13° CONGRESSO NAZIONALE SITA
Società Italiana di Terapia Antinfettiva Antibatterica Antivirale Antifungina

RUOLO DELLA PK/PD DEI NUOVI FARMACI ANTIBATTERICI NELLA REAL LIFE

FEDERICO PEA

DIPARTIMENTO DI SCIENZE MEDICHE E CHIRURGICHE, ALMA MATER STUDIORUM, UNIVERSITA' DI BOLOGNA

SSD FARMACOLOGIA CLINICA, AZIENDA OSPEDALIERO UNIVERSITARIA DI BOLOGNA

PADOVA | 23-24 novembre 2023

DISCLOSURES OF INTEREST

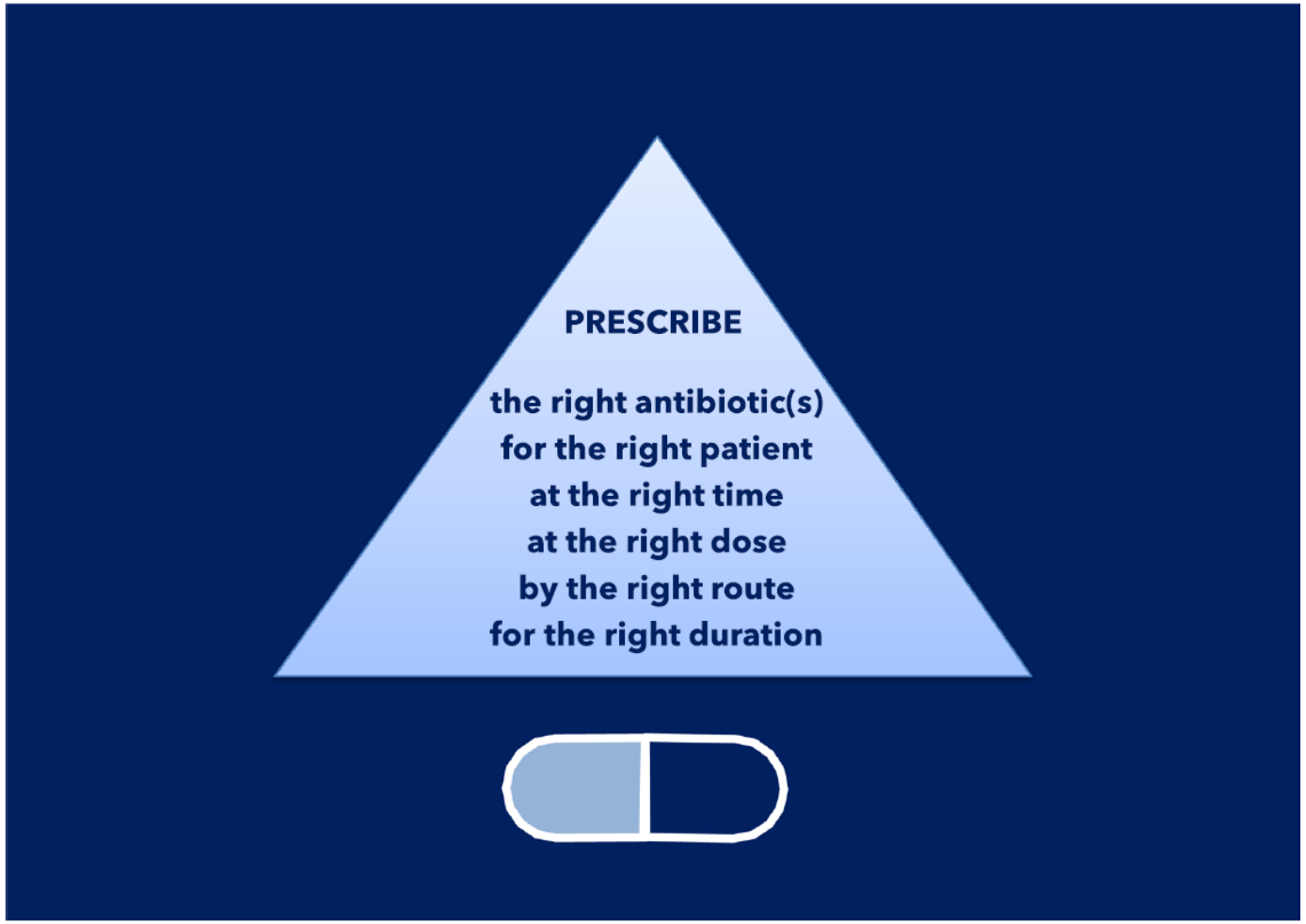
- Speaker's bureau: Advanz Pharma, Angelini, BeiGene, Gilead, InfectoPharm, Menarini, MSD, Pfizer, Shionogi
- Consultant: Advanz Pharma, Angelini, BeiGene, bioMerieux, Gilead, MSD, Pfizer, Shionogi

