125
Ec-13	No KPC	0.25	0.125
Ec-42	KPC-2	1	0.06
Kl-1173	KPC-3	4	0.06
Ct-83	KPC-3	8	0.06

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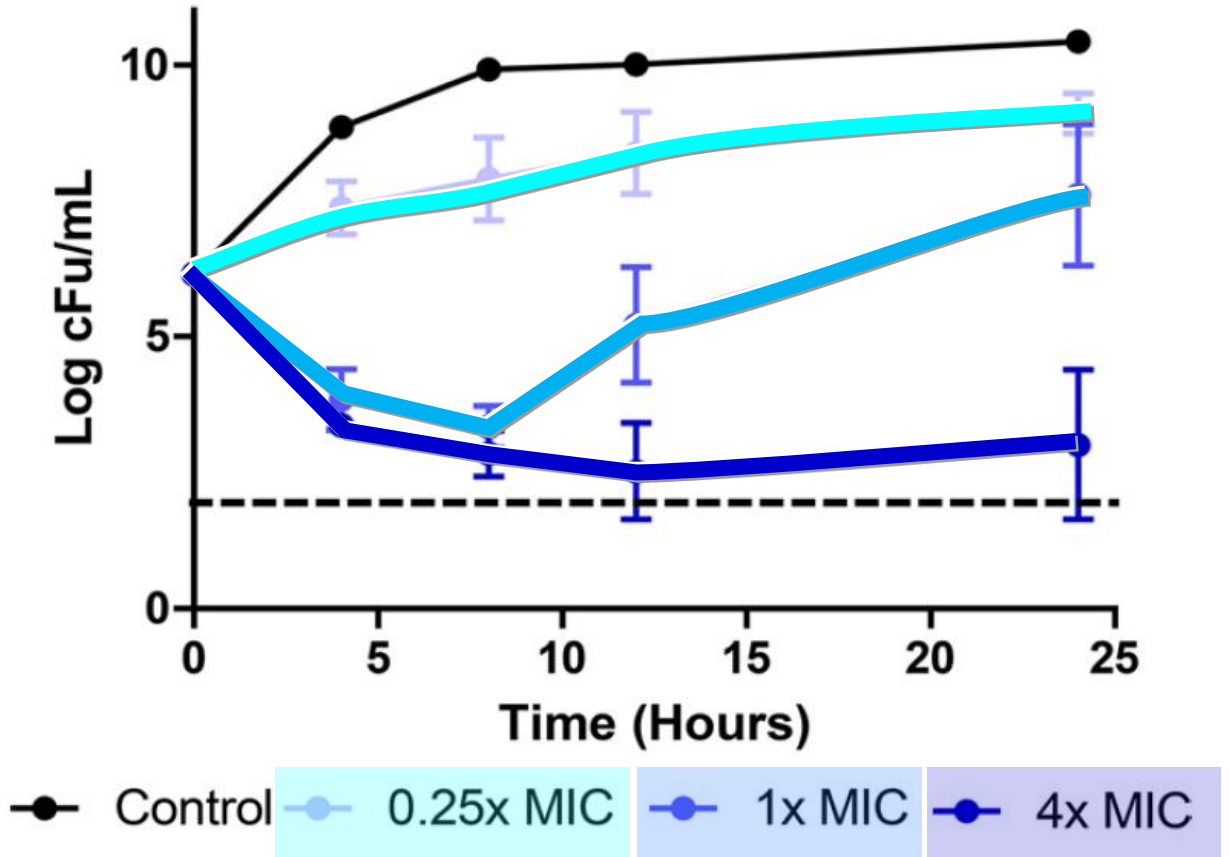
MEAN LOG KILLS OF ALL 24 CRE ISOLATES AT CEFTAZIDIME-AVIBACTAM CONCENTRATIONS RANGING FROM 0.25 TO 4 x MIC. AVIBACTAM WAS FIXED AT 4 µG/ML IN ALL EXPERIMENTS



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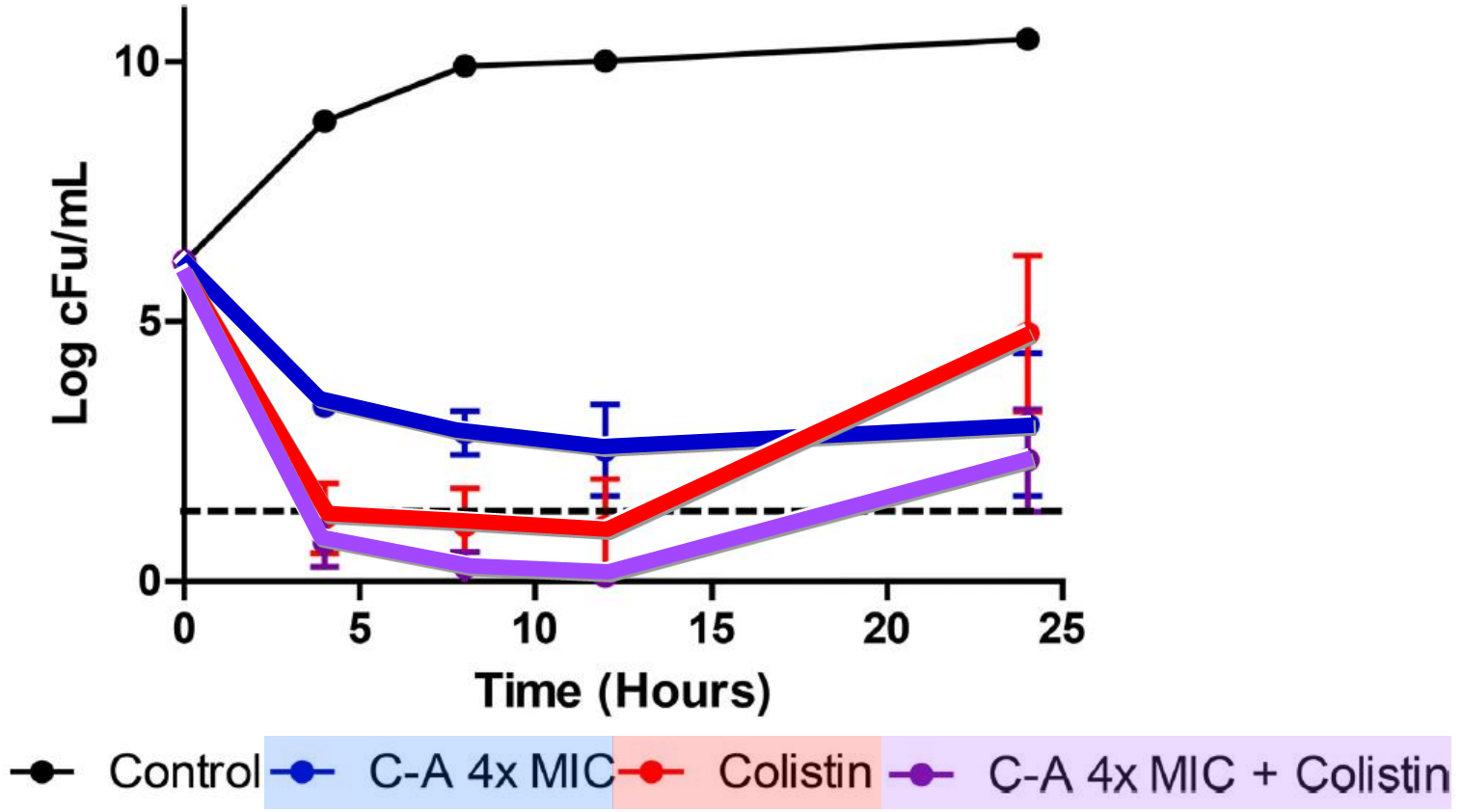
MEAN LOG KILLS OF ALL 24 CRE ISOLATES BY CEFTAZIDIME-AVIBACTAM (C-A, 4xMIC), 2 µG/ML COLISTIN ALONE, OR A COMBINATION OF BOTH AGENTS.



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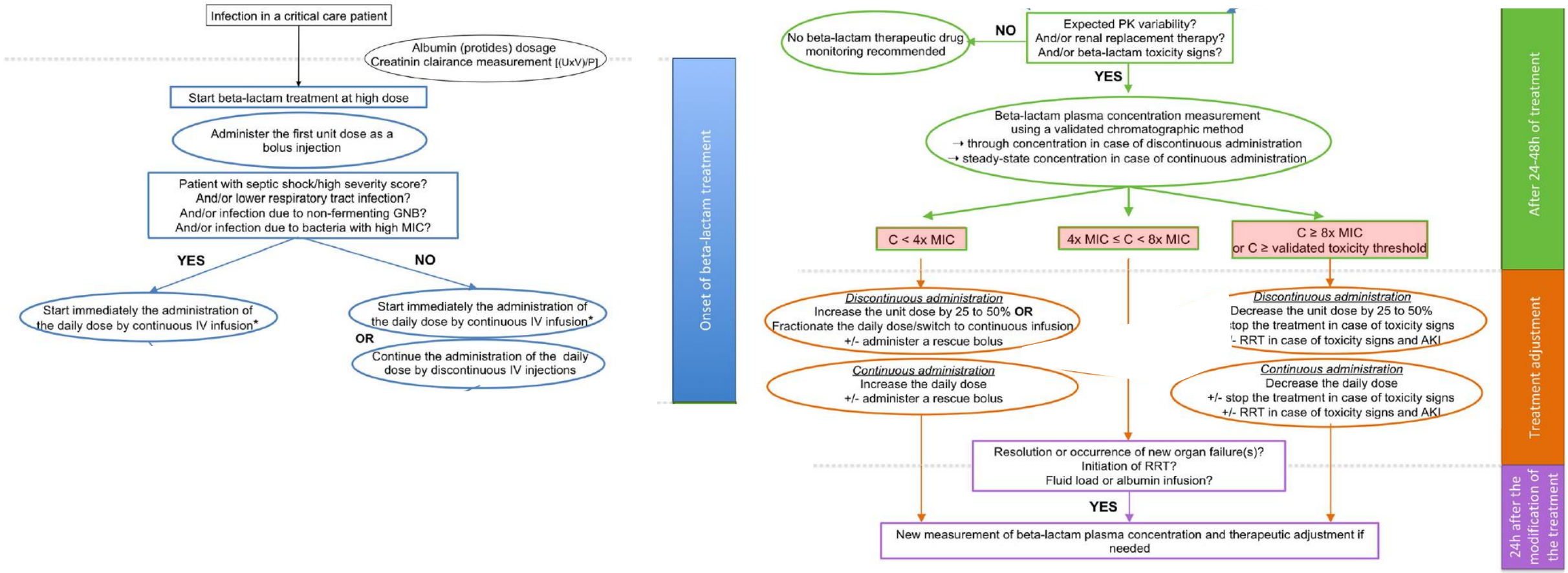
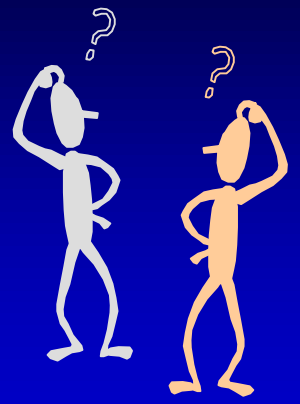
Isolate	bla_{KPC} WT or variant (*ompK36* genotype)[a]	MIC (μg/ml)[b]		Log kill at 12 h (CFU/ml)[c]			Interpretation at 12 h	Log kill at 24 h (CFU/ml)[c]			Interpretation at 24 h
		C-A	COL	C-A at 4× the MIC	2 μg/ml COL	C-A plus COL		C-A at 4× the MIC	2 μg/ml COL	C-A plus COL	
Kp-347	KPC-2 (WT)	0.5	0.25	−0.57	−3.70	−5.96	Synergy	−1.28	−0.99	−5.96	Synergy
Kp-142	KPC-2 (WT)	0.5	0.25	1.97	−6.11	−6.10	Indifferent	4.17	−0.01	−0.62	Indifferent
Kp-465	KPC-2 (WT)	1	0.5	−6.19	−2.01	−6.26	Indifferent	−6.19	3.73	−0.85	Antagonism
Kp-669	KPC-2 (AA134-135)	0.5	0.25	−4.65	−6.18	−6.15	Indifferent	−6.26	−2.67	−6.15	Indifferent
Kp-115	KPC-2 (AA134-135)	1	0.125	−3.80	−3.34	−6.25	Synergy	−4.95	2.54	−0.33	Antagonism
Kp-436	KPC-2 (AA134-135)	1	0.25	−4.47	−6.24	−6.25	Indifferent	−6.25	−2.22	−2.18	Antagonism
Kp-155	KPC-2 (AA134-135)	2	0.25	−3.46	−6.23	−6.04	Indifferent	2.29	−3.85	−2.13	Antagonism
Kp-873	KPC-2 (IS*5*)	1	0.25	−3.24	−6.10	−6.24	Indifferent	−4.07	−0.98	−0.44	Antagonism
Kp-937	KPC-2 (IS*5*)	2	0.25	−3.67	−6.19	−6.21	Indifferent	−4.35	1.39	−6.21	Indifferent
Kp-306	KPC-3 (WT)	0.5	0.5	2.15	−4.18	−6.15	Indifferent	3.33	3.44	−6.15	Synergy
Kp-779	KPC-3 (WT)	1	0.25	−4.80	−6.23	−6.26	Indifferent	−2.39	−6.23	−6.26	Indifferent
Kp-929	KPC-3 (WT)	1	0.125	−4.79	−6.04	−6.15	Indifferent	−4.79	−2.66	−2.90	Antagonism
Kp-928	KPC-3 (WT)	2	0.5	−3.33	1.93	−3.85	Indifferent	−3.99	4.15	−1.70	Antagonism
Kp-930	KPC-3 (WT)	4	0.06	−4.53	−6.24	−6.14	Indifferent	−6.13	−3.82	−6.14	Indifferent
Kp-913	KPC-3 (IS*5*)	0.5	0.25	−3.19	−6.02	−6.05	Indifferent	2.68	−4.11	−1.70	Antagonism
Kp-380	No KPC (IS*5*)	4	0.5	−3.99	−6.13	−6.15	Indifferent	−0.71	1.74	−2.81	Synergy
En-102	KPC-2	0.5	0.06	−3.75	−6.07	−6.11	Indifferent	−4.45	−6.07	−6.11	Indifferent
En-24	KPC-2	1	0.06	−3.47	−6.02	−6.03	Indifferent	−4.32	−3.28	−6.03	Indifferent
En-150	KPC-3	2	0.125	−4.26	−6.09	−6.12	Indifferent	−4.86	−6.09	−3.92	Antagonism
En-6	KPC-3	4	0.125	−3.83	−6.09	−6.09	Indifferent	−4.35	2.96	−6.09	Indifferent
Ec-13	No KPC	0.25	0.125	−3.96	−0.23	−6.18	Synergy	−4.61	3.72	−2.07	Antagonism
Ec-42	KPC-2	1	0.06	−6.19	−6.23	−6.21	Indifferent	−1.61	−6.23	−6.21	Indifferent
Kl-1173	KPC-3	4	0.06	−4.83	−6.17	−6.09	Indifferent	−6.13	−4.39	−6.09	Indifferent
Ct-83	KPC-3	8	0.06	−6.25	−6.25	−6.28	Indifferent	−6.25	−3.10	−2.73	Antagonism

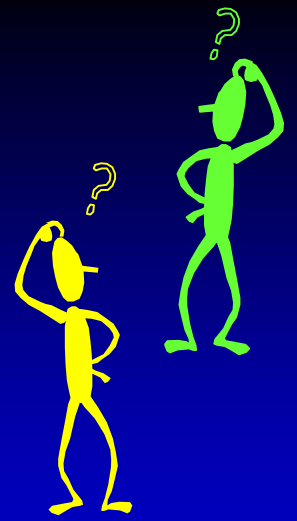
OPTIMIZATION OF THE TREATMENT WITH BETA-LACTAM ANTIBIOTICS IN CRITICALLY ILL PTS GUIDELINES FROM THE FRENCH SOCIETY OF PHARMACOLOGY AND THERAPEUTICS

Guilhaumou R et al. *Crit Care* 2019 Mar 29; 23: 104

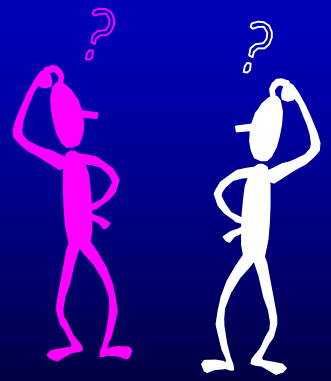
CARE PROTOCOL SUGGESTED BY THE EXPERT

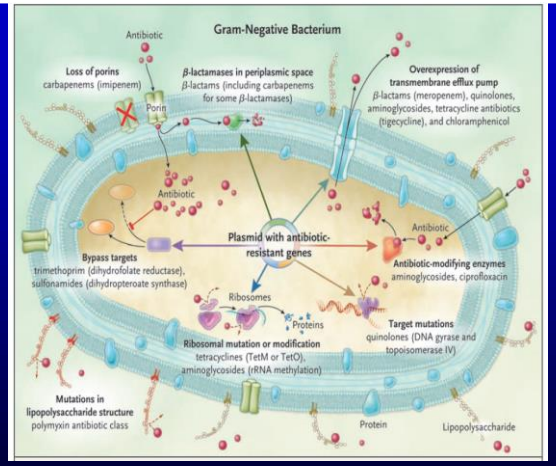


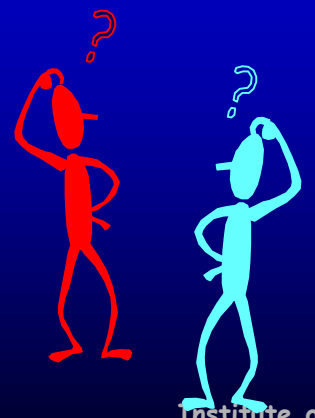




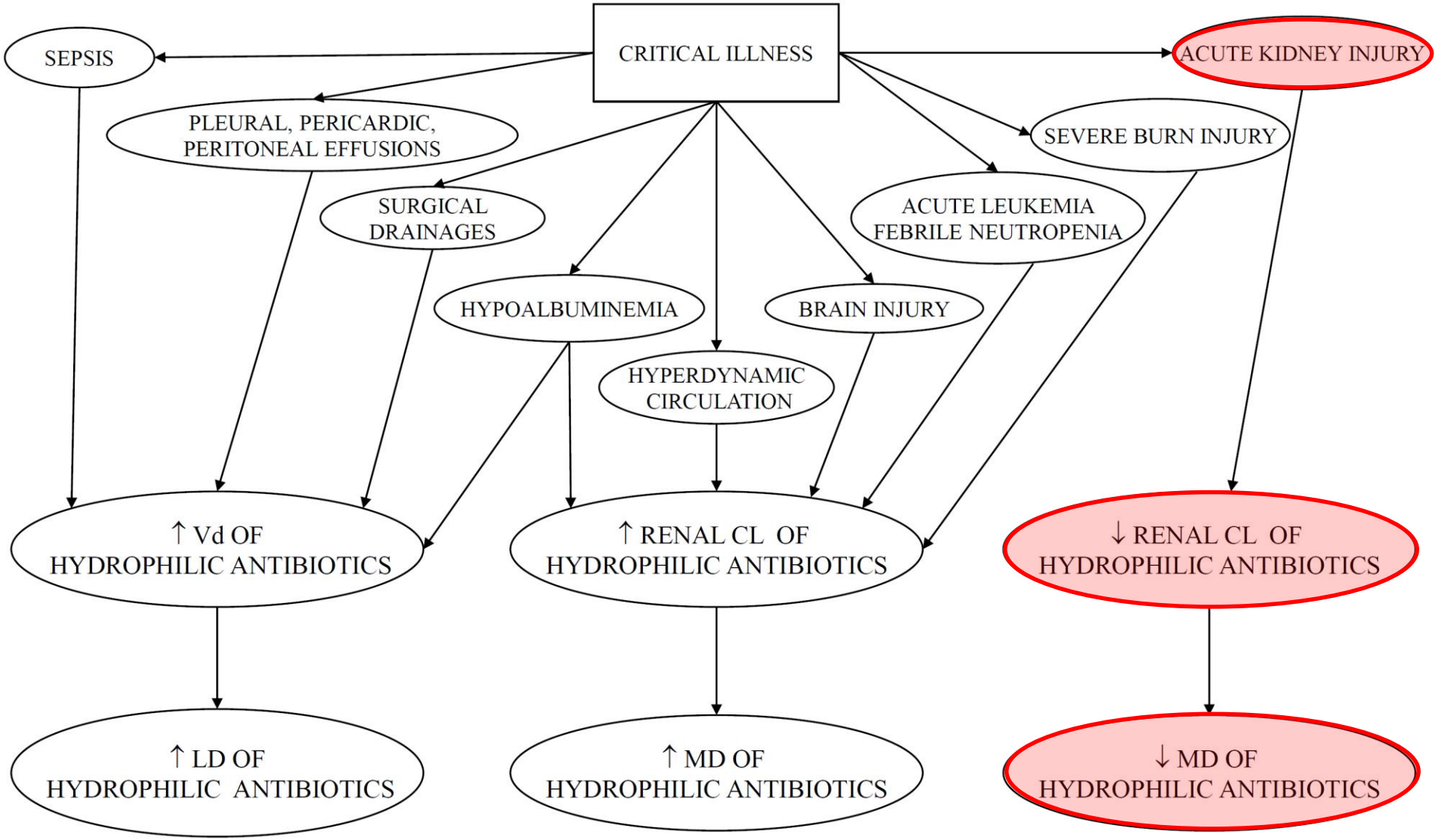
WHAT ABOUT DOSING STRATEGIES ?







FACTORS POTENTIALLY ALTERING THE PK OF ANTIMICROBIALS IN CRITICALLY ILL PATIENTS



Pea F. Physiological Manifestations of Critical Illness. In: Udy AA, Roberts JA, Lipman J, eds. Antibiotic Pharmacokinetic/Pharmacodynamic Considerations in the Critically Ill. Singapore: Springer Singapore, 2018; 31-46.

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RENAL DOSING OF ANTIBIOTICS: ARE WE JUMPING THE GUN?

Crass RL et al. *Clin Infect Dis* 2019 Apr; 68: 1596-1602

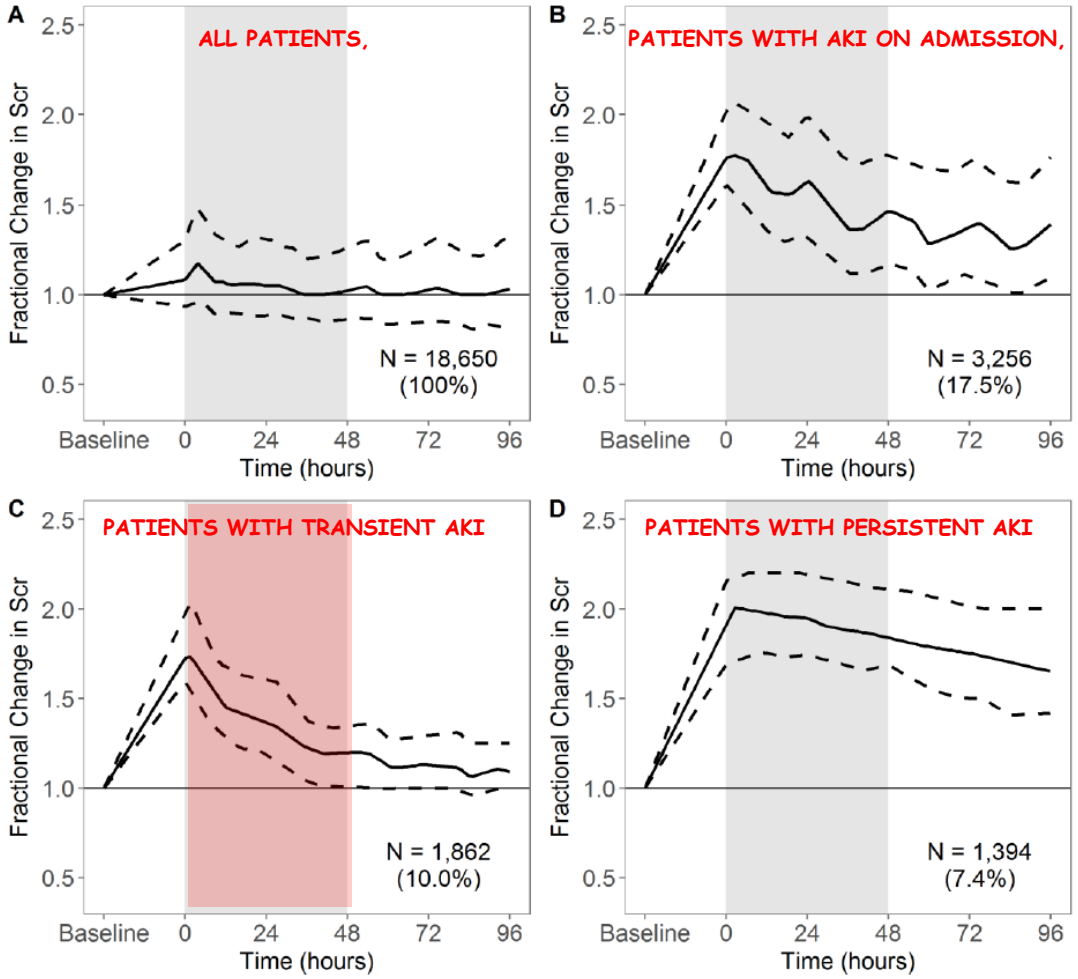
ABSTRACT

- Ceftolozane/tazobactam, ceftazidime/avibactam, and telavancin all carry precautionary statements for reduced clinical response in patients with baseline ClCr 30-50 mL/min, potentially due to unnecessary dose reduction in the setting of acute kidney injury (AKI).
- In this review, we discuss the regulatory landscape for antibiotics eliminated by the kidney and highlight the importance of the first 48 hours of therapy.
- Using a clinical database, we identify AKI on admission in a substantial proportion of patients with pneumonia (27.1%), intra-abdominal (19.5%), urinary tract (20.0%), or skin and skin structure infections (9.7%) that resolved by 48 hours in 57.2% of cases.

RENAL DOSING OF ANTIBIOTICS: ARE WE JUMPING THE GUN?

Crass RL et al. *Clin Infect Dis* 2019 Apr; 68: 1596-1602

FRACTIONAL CHANGE IN SERUM CREATININE RELATIVE TO BASELINE THROUGH THE FIRST 4 DAYS OF ADMISSION.



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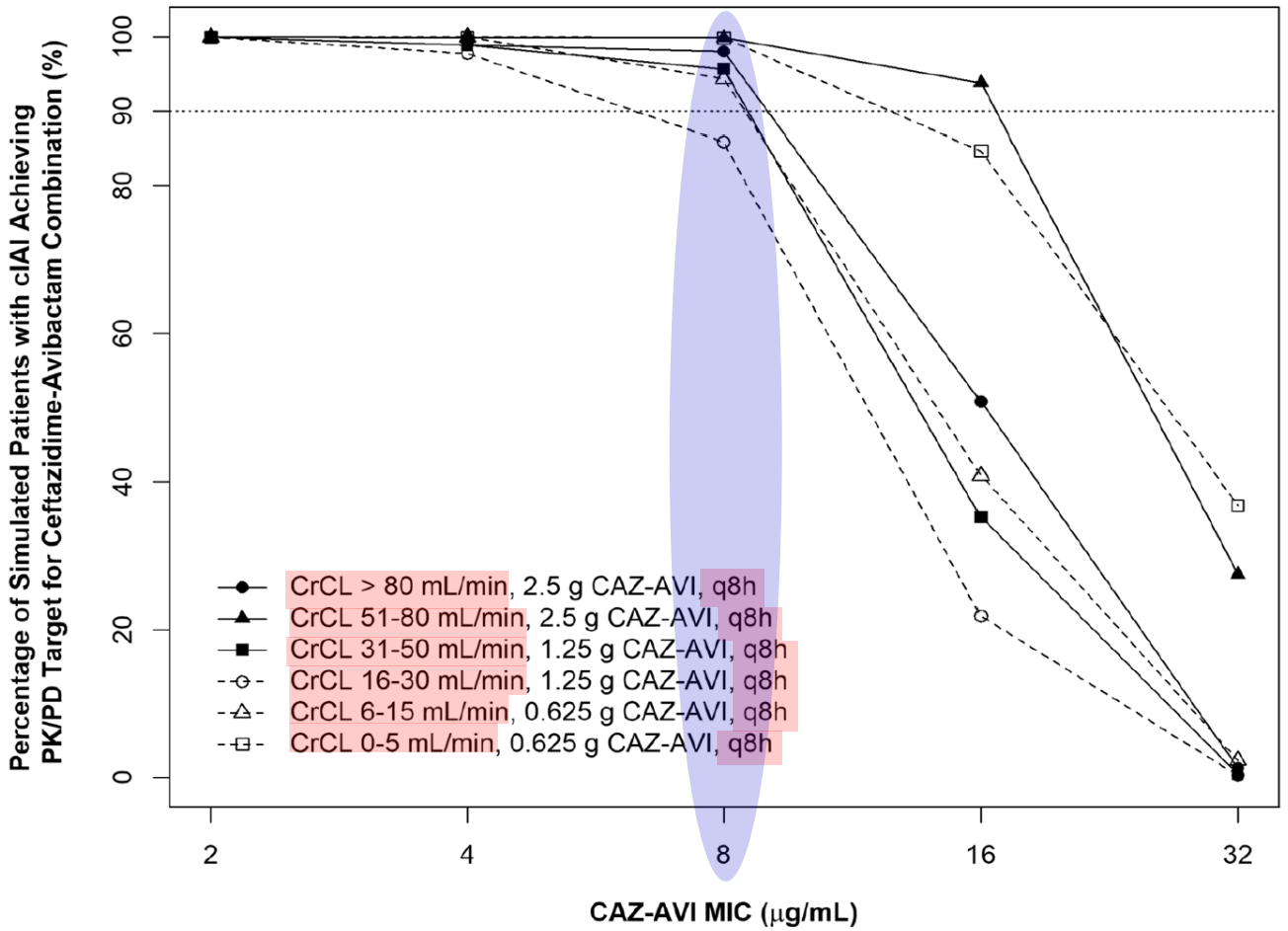
- We suggest that deferred renal dose reduction of wide therapeutic index antibiotics could improve outcomes in patients with infectious diseases.

CLINICAL PK/PD OF CEFTAZIDIME-AVIBACTAM COMBINATION: A MODEL-INFORMED STRATEGY FOR ITS CLINICAL DEVELOPMENT

Sy SKB et al. *Clin Pharmacokinet* 2019 May; 58(5): 545-564

PROBABILITY OF TARGET ATTAINMENT OF 50% fT > MIC FOR CEFTAZIDIME AND 50% fT >CT OF 1.0 MG/L AVIBACTAM IN PATIENTS WITH CIAI FOR VARIOUS RENAL FUNCTION GROUPS, WITH CEFTAZIDIME-AVIBACTAM ADMINISTERED AS A 2-H INTRAVENOUS INFUSION



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

BETA-LACTAMASE INHIBITORS: WHAT YOU REALLY NEED TO KNOW

Ambrose P et al. *Curr Opin Pharmacol* 2017; 36:86–93

KNOW THE B-LACTAM-B-LACTAMASE INHIBITOR EXPOSURE THAT PREVENTS RESISTANCE AMPLIFICATION

- Establishing a β-lactam-β-lactamase inhibitor dosage regimen based on exposures required for the **suppression** of **resistance amplification**, instead of just inhibition of bacterial growth, **may necessitate** the use of **extended infusions**, large doses, and requires substantial safety margins for both the β-lactam-β-lactamase inhibitor

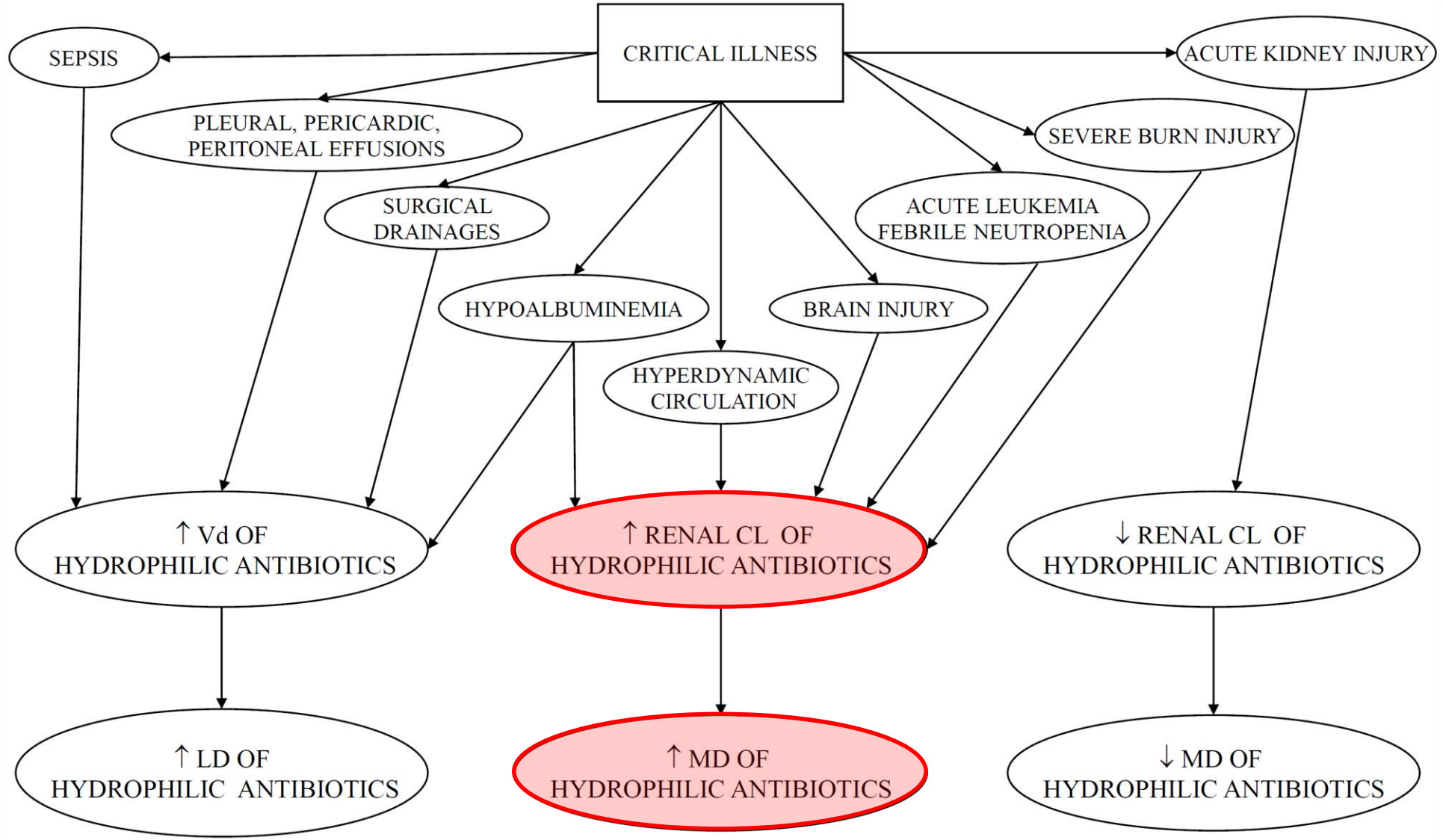
PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES OF ANTIMICROBIAL AGENTS

	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
			Tigecycline
			Vancomycin

MDD → EI-CI

Blot S, Pea F, Lipman J. *Adv Drug Deliv Rev* 2014; 77: 3-11

FACTORS POTENTIALLY ALTERING THE PK OF ANTIMICROBIALS IN CRITICALLY ILL PATIENTS



Pea F. Physiological Manifestations of Critical Illness. In: Udy AA, Roberts JA, Lipman J, eds. Antibiotic Pharmacokinetic/Pharmacodynamic Considerations in the Critically Ill. Singapore: Springer Singapore, 2018; 31-46.