TEN GOLDEN RULES FOR OPTIMAL ANTIBIOTIC USE IN HOSPITAL SETTINGS: THE WARNING CALL TO ACTION

Worldwide Antimicrobial Resistance National/International Network Group (WARNING) Collaborators

World J Emerg Surg 2023 Oct 16; 18(1):50. doi: 10.1186/s13017-023-00518-3

SELECTING THE MOST APPROPRIATE ANTIBIOTIC(S) FOR A SPECIFIC PATIENT



› Antimicrob Agents Chemother. 2018 Apr 26;62(5):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

Ryan K Shields [1 2], M Hong Nguyen [3 2], Liang Chen [4], Ellen G Press [1], Barry N Kreiswirth [4], Cornelius J Clancy [1 2 5]

DOSING ADJUSTMENTS OF NOVEL BL AND/OR BL/BLIS IN RENAL PATIENTS RETRIEVED FROM SUMMARY OF PRODUCT CHARACTERISTICS AND PIVOTAL TRIALS

BL and/or BL/BLIs	PK/PD target adopted in pivotal trials	Dosing adjustments in patients with various classes of renal function (CLCr in mL/min)
Cefiderocol	75% $fT_{>MIC}$	CLCr ≥ 120: 2 g every 6 h CLCr 60–120: 2 g every 8 h CLCr 30–59: 1.5 g every 8 h CLCr 15–29: 1 g every 8 h CLCr< 15/IHD: 0.75 g every 12 h
Ceftazidime-Avibactam	50% $fT_{>MIC}$	CLCr> 50: 2.5 g every 8 h CLCr 31–50: 1.25 g every 8 h CLCr 16–30: 0.9375 g every 12 h CLCr 6–15: 0.9375 g every 24 h CLCr ≤ 5/IHD: 0.9375 g every 48 h
Ceftolozane-Tazobactam	30% $fT_{>MIC}$	CLCr> 50: 3.0*/1.5 g every 8 h CLCr 30–50: 1.5*/0.75 g every 8 h CLCr 15–29: 0.75*/0.375 g every 8 h CLCr< 15/IHD: LD 1.5*/0.75 g → MD 0.30*/0.15 g every 8 h
Imipenem-Relebactam	40% $fT_{>MIC}$	CLCr 90–150: 1.25 g every 6 h CLCr 60–89: 1 g every 6 h CLCr 30–59: 750 mg every 6 h CLCr 15–29: 500 mg every 6 h IHD: 500 mg every 6 h CLCr< 15 and not IHD: should not be administered
Meropenem-Vaborbactam	45% $fT_{>MIC}$	sCLCr≥ 40: 4 g every 8 h CLCr 20–39: 2 g every 8 h CLCr 10–19: 2 g every 12 h CLCr< 10: 1 g every 12 h

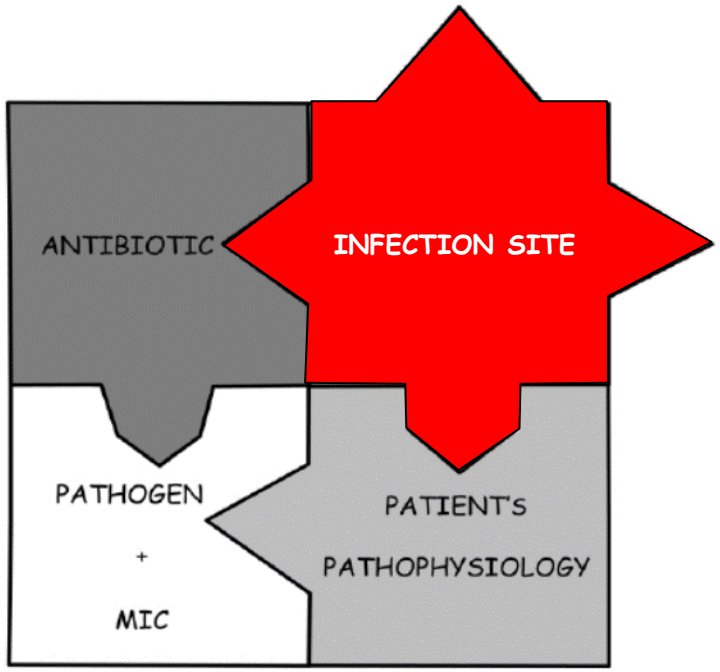
* The doubled dose is indicated for nosocomial pneumonia including ventilator-associated pneumonia
** Dosing schedule predicted on the basis of the CL_{CRRT} of cefepime, according to the principle of similar PK features shared by cefepime and cefiderocol in terms of molecular weight and protein binding
ARC: augmented renal clearance; CVVH: continuous veno-venous haemofiltration; CVVHD: continuous veno-venous hemodialysis; CVVHDF: continuous veno-venous haemodiafiltration; CRRT: continuous renal replacement therapy; IHD: intermittent hemodialysis LD: loading dose; MD: maintenance dose; PK/PD: pharmacokinetic/pharmacodynamic.