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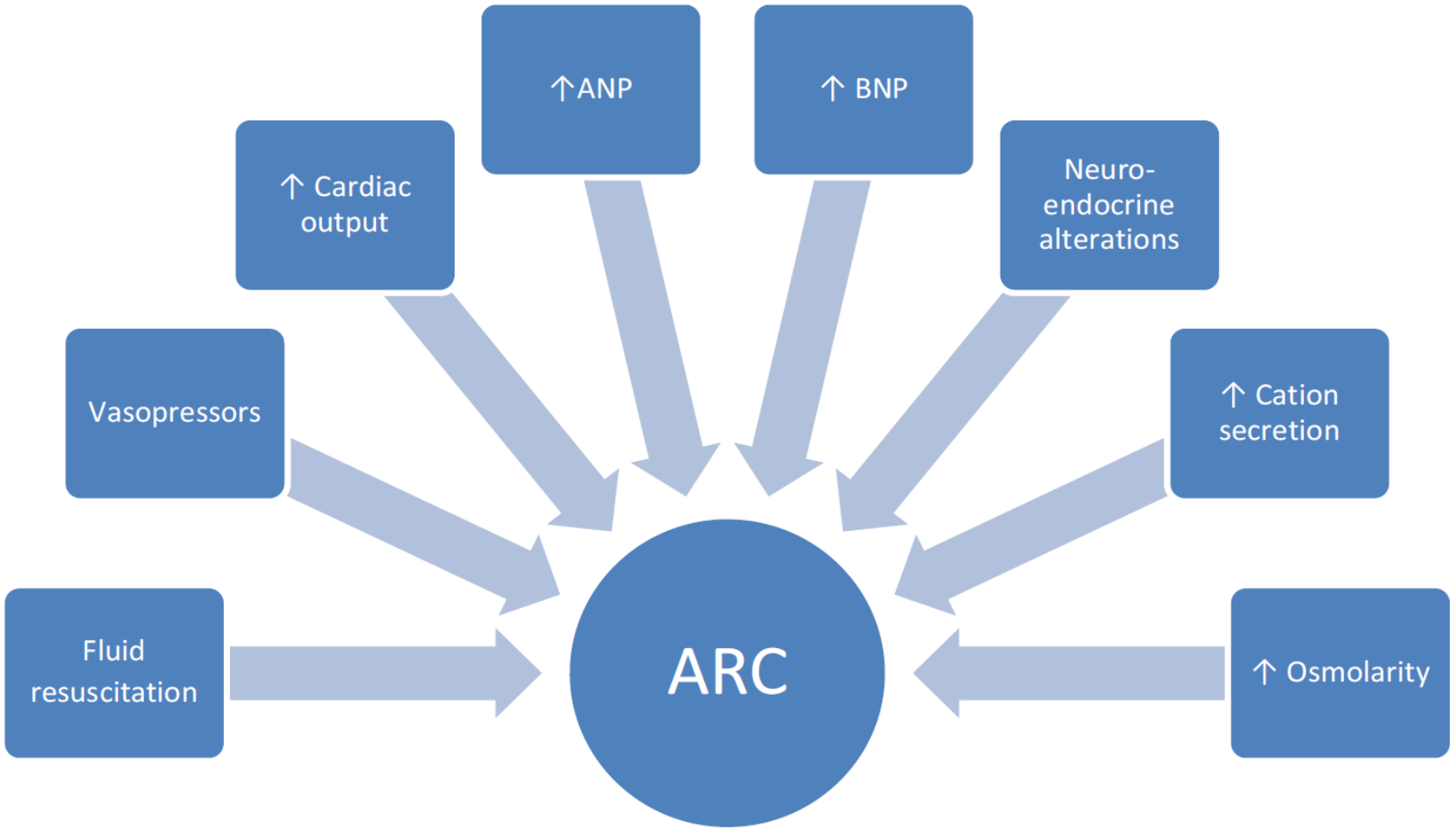
AUGMENTED RENAL CLEARANCE

Cook AM and Hatton-Kolpek J. *Pharmacotherapy* 2019 Mar; 39(3): 346-354

POTENTIAL CONTRIBUTING FACTORS TO AUGMENTED RENAL CLEARANCE



AUGMENTED RENAL CLEARANCE

Cook AM and Hatton-Kolpek J. *Pharmacotherapy* 2019 Mar; 39(3): 346-354

SUMMARY OF POPULATIONS EXHIBITING AUGMENTED RENAL CLEARANCE

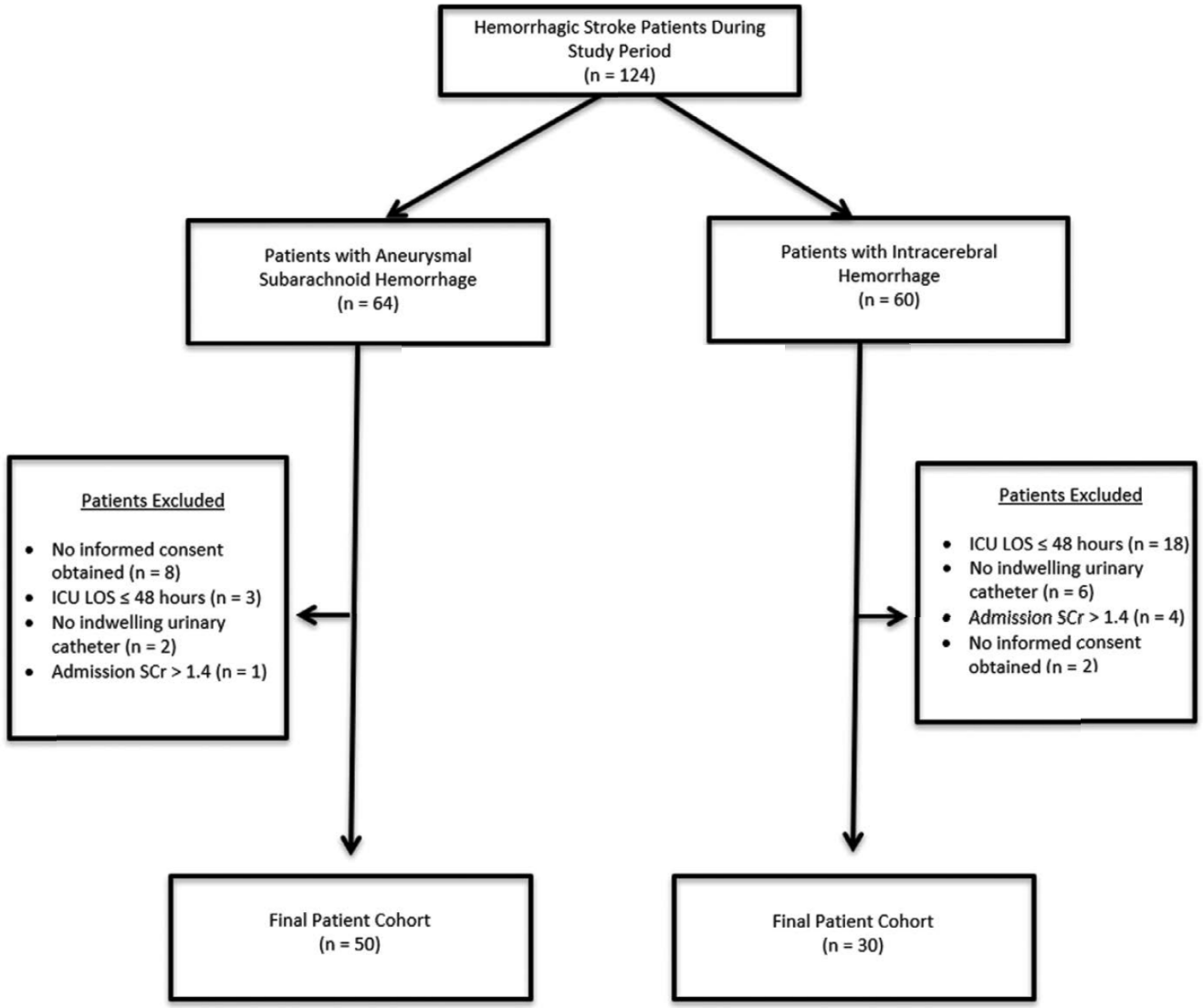
Population	Prevalence (%)	Mean Cl_{cr} values
Burn[5]	65	172.1 ml/min/1.73 m^2
Febrile neutropenia[19]	16.4	157.4 ml/min/1.73 m^2
Sepsis[14, 18]	39.5–56	154–210 ml/min/1.73 m^2
Subarachnoid hemorrhage[11]	100	326 ml/min
Trauma[10]	85.7	166 ml/min/1.73 m^2
Traumatic brain injury[9]	85	179 ml/min/1.73 m^2 150 ml/min/1.73 m^2 (while not receiving CPP treatment)

Cl_{cr} = creatinine clearance; CPP = cerebral perfusion pressure.

ENHANCED RENAL CLEARANCE IN PATIENTS WITH HEMORRHAGIC STROKE

Morbitzer KA et al. *Crit Care Med* 2019 Jun;47(6):800-808

HEMORRHAGIC STROKE PATIENT COHORT TREE



ENHANCED RENAL CLEARANCE IN PATIENTS WITH HEMORRHAGIC STROKE

Morbitzer KA et al. *Crit Care Med* 2019 Jun;47(6):800-808

BASELINE PATIENT CHARACTERISTICS

Variables	Aneurysmal Subarachnoid Hemorrhage ($n = 50$)	Intracerebral Hemorrhage ($n = 30$)
Age (yr), mean ± SD	57.2 ± 10.7	70.0 ± 13.7
Weight (kg), mean ± SD	81.2 ± 21.7	82.9 ± 15.1
Female gender, *n* (%)	34 (68)	12 (40)
Admission Glasgow Coma Scale, median (IQR)	12.5 (6–14)	7.5 (5–13)
Admission Sequential Organ Failure Assessment score, median (IQR)	2 (2–4)	4.5 (2–5)
Hunt and Hess scale grade, median (IQR)	3 (2–4)	N/A
Modified Fisher grade, median (IQR)	3 (3–4)	N/A
Aneurysm intervention, *n* (%)		
Angiography negative	11 (22)	
Coiled	27 (54)	N/A
Clipped	10 (20)	
No intervention	2 (4)	
Symptomatic cerebral vasospasm, *n* (%)	18 (36)	N/A
Admission ICH score, median (IQR)	N/A	3 (2–4)
Admission ICH volume, mean ± SD	N/A	64 ± 64.1
Admission serum creatinine (mg/dL), mean ± SD	0.8 ± 0.2	0.9 ± 0.3
Selected comorbidities, *n* (%)		
Hypertension	28 (56)	18 (60)
Type 2 diabetes mellitus	6 (12)	9 (30)

ICH = intracerebral hemorrhage, IQR = interquartile range.

ENHANCED RENAL CLEARANCE IN PATIENTS WITH HEMORRHAGIC STROKE

Morbitzer KA et al. *Crit Care Med* 2019 Jun;47(6):800-808

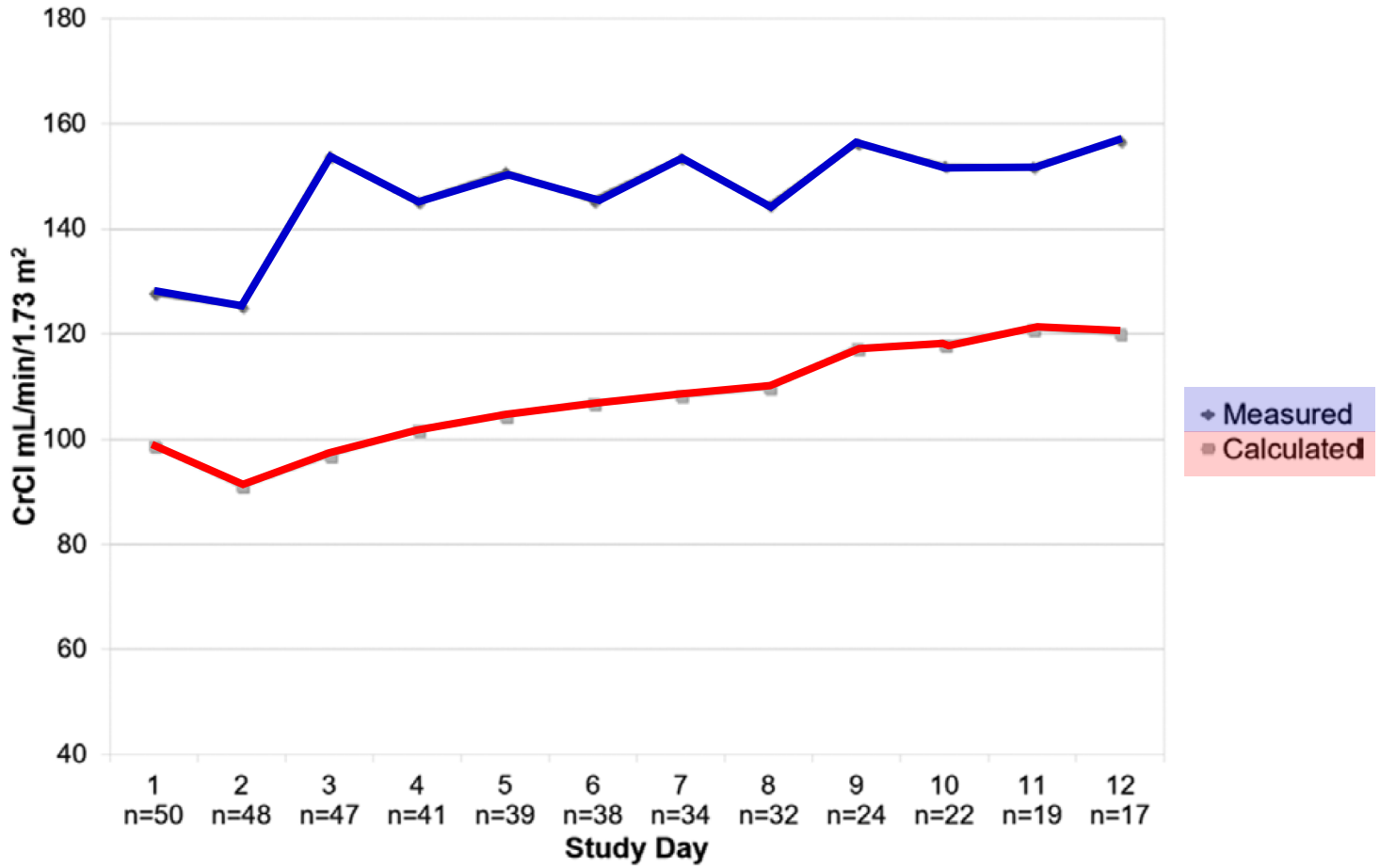
STUDY PERIOD AND DISEASE SEVERITY DATA

Variables	Aneurysmal Subarachnoid Hemorrhage ($n = 50$)	Intracerebral Hemorrhage ($n = 30$)
Days from injury to study start, mean ± SD	1.6 ± 1.1	1.0 ± 0.7
Study days, mean ± SD	9.0 ± 4.1	5.2 ± 3.0
Measured serum creatinine over study period (mg/dL), mean ± SD	0.6 ± 0.2	0.8 ± 0.3
Measured CrCl over study period (mL/min/1.73 m^2), mean ± SD[a]	147.9 ± 50.2	119.5 ± 57.2
Calculated CrCl over study period (mL/min/1.73 m^2), mean ± SD[b]	109.1 ± 32.7[c]	77.8 ± 27.6[d]
Calculated Modification of Diet in Renal Disease over study period (mL/min/1.73 m^2), mean ± SD[b]	126.0 ± 41.9[e]	93.0 ± 32.8[f]
Experienced augmented renal clearance on at least 1 d during study period, *n* (%)	47 (94)	15 (50)
24-hr fluid balance (mL), mean ± SD	+498 ± 1276.0	+433.2 ± 1282.4
Concomitant medications, *n* (%)		
Vasopressor	16 (32)	8 (26.7)
Diuretic	10 (20)	12 (40)
Hypertonic saline	22 (44)	16 (53.3)
ICU LOS (d), mean ± SD	13.7 ± 6.1	10.0 ± 8.3
Hospital LOS (d), mean ± SD	18.6 ± 10.0	14.9 ± 11.1
Mortality, *n* (%)	7 (14)	12 (40)

ENHANCED RENAL CLEARANCE IN PATIENTS WITH HEMORRHAGIC STROKE

Morbitzer KA et al. *Crit Care Med* 2019 Jun;47(6):800-808

MEASURED MEAN CRCL VIA 8-HR URINE COLLECTION AND CALCULATED MEAN CRCL BASED ON COCKCROFT-GAULT EQUATION OVER TIME IN PATIENTS WITH ANEURYSMAL SUBARACHNOID HEMORRHAGE

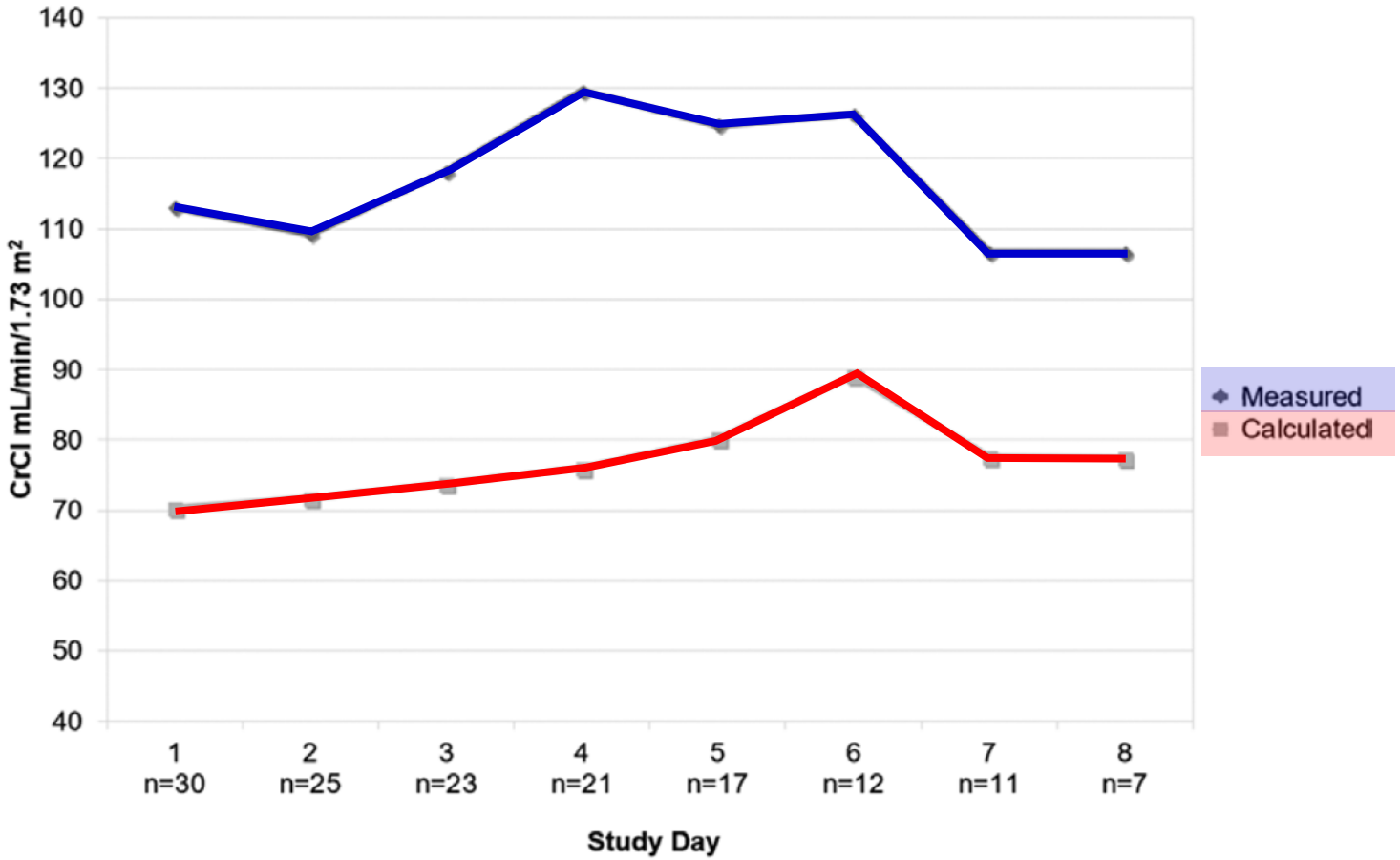


CrCl Standard Deviation per Study Day (mL/min/1.73 m²)												
Study Day	1	2	3	4	5	6	7	8	9	10	11	12
Measured CrCl	±45.9	±58.5	±46.4	±48.6	±62.2	±42.6	±54.2	±47.1	±48.1	±49.2	±39.2	±61.5
Calculated CrCl	±26.8	±29.9	±30.4	±34.8	±34.5	±32.8	±34.6	±30.0	±39.6	±30.9	±24.8	±36.7

ENHANCED RENAL CLEARANCE IN PATIENTS WITH HEMORRHAGIC STROKE

Morbitzer KA et al. *Crit Care Med* 2019 Jun;47(6):800-808

MEASURED MEAN CRCL VIA 8-HR URINE COLLECTION AND CALCULATED MEAN CRCL BASED ON COCKCROFT-GAULT EQUATION OVER TIME IN PATIENTS WITH WITH INTRACEREBRAL HEMORRHAGE



CrCl Standard Deviation per Study Day (mL/min/1.73 m²)								
Study Day	1	2	3	4	5	6	7	8
Measured CrCl	±54.5	±42.5	±85.7	±69.7	±49.7	±31.1	±46.6	±31.3
Calculated CrCl	±26.8	±28.3	±28.5	±31.0	±30.4	±27.7	±21.0	±27.9

ENHANCED RENAL CLEARANCE IN PATIENTS WITH HEMORRHAGIC STROKE

Morbitzer KA et al. *Crit Care Med* 2019 Jun;47(6):800-808

CONCLUSIONS

- These findings from a prospective, observational study suggest that a substantial proportion of patients with aSAH or ICH will experience enhanced renal clearance across several days following injury, which may be otherwise unknown to the patient's care providers
- Enhanced renal clearance may lead to increased renal solute elimination over what is expected, resulting in subtherapeutic renally eliminated drug concentrations
- Future studies are warranted to determine optimal dosing regimens for renally eliminated medications in patients with aSAH or ICH and the impact of enhanced renal clearance on clinical outcomes

POPULATION PHARMACOKINETICS OF UNBOUND CEFTOLOZANE AND TAZOBACTAM IN CRITICALLY ILL PATIENTS WITHOUT RENAL DYSFUNCTION

Sime FB et al. *Antimicrob Agents Chemother* 2019 Jul 29. pii: AAC.01265-19

CHARACTERISTICS OF STUDY PARTICIPANTS

Characteristic	n (%) or median (IQR)
Age (years)	56 (52-61)
Sex	
Male	4 (33%)
Female	8 (67%)
Body mass index (kg/m^2)	28.5 (22.1-32.9)
Weight (kg)	79.5 (64-99)
Serum creatinine (µmol/liter)	46 (39-77)
Urinary creatinine clearance (mL/min/1.73m^2)	107 (74-145)
Albumin (g/L)	25 (19-28)
Alanine transaminase (IU/mL)	35 (23-45)
Aspartate transaminase (IU/mL)	37 (30-67)
Alkaline phosphatase (IU/mL)	102 (75-222)
Total bilirubin (µmol/liter)	12 (7-26)
APACHE II score (admission)	19.5 (16-26)
SOFA Score	6 (3, 8)

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PROBABILITY OF TARGET ATTAINMENT (PTA) FOR CEFTOLOZANE FROM DIFFERENT CEFTOLOZANE/TAZOBACTAM DOSING REGIMENS

PK/PD target	Dose	PTA(%) by MIC (mg/L) during the fist 24 hours										PTA (%) by MIC (mg/L) at steady state (48h-72h)									
		0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16
40%$fT_{>MIC}$	1.5g q8h	100	100	100	100	100	100	100	100	93	41	100	100	100	100	100	100	100	100	97	59
	1.5g 4hEI q8h	100	100	100	100	100	100	100	100	100	52	100	100	100	100	100	100	100	100	100	72
	1.5g LD + 4.5g CI	100	100	100	100	100	100	100	100	100	70	100	100	100	100	100	100	100	100	100	68
	3g TDS	100	100	100	100	100	100	100	100	100	93	100	100	100	100	100	100	100	100	100	97
	3g 4h EI q8h	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
	3g LD + 9g CI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
60%$fT_{>MIC}$	1.5g q8h	100	100	100	100	100	100	100	100	73	3	100	100	100	100	100	100	100	100	78	31
	1.5g 4hEI q8h	100	100	100	100	100	100	100	100	82	17	100	100	100	100	100	100	100	100	94	55
	1.5g LD + 4.5g CI	100	100	100	100	100	100	100	100	100	68	100	100	100	100	100	100	100	100	100	67
	3g q8h	100	100	100	100	100	100	100	100	100	73	100	100	100	100	100	100	100	100	100	78
	3g 4h EI q8h	100	100	100	100	100	100	100	100	100	82	100	100	100	100	100	100	100	100	100	93
	3g LD + 9g CI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
100%$fT_{>MIC}$	1.5g q8h	100	100	100	100	100	100	99	69	5	0	100	100	100	100	100	100	100	81	55	2
	1.5g 4hEI q8h	100	100	100	100	100	100	100	69	0	0	100	100	100	100	100	100	100	96	69	10
	1.5g LD + 4.5g CI	100	100	100	100	100	100	100	100	98	3	100	100	100	100	100	100	100	100	100	61
	3g q8h	100	100	100	100	100	100	100	99	69	5	100	100	100	100	100	100	100	100	81	55
	3g 4h EI q8h	100	100	100	100	100	100	100	100	72	0	100	100	100	100	100	100	100	100	97	69
	3g LD + 9g CI	100	100	100	100	100	100	100	100	100	99	100	100	100	100	100	100	100	100	100	100

POPULATION PHARMACOKINETICS OF UNBOUND CEFTOLOZANE AND TAZOBACTAM IN CRITICALLY ILL PATIENTS WITHOUT RENAL DYSFUNCTION

Sime FB et al. *Antimicrob Agents Chemother* 2019 Jul 29. pii: AAC.01265-19

FRACTIONAL TARGET ATTAINMENT (≥ 85%) AGAINST *P. aeruginosa* MIC DISTRIBUTION FOR STEADY STATE CEFTOLOZANE EXPOSURE

Dose of ceftolozane/tazobactam (2:1 ratio)	PK/PD Target	% FTA for Empiric Therapy by Urinary Creatinine Clearance, mL/min/1.73m^2			
		60	100	140	180
1.5g q8h	40% $fT_{>MIC}$	+	+	+	-
	60% $fT_{>MIC}$	+	+	-	-
	100% $fT_{>MIC}$	+	-	-	-
1.5g LD + 4.5g CI	40% $fT_{>MIC}$	+	+	+	+
	60% $fT_{>MIC}$	+	+	+	+
	100% $fT_{>MIC}$	+	+	+	+
3g q8h	40% $fT_{>MIC}$	+	+	+	+
	60% $fT_{>MIC}$	+	+	+	+
	100% $fT_{>MIC}$	+	+	-	-
3g LD + 9g CI	40% $fT_{>MIC}$	+	+	+	+
	60% $fT_{>MIC}$	+	+	+	+
	100% $fT_{>MIC}$	+	+	+	+

PK/PD TARGET ATTAINMENT ANALYSES TO DETERMINE OPTIMAL DOSING OF CEFTAZIDIME-AVIBACTAM FOR THE TREATMENT OF ACUTE PULMONARY EXACERBATIONS IN PATIENTS WITH CYSTIC FIBROSIS

Bensman TJ et al. *Antimicrob Agent Chemother* 2017 Oct; 61: e00988-17

CF STUDY PARTICIPANT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

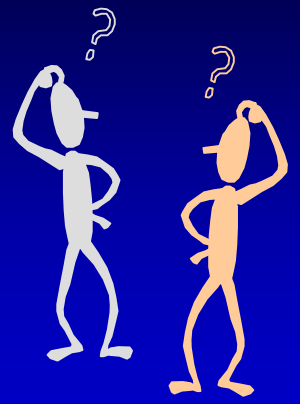
Characteristic	Mean (SD)	Median (range)
Age (yr)	33.1 (11.0)	31.5 (24–65)
Ht (cm)	170.4 (10.1)	169.8 (155.5–184.5)
TBW (kg)	70.91 (10.2)	71.5 (48.8–87.4)
LBW (kg)	51.8 (10.0)	52.91 (33.2–66.3)
BMI (kg/m^2)	24.4 (2.6)	24.4 (19.9–29.6)
Serum creatinine concn (mg/dl)	0.8 (0.2)	0.8 (0.52–1.03)
CL_{CR} (ml/min/1.73 m^2)	121.8 (23.2)	116.8 (77.8–152)
pFEV1[b] (%)	83.8 (21.7)	95 (44–107)

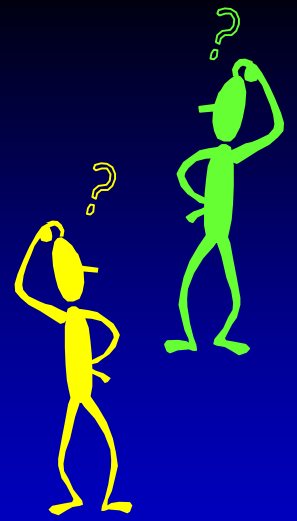
PK/PD TARGET ATTAINMENT ANALYSES TO DETERMINE OPTIMAL DOSING OF CEFTAZIDIME-AVIBACTAM FOR THE TREATMENT OF ACUTE PULMONARY EXACERBATIONS IN PATIENTS WITH CYSTIC FIBROSIS

Bensman TJ et al. *Antimicrob Agent Chemother* 2017 Oct; 61: e00988-17

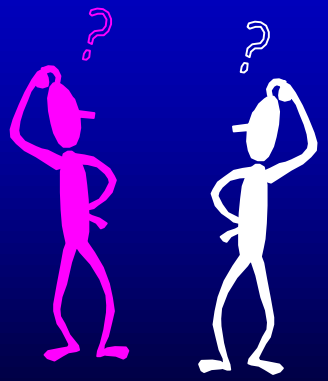
CUMULATIVE RESPONSE PROBABILITY OF CEFTAZIDIME AVIBACTAM 2.5 G Q8H vs. P. aeruginosa CF ISOLATES

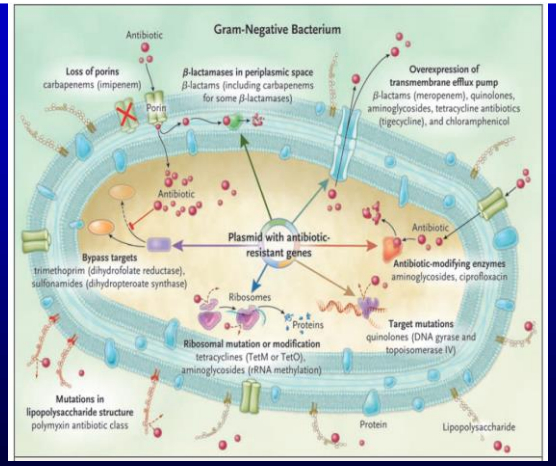
	CRP			
Infusion time (h)	Stasis ($fT_{>MIC}$, 40%)	1- to 2-log drop ($fT_{>MIC}$, 50%)	Nearly maximal response ($fT_{>MIC}$, 65%)	Maximal response ($fT_{>MIC}$, 100%)
0.5	0.824	0.805	0.76	0.449
2	0.836	0.815	0.788	0.554
5	0.844	0.829	0.814	0.757
8	0.825	0.825	0.825	0.825

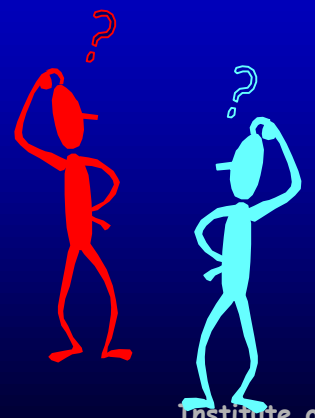




MONOTHERAPY vs. COMBINATION THERAPY ?