Gatti M and Pea F. *Expert Rev Clin Pharmacol* 2021 May;14(5):583-599

THE ANTIMICROBIAL THERAPY PUZZLE:

COULD PK/PD RELATIONSHIPS BE HELPFUL IN ADDRESSING THE ISSUE OF APPROPRIATE PNEUMONIA TREATMENT IN THE CRITICALLY ILL PATIENTS ?

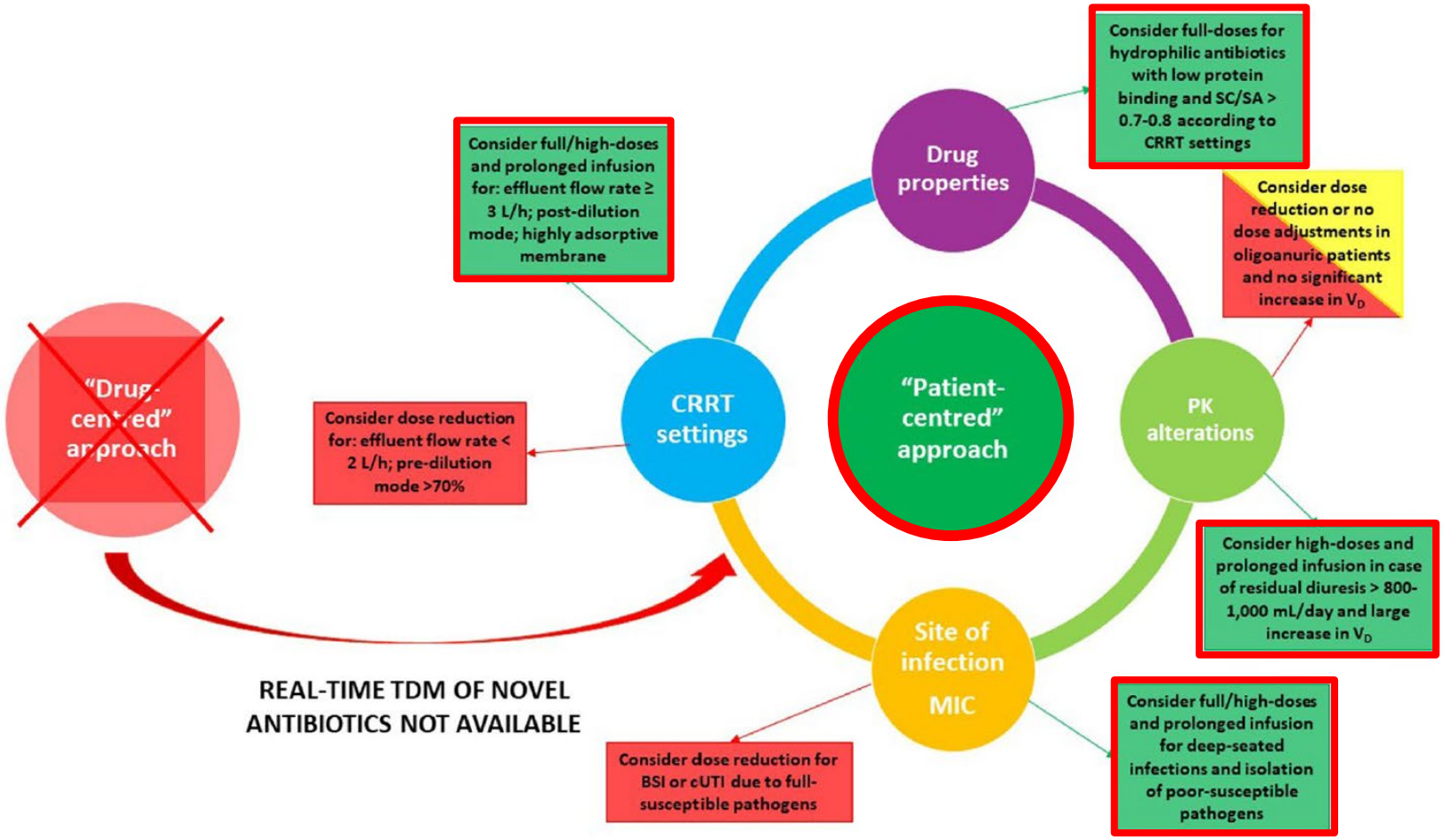
Pea F and Viale P. *Clin Infect Dis* 2006; 42: 1764-1771



HYDROPHILIC ANTIMICROBIALS

Overall, the lower ELF concentrations and ELF-to-plasma ratios exhibited by the hydrophilic antimicrobials seem to support the hypothesis that dosages higher than needed for the treatment of bacteriemia should be advisable when treating pneumonia with these agents in order to ensure optimal pharmacodynamic exposure at the infection site.