EFFICACY OF CEFTAZIDIME-AVIBACTAM IN MONOTHERAPY OR COMBINATION THERAPY AGAINST CARBAPENEM RESISTANT GRAM NEGATIVE ORGANISMS: A META-ANALYSIS

Onorato L et al. *Int J Antimicrob Agents* 2019 Aug 31 online published

CHARACTERISTICS OF THE STUDIES INCLUDED IN THE META-ANALYSIS

First author, year (Ref)	No. of patients	Enrolment period	Country	Study design	Age, median (IQR)	Males (%)	Charlson Comorbidity Index (median, IQR)	Pts with bacteremia, n (%)	Clinical isolates, n (%)				Combination therapy, n (%)	Outcomes	
									K. pneumoniae	*P. aeruginosa*	polimicrobic	other		Mortality (%)	microbiological cure (%)
King, 2017 [9]	60	May 15 April 16	USA	RS	60 (51-69)	36 (60)	4.5 (3-7)	23 (38)	50 (83)	0 (0)	32 (53.3)	12 (0.2)	27 (45)	19* (31.6)	32[a] (53.3)
Krapp, 2017 [10]	6	August 15 December 15	USA	RS	53 (41.2-60.2)	3 (50)	NR	0 (0)	6 (100)	0 (0)	0 (0)	0 (0)	4 (66.7)	2 (33.3)*	3 (100)[b$]
Temkin, 2017 [8]	38	2013 2016	Different countries[^]	CS	61 (47-67)	25 (65.8)	NR	26 (68.4)	34 (89.5)	2 (5.3)	11 (28.9)	2 (5.3)	25 (65.8)	15/38*	24 (63.1)[b]
Caston, 2017 [16]	8	June 2012 March 2016	Spain/Israel	RS	61 (42)°°	4 (50)	2.5 (0-7)	8 (100)	6 (75)	0 (0)	0 (0)	2 (25)	7 (87.5)	2 (25)**	NR
Shields, 2018 [11]	77	April 15 April 17	USA	RS	62 (19-91)°	47 (61)	4 (0-10)°	**20** (26)	60 (77)	0 (0)	0 (0)	17	24 (31.2)	15** (19)	52 (67.5)[c]
Algwizani, 2018 [6]	6	NR	Saudi Arabia	CS	38.5 (15.7-65.7)	6 (100)	NR	3 (50)	3 (50)	3 (50)	0 (0)	0 (0)	3 (50)	1 (16.7)*	5 (83.3)[a]

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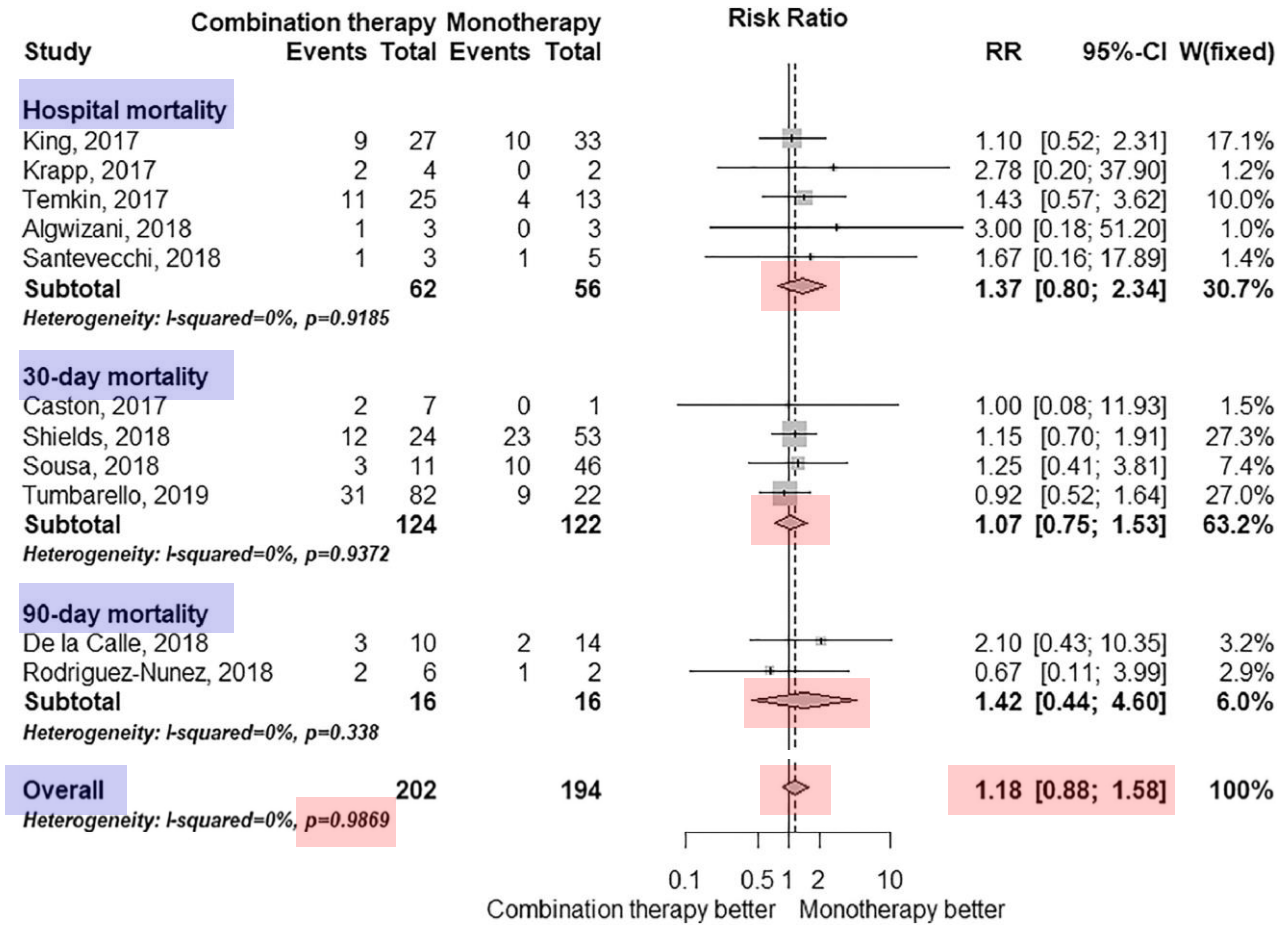
									K. pneumoniae	*P. aeruginosa*	polimicrobic	other		Mortality (%)	microbiological cure (%)
De la Calle, 2018 [12]	24	October 14 December 16	Spain	RS	58.8 (16)°°	19 (82.6)	4.3 (2.9)°°	8 (33.3)	23 (95.8)	0 (0)	0 (0)	1 (4.2)	10 (41.7)	5 (20.8)***	NR
Rodriguez-Nunez, 2018 [13]	8	January 16 May 17	Spain	RS	64.5 (62.5-69.2)	7 (87.5)	NR	2 (25)	1 (12.5)	8 (100)	1 (12.5)	0 (0)	6 (75)	3 (37.5)***	NR
Sousa, 2018 [14]	57	April 16 December 17	Spain	RS	64 (26-86)	44 (77)	3 (0-13)	26 (46)	54 (94.7)	0 (0)	0 (0)	3 (5.3)	11 (19.3)	13 (22.8)**	37 (64.9)[c]
Santevecchi, 2018 [7]	8	July 15 July16	USA	CS	53 (32-74)°	5 (50)	NR	2 (25)	1 (12.5)	6 (75)	6 (75)	1 (12.5)	3 (37.5)	2 (25)*	5 (71.4)[b$$]
Tumbarello, 2019 [15]	138	April 16 December 17	Italy	RS	60 (25-79)	94 (68.1)	>3, n (%): 47 (34.1)	104 (73.3)	138 (100)	0 (0)	12 (8.7)	0 (0)	109 (78.9)	47** (34.1)	NR

EFFICACY OF CEFTAZIDIME-AVIBACTAM IN MONOTHERAPY OR COMBINATION THERAPY AGAINST CARBAPENEM RESISTANT GRAM NEGATIVE ORGANISMS: A META-ANALYSIS

Onorato L et al. *Int J Antimicrob Agents* 2019 Aug 31 online published

META-ANALYSIS OF THE CLINICAL OUTCOME IN THE OVERALL POPULATION



In the present meta-analysis we found no difference in the mortality rate and microbiological cure in patients treated with ceftazidime/avibactam in monotherapy or in combination therapy for infections due to carbapenem-resistant Enterobacteriaceae or *P. aeruginosa*

EVALUATION OF THE SYNERGY OF CEFTAZIDIME-AVIBACTAM IN COMBO WITH MEROPENEM, AMIKACIN, AZTREONAM, COLISTIN, OR FOSFOMYCIN AGAINST WELL-CHARACTERIZED MDR *K. pneumoniae* AND *P. aeruginosa*

Mikhail S et al. *Antimicrob Agents Chemother 2019 Jul 25;63(8). pii: e00779-19*

ACQUIRED RESISTANCE GENES DETECTED AMONG *K. pneumoniae*

Organism	CZA MIC (μg/ml)	Genes for aminoglycoside-modifying enzymes	Macrolide resistance	Fosfomycin resistance	Acquired β-lactamase gene(s)
K. pneumoniae					
R8375	2	*aph(4)-Ia, aph(3')-Ia, aadA2, aadA1, aac(6')-Ib, aac(3)-IV*	*mph*(A)	*fosA*-like	bla_{KPC-3}, bla_{SHV-12}, bla_{TEM-1}, bla_{SHV-11}, bla_{OXA-2}, bla_{OXA-9}
R9009	2	*ant(3')-Ia, aadA2, aac(6')-Ib*	*mph*(A)	*fosA*-like	bla_{KPC-3}, bla_{SHV-12}, bla_{LAP-1}, bla_{TEM-1}, bla_{SHV-11}, bla_{OXA-2}, bla_{OXA-9}
R9064	1	*ant(3')-Ia, aac(6')-Ib*		*fosA*-like	bla_{KPC-3}, bla_{TEM-1}, bla_{SHV-11}, bla_{OXA-2}, bla_{C}
R10277	0.5	*ant(3')-Ia, aadA2, aac(6')-Ib*	*mph*(A)	*fosA*-like	bla_{KPC-2}, bla_{TEM-1}, bla_{SHV-11}
R10278	0.5	*aph(4)-Ia, aph(3')-Ia, ant(3')-Ia, aadA2, aac(6')-Ib, aac(3)-IV*	*mph*(A)	*fosA*-like	bla_{KPC-2}, bla_{TEM-1}, bla_{SHV-11}
R10501	1	*aadA2, aac(6')-Ib*	*mph*(A)	*fosA*-like	bla_{KPC-2}
R10506	0.5	*aph(3')-Ia, aadA2, ant(2'')-Ia, aac(6')-Ib-cr*	*msr*(E), *mph*(E), *mph*(A)	*fosA*-like	$bla_{CTX-M-15}$, bla_{OXA-1}
R10508	0.5			*fosA*-like	bla_{KPC-2}, $bla_{CTX-M-15}$, bla_{TEM-1}, bla_{SHV-11}
R9011	0.5	*ant(3')-Ia, aadA2*	*mph*(A)	*fosA*-like	bla_{KPC-2}, $bla_{CTX-M-15}$, bla_{TEM-1}, bla_{SHV-11}
R9158	1	*ant(3')-Ia, aadA2*	*mph*(A)	*fosA*-like	bla_{KPC-2}, $bla_{CTX-M-15}$, bla_{TEM-1}, bla_{SHV-11}
R10197	0.5	*ant(3')-Ia, aadA2*	*mph*(A)	*fosA*-like	bla_{KPC-2}, $bla_{CTX-M-15}$, bla_{TEM-1}, bla_{SHV-11}
R10279		*aph(4)-Ia, aph(3')-Ia, ant(3')-Ia, aadA2, aac(6')-Ib, aac(3)-IV*-like	*mph*(A)	*fosA*-like	bla_{KPC-2}, bla_{TEM-1}, bla_{SHV-11}
R10428	1	*aph(6)-Ia, aph(6)-Id*		*fosA*	bla_{KPC-2}, $bla_{CTX-M-15}$, $bla_{TEM-206}$, bla_{SHV-28}
R10499	0.5	*ant(3')-Ia, aadA2*	*mph*(A)	*fosA*-like	bla_{KPC-2}, $bla_{CTX-M-15}$, bla_{TEM-1}, bla_{SHV-11}
R10500	0.5	*ant(3')-Ia, aadA2*	*mph*(A)	*fosA*-like	bla_{KPC-2}, $bla_{CTX-M-15}$, bla_{TEM-1}, bla_{SHV-11}
R10502	0.5	*aphA16, ant(3')-Ia, ant(2'')-Ia, aac(6')-Ib*		*fosA*-like	bla_{KPC-3}, bla_{SHV-12}, bla_{TEM-1}, bla_{SHV-11}, bla_{OXA-2}, bla_{OXA-9}
R10504	1	*aph(4)-Ia, aadA2, aadA1, aac(6')-Ib, aac(3)-IV*		*fosA*-like	bla_{KPC-3}, bla_{SHV-12}, bla_{TEM-1}, bla_{SHV-11}, bla_{OXA-2}, bla_{OXA-9}
R10507	0.5	*ant(3')-Ia, aadA2, aac(6')-Ib*	*mph*(A)	*fosA*-like	bla_{KPC-3}, bla_{SHV-12}, bla_{TEM-1}, bla_{SHV-11}, bla_{OXA-2}, bla_{OXA-9}
R10503	0.5	*ant(3')-Ia, aadA2, aac(6')-Ib*	*mph*(A)	*fosA*-like	bla_{KPC-3}, bla_{SHV-12}, bla_{TEM-1}, bla_{SHV-11}, bla_{OXA-2}, bla_{OXA-9}
R10505	0.5	*ant(3')-Ia, aadA2, aac(6')-Ib*	*mph*(A)	*fosA*-like	bla_{KPC-3}, $bla_{CTX-M-3}$, bla_{SHV-12}, bla_{TEM-1}, bla_{SHV-11}, bla_{OXA-2}, bla_{OXA-9}
10831#1	4	*aadA16, aac(6')-Ib-cr*		*fosA*-like	bla_{KPC-2}, bla_{TEM-1}, bla_{SHV-11}

EVALUATION OF THE SYNERGY OF CEFTAZIDIME-AVIBACTAM IN COMBO WITH MEROPENEM, AMIKACIN, AZTREONAM, COLISTIN, OR FOSFOMYCIN AGAINST WELL-CHARACTERIZED MDR *K. pneumoniae* AND *P. aeruginosa*

Mikhail S et al. *Antimicrob Agents Chemother 2019 Jul 25;63(8). pii: e00779-19*

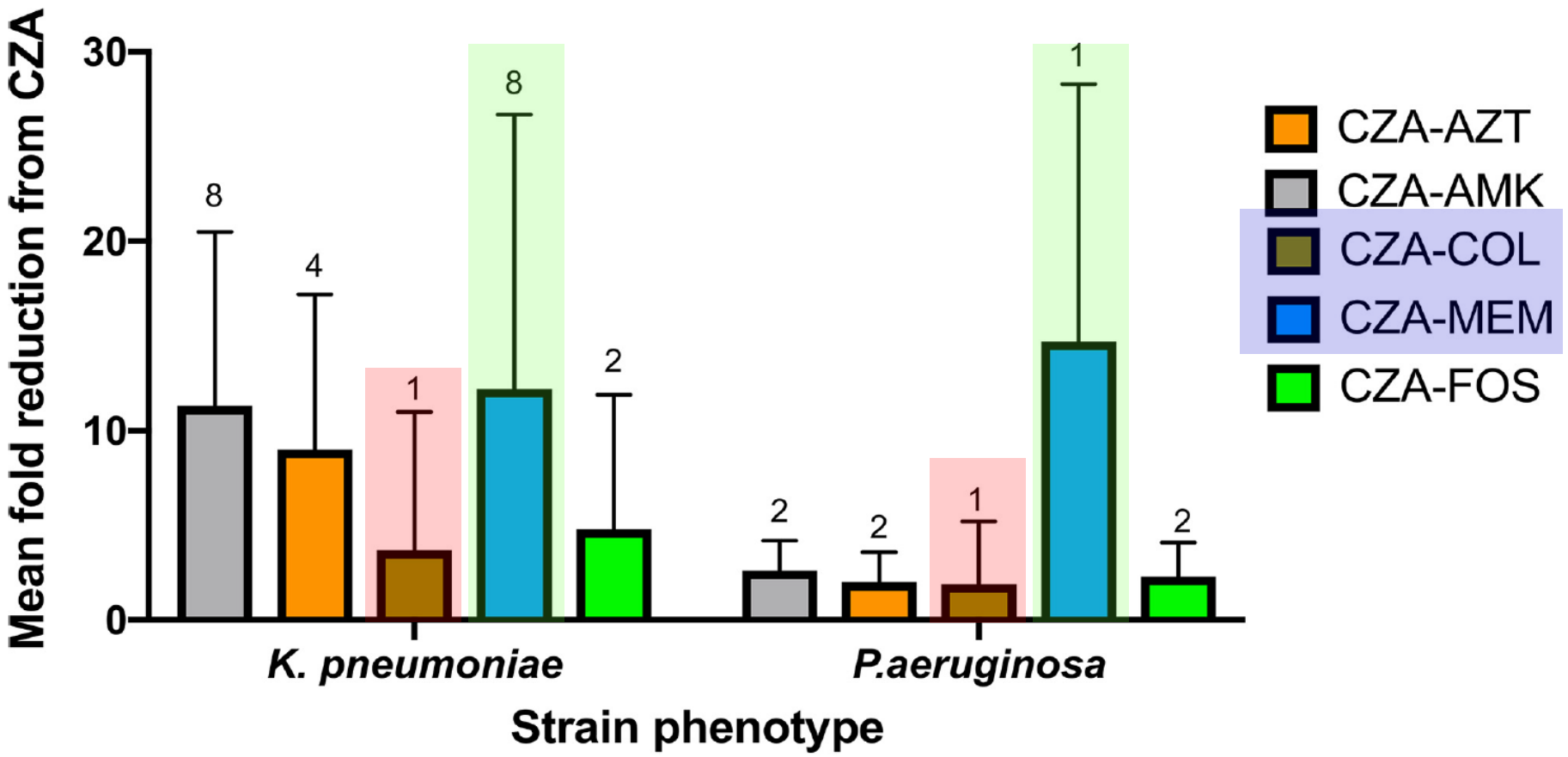
ACQUIRED RESISTANCE GENES DETECTED AMONG *P. aeruginosa*

Organism	CZA MIC (μg/ml)	Genes for aminoglycoside-modifying enzymes	Macrolide resistance	Fosfomycin resistance	Acquired β-lactamase gene(s)
P. aeruginosa					
R9316	8	*aph(3′)-IIb-like*		*fosA*-like	
R9647	1	*aph(3′)-IIb*		*fosA*	
R10149	128	*aph(3′)-Iib, ant(2″)-Ia, aac(6′)-Ib*		*fosA*-like	bla_{IMP-48}, bla_{OXA-10}
R10266	16	*aph(3′)-IIb*-like		*fosA*	
R10267	64	*aph(3′)-IIb*-like		*fosA*	
R10268	4	*aph(3′)-IIb, aadA6, aadA1, ant(2″)-Ia, aac(6′)-Il, aac(6′)-Ib4*		*fosA*	bla_{GES-1}, bla_{OXA-2}
R10269	1	*aph(6)-Ia, aph(6)-Id, aph(3′)-IIb*-like, *aadA11, ant(2″)-Ia*		*fosA*-like	
R10272	8	*aph(3′)-IIb*-like, *aadA6, aadA2, aadA1, ant(2″)-Ia, aacA16*		*fosA*-like	bla_{VEB-1}, bla_{OXA-10}
R10274	1	*aph(3′)-IIb*		*fosA*	
R10275	2	*aph(3′)-IIb*-like		*fosA*-like	
R10378	2	*aph(3′)-IIb*-like		*fosA*	
R9333	1	*aph(3′)-IIb*		*fosA*	
R10271	1	*aadA16*-like, *aac(6′)-Ib4*			bla_{KPC-2}
R10273	4	*aph(3′)-IIb*-like, *ant(2″)-Ia*		*fosA*	
R8381	2	*aph(3′)-IIb*-like		*fosA*	
R9010	8	*aph(3′)-IIb*-like		*fosA*-like	
R9042	2			*fosA*	
R10155	128	*aph(3′)-Iib, ant(2″)-Ia, aac(6′)-Ib*		*fosA*-like	bla_{IMP-48}, bla_{OXA-10}
R10270	2	*aph(6)-Ia, aph(6)-Id, aph(3′)-Iib*		*fosA*	
9260#1	8	*aph(3′)-IIb*-like, *aac(3)-IIIa*		*fosA*	
9275#1	64	*aph(3′)-IIb*-like, *aadA2, aac(6′)-Ib*		*fosA*-like	bla_{CARB-2}

EVALUATION OF THE SYNERGY OF CEFTAZIDIME-AVIBACTAM IN COMBO WITH MEROPENEM, AMIKACIN, AZTREONAM, COLISTIN, OR FOSFOMYCIN AGAINST WELL-CHARACTERIZED MDR *K. pneumoniae* AND *P. aeruginosa*

Mikhail S et al. *Antimicrob Agents Chemother 2019 Jul 25;63(8). pii: e00779-19*

MIC REDUCTIONS OF CZA IN COMBINATION WITH ADJUNCTIVE ANTIMICROBIALS AGAINST *K. pneumoniae* AND *P. aeruginosa*
NUMBERS ABOVE EACH BAR REPRESENT THE AMOUNT OF MIC50 FOR THAT COMBINATION.



CEFTOLOZANE/TAZOBACTAM FOR THE TREATMENT OF SERIOUS *P. aeruginosa* INFECTIONS: A MULTICENTRE NATIONWIDE CLINICAL EXPERIENCE

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

UNIVARIATE ANALYSIS OF RISK FACTORS FOR CLINICAL FAILURE OF CEFTOLOZANE/TAZOBACTAM (C/T) THERAPY AMONG PATIENTS WITH *P. aeruginosa* INFECTION

Variable	*n* (%)[a]		*P*-value
	Clinical success (*n* = 84)	Clinical failure (*n* = 17)	
Age (years) (mean ± S.D.)	61.3 ± 18.3	58.2 ± 16.7	0.51
Sex male	55 (65.5)	11 (64.7)	1
Charlson comorbidity index (mean ± S.D.)	4.5 ± 2.5	4.1 ± 2.2	0.50
Underlying diseases			
Cardiac disease	29 (34.5)	7 (41.2)	0.59
Neurological disease	27 (32.1)	6 (35.3)	0.78
Chronic renal disease	25 (29.8)	6 (35.3)	0.77
Diabetes mellitus	17 (20.2)	5 (29.4)	0.51
Gastrointestinal disease	17 (20.2)	4 (23.5)	0.75
Solid-organ tumour	14 (16.7)	3 (17.6)	1
Solid-organ transplant	8 (9.5)	3 (17.6)	0.39
Haematological malignancy	11 (13.1)	2 (11.8)	1
COPD	6 (7.1)	3 (17.6)	0.17
Cystic fibrosis	5 (6.0)	3 (17.6)	0.13
Liver disease	2 (2.4)	0	1
Other predisposing conditions [b]			
Corticosteroids	28 (33.3)	4 (23.5)	0.57
Other immunosuppressive therapy	17 (20.2)	4 (23.5)	0.74
Chemotherapy	11 (13.1)	1 (5.9)	0.68
Neutropenia [c]	9 (10.7)	2 (11.8)	1
Invasive procedures			
Central venous catheter	50 (59.5)	13 (76.5)	0.27
Urinary catheter	44 (52.4)	13 (76.5)	0.10
Previous surgery [b]	32 (38.1)	9 (52.9)	0.28
Mechanical ventilation	15 (17.9)	4 (23.5)	0.73
Percutaneous endoscopic gastrostomy	7 (8.3)	2 (11.8)	0.64
Severity of clinical presentation			
No sepsis	54 (64.3)	8 (47.1)	0.27
Sepsis	19 (22.6)	8 (47.1)	0.05
Septic shock	11 (13.1)	1 (5.9)	0.68
ICU admission due to *P. aeruginosa* infection	17 (20.2)	7 (41.2)	0.11
Polymicrobial infection	25 (29.8)	11 (64.7)	0.01
Off-label indication	61 (72.6)	13 (76.5)	1
Type of infection			
Nosocomial pneumonia	24 (28.6)	8 (47.1)	0.15
ABSSSI	19 (22.6)	2 (11.8)	0.51
cUTI	13 (15.5)	1 (5.9)	0.45
cIAI	10 (11.9)	3 (17.6)	0.45
Bone infection	8 (9.5)	1 (5.9)	1
Primary bacteraemia	6 (7.1)	0	0.58
Other infections	4 (4.8)	2 (11.8)	0.26
Life-threatening infection	46 (54.8)	11 (64.7)	0.59
C/T treatment			
Combination therapy	30 (35.7)	6 (35.3)	1
Days of treatment (mean ± S.D.)	18.3 ±13.7	18.3 ± 16.6	0.99
Standard dosage	61 (72.6)	9 (52.9)	0.14
Off-label dosage	23 (27.4)	8 (47.1)	0.14
Intermittent haemodialysis	5 (6.0)	1 (5.9)	1
CRRT	7 (8.3)	5 (29.4)	0.03
Adequate source control of the infection	23/33 (69.7)	4/8 (50.0)	0.59

CEFTOLOZANE/TAZOBACTAM FOR THE TREATMENT OF SERIOUS *P. aeruginosa* INFECTIONS: A MULTICENTRE NATIONWIDE CLINICAL EXPERIENCE

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Chemotherapy	11 (13.1)	1 (5.9)	0.68
Neutropenia [c]	9 (10.7)	2 (11.8)	1
Invasive procedures			
Central venous catheter	50 (59.5)	13 (76.5)	0.27
Urinary catheter	44 (52.4)	13 (76.5)	0.10
Previous surgery [b]	32 (38.1)	9 (52.9)	0.28
Mechanical ventilation	15 (17.9)	4 (23.5)	0.73
Percutaneous endoscopic gastrostomy	7 (8.3)	2 (11.8)	0.64
Severity of clinical presentation			
No sepsis	54 (64.3)	8 (47.1)	0.27
Sepsis	19 (22.6)	8 (47.1)	0.05
Septic shock	11 (13.1)	1 (5.9)	0.68
ICU admission due to *P. aeruginosa* infection	17 (20.2)	7 (41.2)	0.11
Polymicrobial infection	25 (29.8)	11 (64.7)	0.01
Off-label indication	61 (72.6)	13 (76.5)	1
Type of infection			
Nosocomial pneumonia	24 (28.6)	8 (47.1)	0.15
ABSSSI	19 (22.6)	2 (11.8)	0.51
cUTI	13 (15.5)	1 (5.9)	0.45
cIAI	10 (11.9)	3 (17.6)	0.45
Bone infection	8 (9.5)	1 (5.9)	1
Primary bacteraemia	6 (7.1)	0	0.58
Other infections	4 (4.8)	2 (11.8)	0.26
Life-threatening infection	46 (54.8)	11 (64.7)	0.59
C/T treatment			
Combination therapy	30 (35.7)	6 (35.3)	1
Days of treatment (mean ± S.D.)	18.3 ±13.7	18.3 ± 16.6	0.99
Standard dosage	61 (72.6)	9 (52.9)	0.14
Off-label dosage	23 (27.4)	8 (47.1)	0.14
Intermittent haemodialysis	5 (6.0)	1 (5.9)	1
CRRT	7 (8.3)	5 (29.4)	0.03
Adequate source control of the infection	23/33 (69.7)	4/8 (50.0)	0.59

EFFICACY OF CEFTOLOZANE/TAZOBACTAM, ALONE AND IN COMBINATION WITH COLISTIN, AGAINST MDR *P. aeruginosa* IN AN *in vitro* BIOFILM PHARMACODYNAMIC MODEL

Gómez-Junyent J et al. *Int J Antimicrob Agents* 2019 May; 53(5): 612-619

MINIMUM INHIBITORY CONCENTRATIONS, MINIMUM BACTERICIDAL CONCENTRATIONS, MINIMUM BIOFILM INHIBITORY CONCENTRATIONS, AND MINIMUM ERADICATION CONCENTRATIONS FOR THE DIFFERENT ANTIBIOTICS AMONG ALL PSEUDOMONAS AERUGINOSA STRAINS

Antibiotics	MDR-HUB1				XDR-HUB2				MDR-HUB3			
	MIC	MBC	MBIC	MBEC	MIC	MBC	MBIC	MBEC	MIC	MBC	MBIC	MBEC
CST	1	4	8	> 64	2	2	8	64	2	2	8	> 64
CAZ	64	128	> 256	> 256	32	32	> 256	> 256	64	> 256	> 256	> 256
MEM	2	4	2	> 256	16	16	16	> 256	2	4	2	> 256
*TOL/TZB	2	4	8	> 256	4	4	16	> 256	8	8	16	> 256

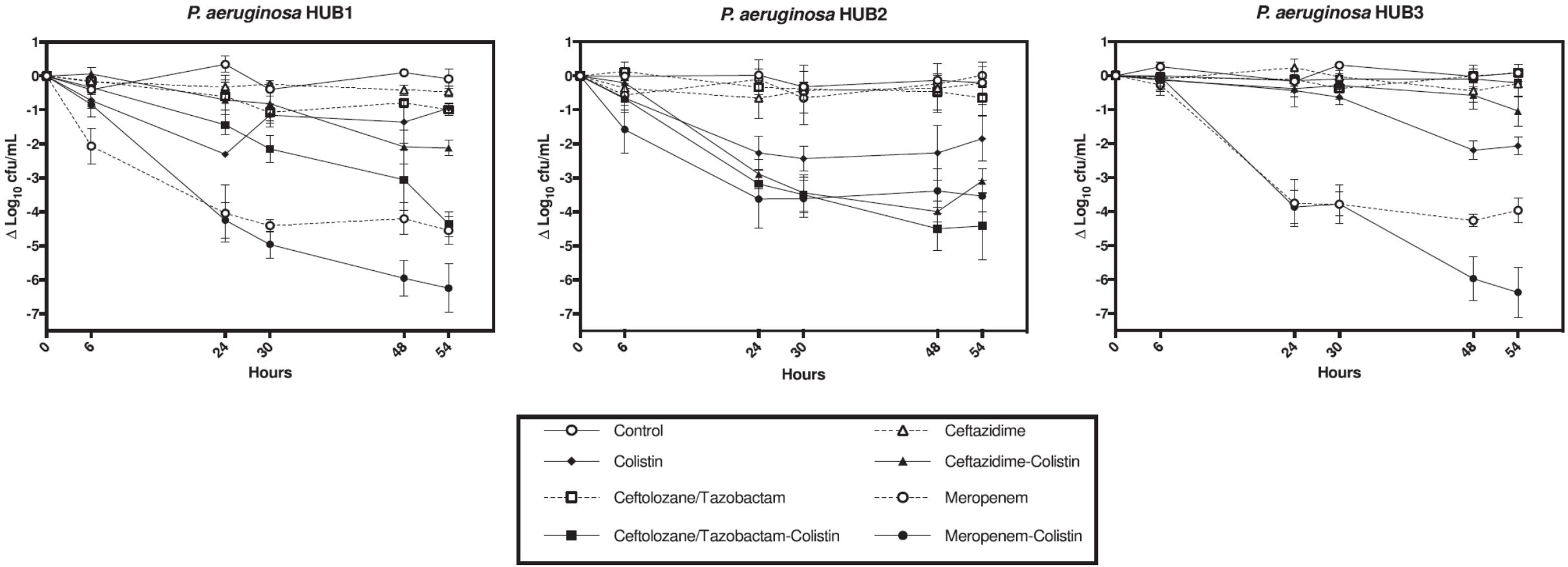
MIC = minimum inhibitory concentration; MBC = minimum bactericidal concentration; MBIC = minimum biofilm inhibitory concentration; MBEC = minimum biofilm eradication concentration; CST = colistin; CAZ = ceftazidime; MEM = meropenem; TOL/TZB = ceftolozane/tazobactam.

* The MIC, MBC, MBIC and MBEC values refer to the concentration of ceftolozane in the presence of a fixed concentration of tazobactam at 4 mg/L.

EFFICACY OF CEFTOLOZANE/TAZOBACTAM, ALONE AND IN COMBINATION WITH COLISTIN, AGAINST MDR *P. aeruginosa* IN AN *in vitro* BIOFILM PHARMACODYNAMIC MODEL

Gómez-Junyent J et al. *Int J Antimicrob Agents* 2019 May; 53(5): 612-619

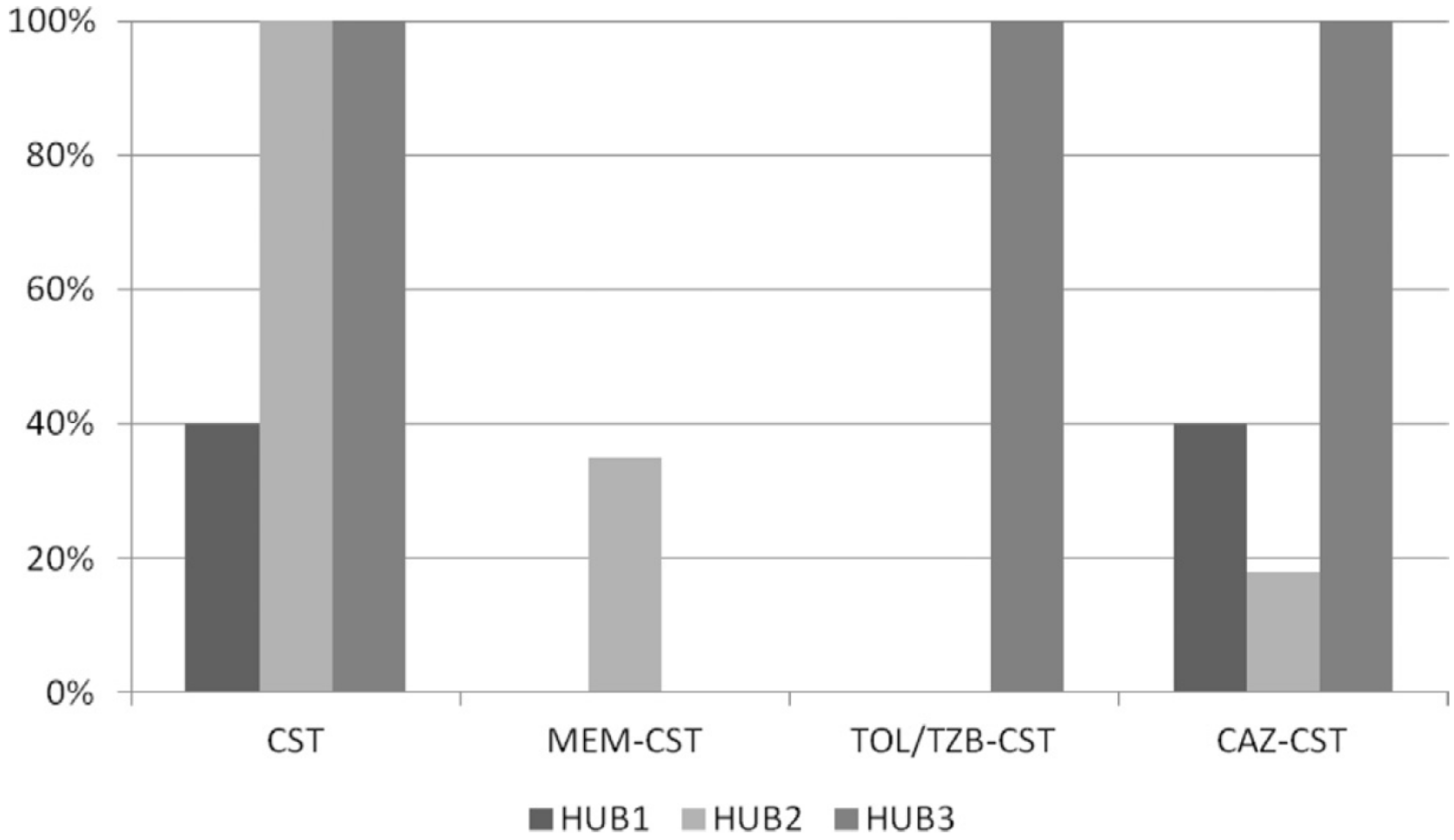
BACTERIAL KILLING BY MONOTHERAPIES AND THE COMBINATIONS AGAINST BIOFILM-EMBEDDED CELLS OF THREE DIFFERENT *P. aeruginosa* STRAINS



EFFICACY OF CEFTOLOZANE/TAZOBACTAM, ALONE AND IN COMBINATION WITH COLISTIN, AGAINST MDR *P. aeruginosa* IN AN *in vitro* BIOFILM PHARMACODYNAMIC MODEL

Gómez-Junyent J et al. *Int J Antimicrob Agents* 2019 May; 53(5): 612-619

EMERGENCE OF RESISTANT COLISTIN SUBPOPULATIONS AMONG BIOFILM-EMBEDDED CELLS OF THE THREE *P. aeruginosa* STRAINS ACCORDING TO THE TREATMENT REGIMEN AT 54 HOURS

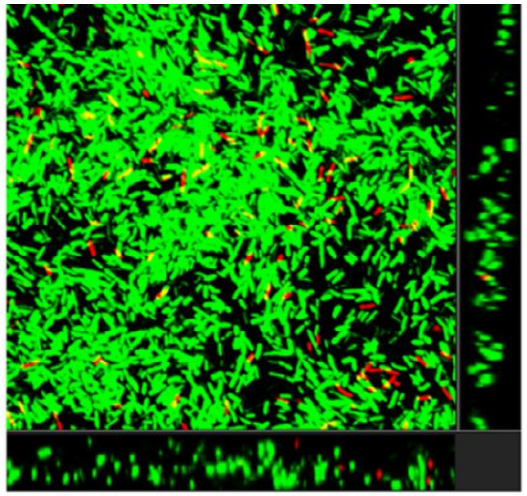


EFFICACY OF CEFTOLOZANE/TAZOBACTAM, ALONE AND IN COMBINATION WITH COLISTIN, AGAINST MDR *P. aeruginosa* IN AN *in vitro* BIOFILM PHARMACODYNAMIC MODEL

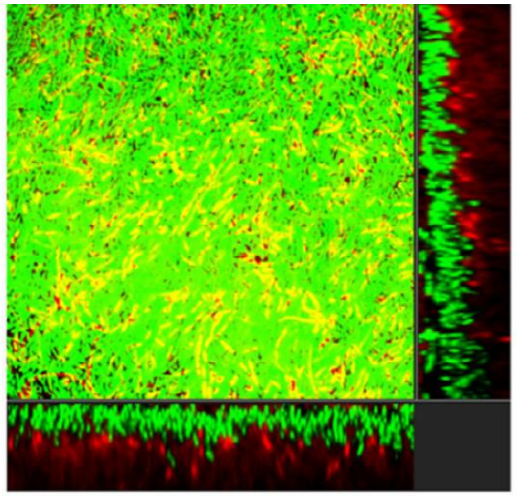
Gómez-Junyent J et al. *Int J Antimicrob Agents* 2019 May; 53(5): 612-619

CONFOCAL LASER SCANNING MICROSCOPY IMAGES OF BIOFILM-EMBEDDED CELLS OF *P. aeruginosa* HUB2

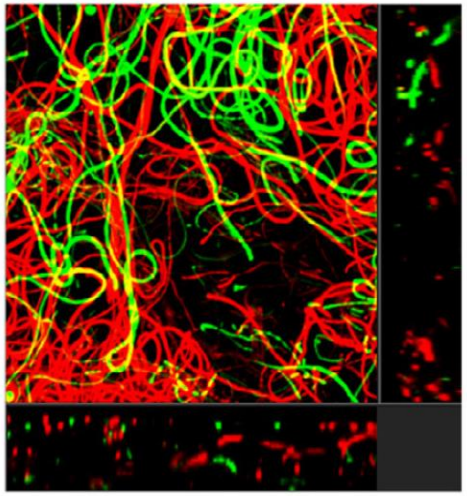
CONTROL



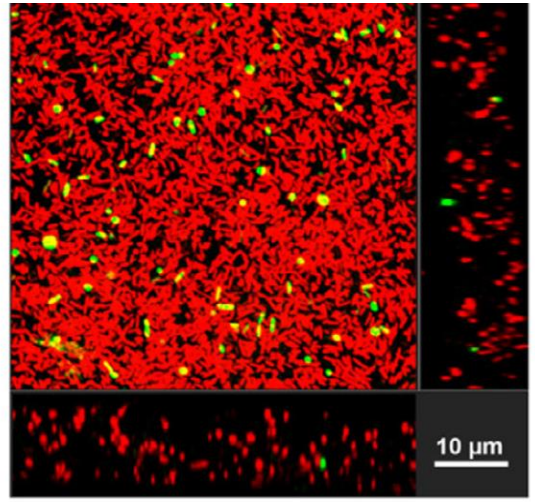
COLISTIN

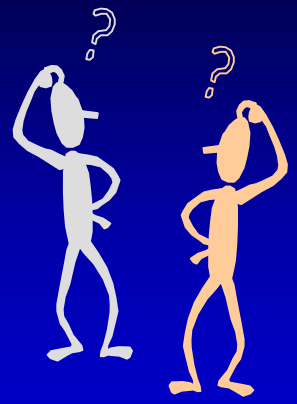


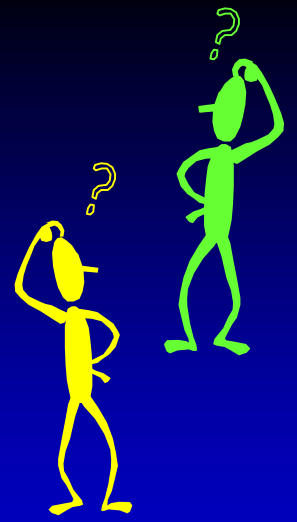
CEFTOLOZANE/TAZOBACTAM



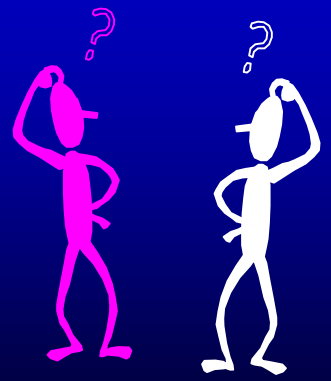
CEFTOLOZANE/TAZOBACTAM plus COLISTIN

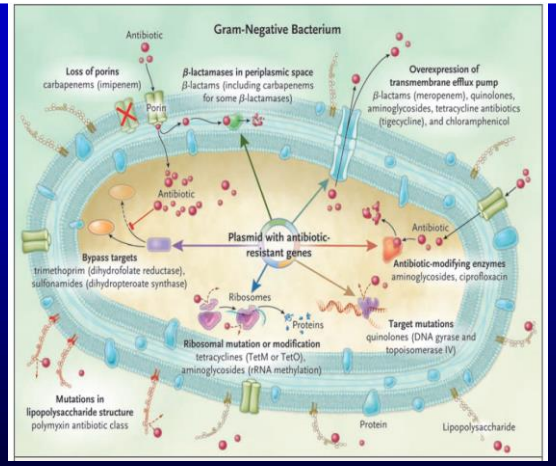


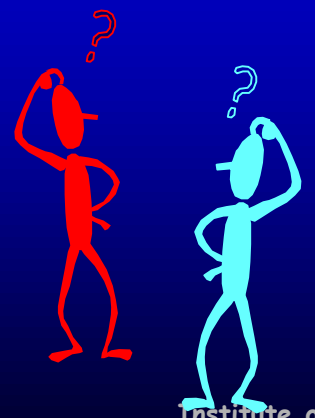




ACTIVITY vs. ESBL+ Enterobacteriaceae?







JAMA. 2018 Sep 11;320(10):984-994. doi: 10.1001/jama.2018.12163.

Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With E coli or Klebsiella pneumoniae Bloodstream Infection and Ceftriaxone Resistance: A Randomized Clinical Trial.

Harris PNA[1,2,3], Tambyah PA[4], Lye DC[5,6,7], Mo Y[4], Lee TH[5,6,7], Yilmaz M[8], Alenazi TH[9], Arabi Y[9], Falcone M[10], Bassetti M[11], Righi E[11], Rogers BA[12,13], Kanj S[14], Bhally H[15], Iredell J[16,17], Mendelson M[18], Boyles TH[18], Looke D[3,19], Miyakis S[20,21,22], Walls G[23], Al Khamis M[24], Zikri A[24], Crowe A[25,26], Ingram P[27,28,29], Daneman N[30], Griffin P[19,31,32], Athan E[33], Lorenc P[1], Baker P[34], Roberts L[35], Beatson SA[35], Peleg AY[36,37,38], Harris-Brown T[1], Paterson DL[1,39], MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN).

⊕ Collaborators (92)

⊕ Author information

Abstract

IMPORTANCE: Extended-spectrum β-lactamases mediate resistance to third-generation cephalosporins (eg, ceftriaxone) in Escherichia coli and Klebsiella pneumoniae. Significant infections caused by these strains are usually treated with carbapenems, potentially selecting for carbapenem resistance. Piperacillin-tazobactam may be an effective "carbapenem-sparing" option to treat extended-spectrum β-lactamase producers.

OBJECTIVES: To determine whether definitive therapy with piperacillin-tazobactam is noninferior to meropenem (a carbapenem) in patients with bloodstream infection caused by ceftriaxone-nonsusceptible E coli or K pneumoniae.

DESIGN, SETTING, AND PARTICIPANTS: Noninferiority, parallel group, randomized clinical trial included hospitalized patients enrolled from 26 sites in 9 countries from February 2014 to July 2017. Adult patients were eligible if they had at least 1 positive blood culture with E coli or Klebsiella spp testing nonsusceptible to ceftriaxone but susceptible to piperacillin-tazobactam. Of 1646 patients screened, 391 were included in the study.

INTERVENTIONS: Patients were randomly assigned 1:1 to intravenous piperacillin-tazobactam, 4.5 g, every 6 hours (n = 188 participants) or meropenem, 1 g, every 8 hours (n = 191 participants) for a minimum of 4 days, up to a maximum of 14 days, with the total duration determined by the treating clinician.

2g tazobactam

MAIN OUTCOMES AND MEASURES: The primary outcome was all-cause mortality at 30 days after randomization. A noninferiority margin of 5% was used.

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

3g tazobactam

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

Pneumonia study recently completed (ClinicalTrials.gov ID: NCT02070757)
IV dose: 3.0g q8h (2g ceftolozane; 1g tazobactam)

ASPECT-NP: a randomized, double-blind, phase III trial comparing efficacy and safety of ceftolozane/tazobactam versus meropenem in patients with ventilated nosocomial pneumonia (VNP)

Per-pathogen clinical cure at TOC in patients with key gram-negative LRT pathogens at baseline

Outcome	C/T n/N (%)	Meropenem n/N (%)	% Treatment Difference (95% CI)[a]
Clinical cure (mITT)	157/259 (60.6%)	137/240 (57.1%)	3.5 (-5.07, 12.08)
Enterobacteriaceae	120/195 (61.5%)	105/185 (56.8%)	4.8 (-5.06, 14.51)
ESBL+ Enterobacteriaceae	48/84 (57.1%)	45/73 (61.6%)	-4.5 (-19.33, 10.74)
Escherichia coli	32/51 (62.7%)	26/42 (61.9%)	0.8 (-18.13, 20.08)
ESBL+ *E. coli*	11/20 (55.0%)	5/10 (50.0%)	5.0 (-28.56, 37.58)
Klebsiella pneumoniae	53/86 (61.6%)	58/91 (63.7%)	-2.1 (-16.08, 11.91)
ESBL+ *K. pneumoniae*	31/53 (58.5%)	34/52 (65.4%)	-6.9 (-24.53, 11.39)
Pseudomonas aeruginosa	36/63 (57.1%)	39/65 (60.0%)	-2.9 (-19.36, 13.84)
MDR	13/24 (54.2%)	6/11 (54.5%)	-0.4 (-31.19, 31.65)
Haemophilus influenzae	19/22 (86.4%)	8/16 (50.0%)	36.4 (6.83, 60.09)
Clinical cure (ME)	85/113 (75.2%)	78/117 (66.7%)	8.6 (-3.19, 19.94)
Enterobacteriaceae	62/83 (74.7%)	58/90 (64.4%)	10.3 (-3.50, 23.36)
ESBL+ Enterobacteriaceae	33/45 (73.3%)	27/39 (69.2%)	4.1 (-14.75, 23.06)
Escherichia coli	17/23 (73.9%)	16/23 (69.9%)	4.3 (-20.86, 28.86)
ESBL+ *E. coli*	8/12 (66.7%)	5/7 (71.4%)	-4.8 (-39.06, 35.78)
Klebsiella pneumoniae	32/42 (76.2%)	33/48 (68.8%)	7.4 (-11.12, 24.91)
ESBL+ *K. pneumoniae*	22/30 (73.3%)	19/27 (70.4%)	3.0 (-19.53, 25.57)
Pseudomonas aeruginosa	23/29 (79.3%)	28/38 (73.7%)	5.6 (-15.40, 24.70)
MDR	9/11 (81.8%)	4/6 (66.7%)	15.2 (-22.67, 54.07)
Haemophilus influenzae	11/12 (91.7%)	4/8 (50.0%)	41.7 (2.39, 70.96)

CI, confidence interval. C/T, ceftolozane/tazobactam. ESBL, extended-spectrum β-lactamase. LRT, lower respiratory tract. MDR, multidrug resistant. ME, microbiologically evaluable. mITT, microbiologic intent-to-treat. N, number of patients in specific population of pathogen or pathogen category. n, number of patients in specific category with favorable outcome. TOC, test-of-cure.
[a]Unstratified Newcombe CIs.

Per-pathogen microbiologic eradication at TOC in patients with key gram-negative LRT pathogens at baseline

Outcome	C/T n/N (%)	Meropenem n/N (%)	% Treatment Difference (95% CI)[a]
Microbiologic eradication[b] (mITT)	189/259 (73.0%)	163/240 (67.9%)	5.1 (-2.93, 13.01)
Enterobacteriaceae	145/195 (74.4%)	129/185 (69.7%)	4.6 (-4.37, 13.58)
ESBL+ Enterobacteriaceae	56/84 (66.7%)	52/73 (71.2%)	-4.6 (-18.56, 9.93)
Escherichia coli	43/51 (84.3%)	33/42 (78.6%)	5.7 (-9.96, 22.08)
ESBL+ *E. coli*	18/20 (90.0%)	8/10 (80.0%)	10.0 (-14.69 , 41.81)
Klebsiella pneumoniae	63/86 (73.3%)	65/91 (71.4%)	1.8 (-11.30, 14.77)
ESBL+ *K. pneumoniae*	33/53 (62.3%)	38/52 (73.1%)	-10.8 (-27.67, 6.99)
Pseudomonas aeruginosa	47/63 (74.6%)	41/65 (63.1%)	11.5 (-4.51, 26.72)
Haemophilus influenzae	20/22 (90.9%)	11/16 (68.8%)	22.2 (-3.19, 47.37)
Microbiologic eradication[b] (ME)	79/113 (69.9%)	73/117 (62.4%)	7.5 (-4.69, 19.38)
Enterobacteriaceae	57/83 (68.7%)	59/90 (65.6%)	3.1 (-10.80, 16.75)
ESBL+ Enterobacteriaceae	30/45 (66.7%)	27/39 (69.2%)	-2.6 (-21.59, 17.14)
Escherichia coli	18/23 (78.3%)	17/23 (73.9%)	4.3 (-19.94, 28.04)
ESBL+ *E. coli*	10/12 (83.3%)	6/7 (85.7%)	-2.4 (-32.86, 36.53)
Klebsiella pneumoniae	30/42 (71.4%)	32/48 (66.7%)	4.8 (-14.23, 22.92)
ESBL+ *K. pneumoniae*	20/30 (66.7%)	18/27 (66.7%)	0.0 (-23.15, 23.54)
Pseudomonas aeruginosa	23/29 (79.3%)	21/38 (55.3%)	24.0 (1.11, 43.01)
Haemophilus influenzae	11/12 (91.7%)	4/8 (50.0%)	41.7 (2.39, 70.96)

CI, confidence interval. C/T, ceftolozane/tazobactam. ESBL, extended-spectrum β-lactamase. LRT, lower respiratory tract. ME, microbiologically evaluable. mITT, microbiologic intent-to-treat. N, number of patients in specific population of pathogen or pathogen category. n, number of patients in specific category with favorable outcome. TOC, test-of-cure.
[a]Unstratified Newcombe CIs.[b]Includes patients with presumed eradication.

29th ECCMID Amsterdam, Netherlands 13 – 16 April 2019
The congress of ESCMID

P1917 ASPECT-NP: a randomized, double-blind, phase III trial comparing efficacy and safety of ceftolozane/tazobactam versus meropenem in patients with ventilated nosocomial pneumonia (VNP)

Marin Kollef*[1], Martin Novácek[2], Ülo Kivistik[3], Álvaro Réa-Neto[4], Nobuaki Shime[5], Ignacio Martin-Loeches[6], Jean-François Timsit[7], Richard G Wunderink[8], Christopher J. Bruno[9], Jennifer A. Huntington[9], Gina Lin[9], Brian Yu[9], Joan Butterton[9], Elizabeth G. Rhee[9]

Results: Overall, 726 patients were randomized (362 ceftolozane/tazobactam, 364 meropenem) into the ITT population. Most (72%) had VABP, 44% were ≥65 years old, 33% had APACHE-II scores ≥20, 14% had creatinine clearance ≤50 mL/min and 18% ≥150 mL/min, and 13% failed prior antibacterial therapy for VNP. Prior to randomization, 77% had been hospitalized for ≥5 days and 49% ventilated for ≥5 days. Baseline characteristics were balanced between treatment arms. In patients with positive baseline LRT cultures (70%), causative gram-negative pathogens were mainly Enterobacteriaceae (74%) and *P. aeruginosa* (25%). Ceftolozane/tazobactam was non-inferior to meropenem for the primary and key secondary endpoints (Table); mortality was highest in meropenem-treated patients with vHABP. Adverse events deemed drug-related by the investigator (DRAEs) occurred in 11% of ceftolozane/tazobactam and 8% of meropenem patients; 2% and 1%, respectively, experienced serious DRAEs. DRAEs leading to study drug discontinuation occurred in 1% of patients per arm.

CEFTAZIDIME-AVIBACTAM vs. CARBAPENEMS FOR THE TREATMENT OF INFECTIONS CAUSED BY Enterobacteriaceae: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Che H et al. *Int J Antimicrob Agents* 2019 Sep 15 online published

BASIC CHARACTERISTICS OF INCLUDED RCTS

Author/ ear	Primary infections	BSI or not (sample size)	Organism	Phenotype of resistance	β-Lactamase	Sample		Mean age (years)		Treatment regimen		Outcomes
						β	C	β	C	β	C	
Vagenleh er 016[10]	Urinary tract infection	NA	*Enterobacteriaceae* Non- *Enterobacteriaceae*(4.8%*)	NA	NA	393	417	51.4	53.3	CAZ-AVI	doripenem	b c d e
Carmeli 016[9]	Complicated urinary tract infection	BSI (10) Non-BSI (271)	*Enterobacteriaceae* Non-*Enterobacteriaceae* (6.8%*)	Ceftazidime-resistant	NA	144	137	64.3	61.3	2000 mg ceftazidime plus 500 mg avibactam q8h iv	doripenem 11 ertapenem 1 ertapenem sodium 2 imipenem 76 meropenem 57 other 6	a b c d
Vazquez 012[11]	Acute pyelonephritis / complicated urinary tract infection	BSI (7) Non-BSI (128)	*E. coli* *E. cloacae* *P. mirabilis* *C. koseri* Non-*Enterobacteriaceae* (1.5%*)	NA	NA	46	49	46.4	48.2	ceftazidime 500 mg plus avibactam 125 mg q8h iv	imipenem-cilastatin 500 mg q6h iv	b c d e

Note: β, BL/BLIs; C, carbapenem; a, mortality; b, clinical success; c, microbiological success; d, AEs; e, SAEs; iv, intravenous injection; NA, not available; * Proportion of people infected with non-*Enterobacteriaceae*.

CEFTAZIDIME-AVIBACTAM vs. CARBAPENEMS FOR THE TREATMENT OF INFECTIONS CAUSED BY Enterobacteriaceae: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Che H et al. *Int J Antimicrob Agents* 2019 Sep 15 online published

FOREST OF EFFICACY OUTCOMES IN A RANDOM-EFFECTS MODEL

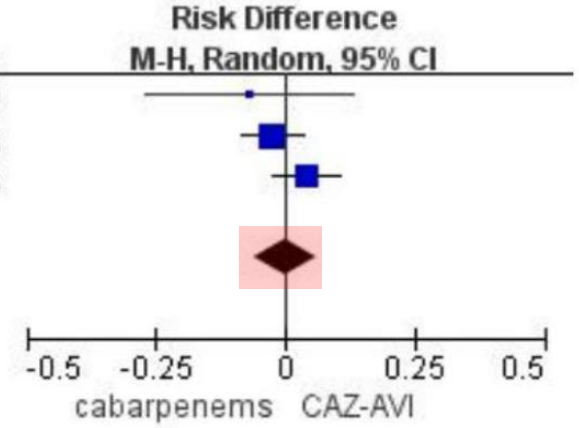
CLINICAL SUCCESS

a

Study or Subgroup	CAZ-AVI Events	Total	carbapenems Events	Total	Weight	Risk Difference M-H, Random, 95% CI	Year
Vazquez 2012	24	46	29	49	7.9%	-0.07 [-0.27, 0.13]	2012
Carmeli 2016	132	144	129	137	47.7%	-0.02 [-0.08, 0.03]	2016
Wagenlehner 2016	276	393	276	417	44.4%	0.04 [-0.02, 0.10]	2016
Total (95% CI)		**583**		**603**	**100.0%**	**0.00 [-0.06, 0.06]**	
Total events	432		434				

Heterogeneity: Tau² = 0.00; Chi² = 3.08, df = 2 (P = 0.21); I² = 35%

Test for overall effect: Z = 0.02 (P = 0.99)



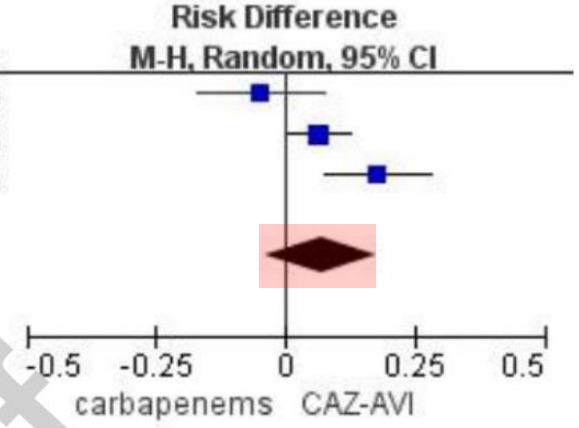
MICROBIOLOGICAL SUCCESS

b

Study or Subgroup	CAZ-AVI Events	Total	carbapenems Events	Total	Weight	Risk Difference M-H, Random, 95% CI	Year
Vazquez 2012	40	46	45	49	28.3%	-0.05 [-0.17, 0.08]	2012
Wagenlehner 2016	304	393	296	417	39.6%	0.06 [0.00, 0.12]	2016
Carmeli 2016	118	144	88	137	32.1%	0.18 [0.08, 0.28]	2016
Total (95% CI)		**583**		**603**	**100.0%**	**0.07 [-0.04, 0.18]**	
Total events	462		429				

Heterogeneity: Tau² = 0.01; Chi² = 7.97, df = 2 (P = 0.02); I² = 75%

Test for overall effect: Z = 1.24 (P = 0.21)



COMPARATIVE ACTIVITIES OF CEFTAZIDIME-AVIBACTAM AND CEFTOLOZANE-TAZOBACTAM AGAINST ENTEROBACTERIACEAE ISOLATES PRODUCING ESBL FROM U.S. HOSPITALS

Castanehira M et al. *Antimicrob Agents Chemother* 2019 Jun 24; 63(7) pii: e00160-19

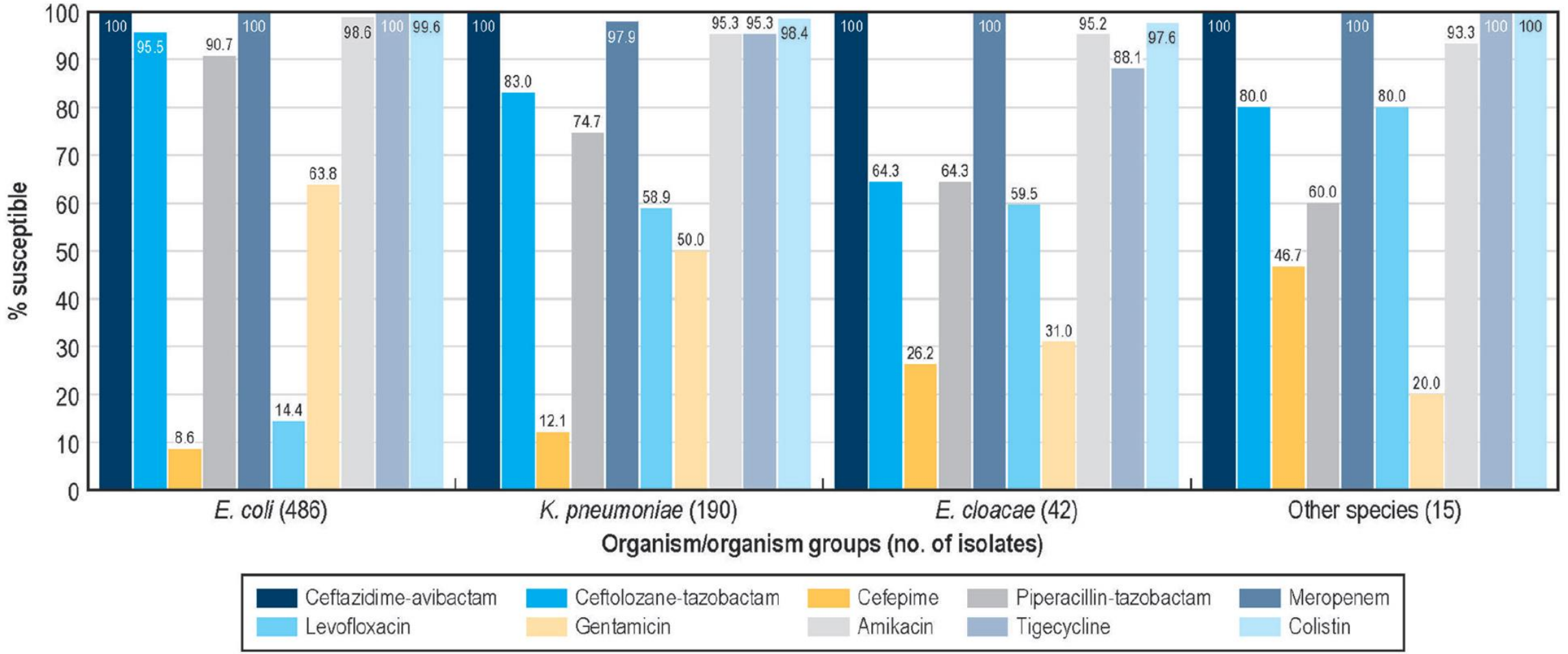
ACTIVITIES OF CEFTAZIDIME-AVIBACTAM, CEFTOLOZANE-TAZOBACTAM, AND COMPARATORS TESTED AGAINST 733 Enterobacteriaceae ISOLATES CARRYING ESBL GENES

	MIC (mg/liter)			CLSI[a]		EUCAST	
Antimicrobial agent	50%	90%	Range	%S	%R	%S	%R
All isolates carrying ESBLs (*n* = 733)							
Ceftazidime-avibactam	0.25	0.5	≤0.015 to 4	100.0	0.0	100.0	0.0
Ceftolozane-tazobactam	0.5	2	≤0.12 to >16	90.2	7.3	83.9	16.1
Ceftazidime	16	>32	0.25 to >32	19.9	67.1	4.5	80.1
Aztreonam	>16	>16	0.5 to >16	10.5	78.7	1.0	89.5
Ceftriaxone	>8	>8	1 to >8	0.1	98.9	0.1	98.9
Cefepime	>16	>16	≤0.12 to >16	11.3	71.2[b]	5.7	80.9
Piperacillin-tazobactam	4	64	0.25 to >128	84.4	7.6	71.2	15.6
Meropenem	0.03	0.06	≤0.015 to 2	99.5	0.0	100.0	0.0
Levofloxacin	8	>16	≤0.03 to >16	29.9	65.9	21.3	72.9
Gentamicin	1	>16	≤0.12 to >16	57.4	40.1	56.2	42.6
Amikacin	2	8	0.5 to >32	97.4	0.7	93.2	2.6
Trimethoprim-sulfamethoxazole	>8	>8	≤0.5 to >8	27.8	72.2	27.8	71.5
Tigecycline	0.25	1	≤0.06 to 8	98.1	0.1[c]	95.8	1.9
Colistin	0.12	0.25	≤0.06 to >8	99.2[d]		99.2	0.8

COMPARATIVE ACTIVITIES OF CEFTAZIDIME-AVIBACTAM AND CEFTOLOZANE-TAZOBACTAM AGAINST ENTEROBACTERIACEAE ISOLATES PRODUCING ESBL FROM U.S. HOSPITALS

Castanehira M et al. *Antimicrob Agents Chemother* 2019 Jun 24; 63(7) pii: e00160-19

ACTIVITIES OF CEFTAZIDIME-AVIBACTAM, CEFTOLOZANE-TAZOBACTAM, AND COMPARATOR AGENTS USING CLSI BREAKPOINTS AGAINST BACTERIAL SPECIES CARRYING ESBL GENES



NOVEL β-LACTAM-β-LACTAMASE INHIBITOR COMBINATIONS: EXPECTATIONS FOR THE TREATMENT OF CARBAPENEM-RESISTANT GRAM-NEGATIVE PATHOGENS

Karaiskos I et al. *Expert Opin Drug Metab Toxicol* 2019 Feb; 15(2): 133-149

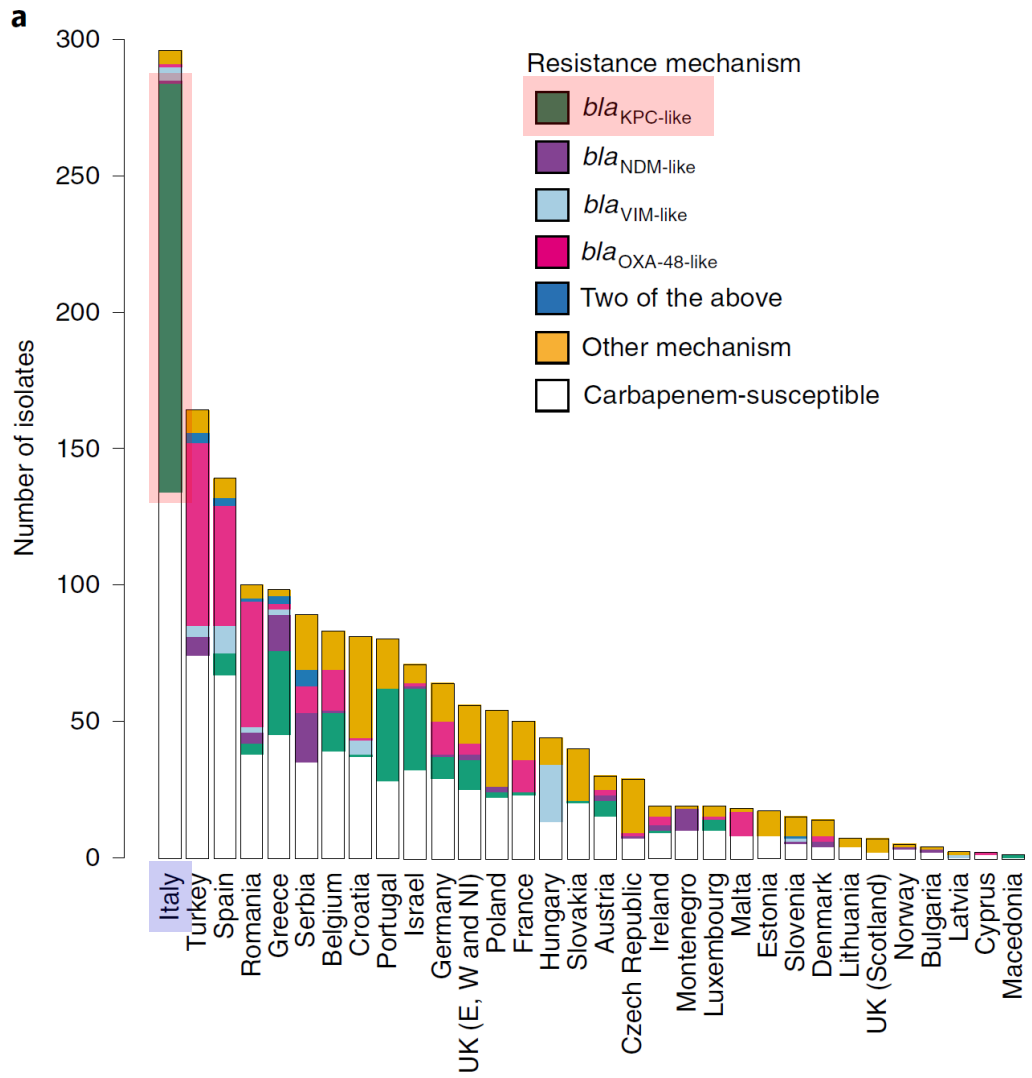
NOVEL B-LACTAMASE INHIBITORS AGAINST CARBAPENEM-RESISTANT *Enterobacteriaceae* (CRE) AND MULTIDRUG-RESISTANT (MDR) GRAM NEGATIVE BACTERIA

Antibiotic	Spectrum	Clinical Development program (since 2018)	Dosage
Ceftazidime-Avibactam	Activity against: Enterobacteriaceae and *P. aeruginosa* producing ESBL, KPC, AmpC and some class D enzymes (OXA-10, OXA-48) No active against MBL, Acinetobacter spp, and less activity against anaerobes	Approved in 2015 in U.S.A and in 2016 in Europe	CrCl >50: 2.5g q8h CrCl: 31–50: 1.25g q8h CrCl: 10–30: 0.94 g q12h CrCl <10: 0.94g q48h Hemodialysis:0.94 g q48h (administer after hemodialysis session) CVVH:1.25g q8h All doses administered over 2 hours
Meropenem-Vaborbactam	Activity against: Enterobacteriaceae producing ESBL, KPC, AmpC. No active against OXA-48-like, or MBL. As active as meropenem alone against *P. aeruginosa, Acinetobacter* spp., and *S. maltophilia*	Approved in 2017 in U.S.A	CrCl >50: 2g q8h CrCl: 30–49: 2g q8h CrCl: 15–29: 2g q12h CrCl <15: 1g q12h Hemodialysis: 1g q12h (administer after hemodialysis session) All doses administered over 3 hours
Aztreonam-Avibactam	Activity against: Enterobacteriaceae producing ESBL, KPC, AmpC, OXA-48 and MBL. As active as Aztreonam alone against *P. aeruginosa* and A. *baumannii*, including MBL-producing isolates	Phase 3	CrCl > 50: ATM 6g/AVI 2g CrCl: 31–50: ATM 3g/AVI 1 g CrCl:16–30: ATM 2025 mg/AVI 675 mg
Imipenem/cilastatin-Relebactam	Activity against: Enterobacteriaceae and *P. aeruginosa* producing ESBL, KPC, AmpC and porin mutations. Diminished inhibitor activity against OXA-48. No activity against MBL and *A. baumannii*	Phase 3	IMI-REL 200/100 mg to 500/250 mg, depending on renal function, q6h All doses administrated as a 30-minute infusion
Ceftaroline fosamil-Avibactam	Activity against: Enterobacteriaceae producing ESBL, KPC, Amp C and some class D enzymes (OXA-like). No activity against MBL. No activity against A. *baumannii* or *P. aeruginosa*.	Phase 2	CPT 600 mg/AVI 600 mg q8h or q12h is under investigation
Cefepime-Zidebactam	Activity against Enterobacteriaceae and *P. aeruginosa* producing ESBL, KPC, AmpC and MBL	Phase 2	N/A
Meropenem-Nacubactam	Activity against class A and class C β-lactamases	Phase 1	N/A

EPIDEMIC OF CARBAPENEM-RESISTANT *K pneumoniae* IN EUROPE IS DRIVEN BY NOSOCOMIAL SPREAD

David S et al. *Nat Microbiol* 2019 Jul 29 Epub ahead of print

GEOGRAPHICAL DISTRIBUTION OF CARBAPENEM RESISTANCE MECHANISMS AMONG ISOLATES SUBMITTED DURING THE EuSCAPE SURVEY



EPIDEMIC OF CARBAPENEM-RESISTANT *K pneumoniae* IN EUROPE IS DRIVEN BY NOSOCOMIAL SPREAD

David S et al. *Nat Microbiol* 2019 Jul 29 Epub ahead of print

DISTRIBUTION OF MIC VALUES AMONG 1,518 RETESTED K. PNEUMONIAE SENSU STRICTO ISOLATES WITH DIFFERENT B-LACTAM RESISTANCE DETERMINANTS