'PATIENT-CENTRED' APPROACH FOR DOSING ADJUSTMENT OF NOVEL ANTIBIOTICS IN CRITICALLY ILL PATIENTS DURING CONTINUOUS RENAL REPLACEMENT THERAPY

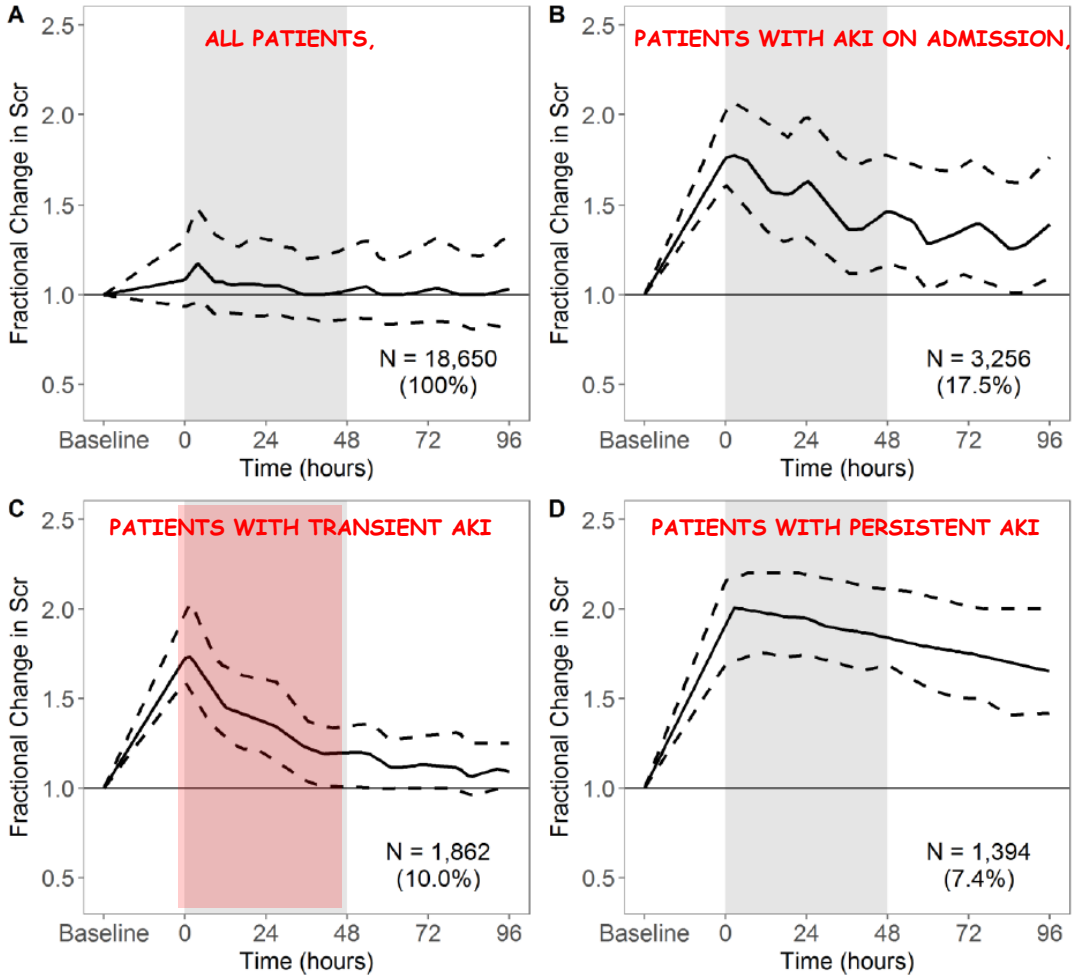


Gatti M and Pea F. *Clin Pharmacokinet* 2021 Oct; 60(10): 1271-1289

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 (N = 18,650)



- 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.

WEIGHING THE ODDS: NOVEL B-LACTAM/B-LACTAMASE INHIBITOR USE IN HOSPITAL-ACQUIRED AND VENTILATOR-ASSOCIATED *P. aeruginosa* PNEUMONIA FOR PATIENTS WHO ARE MORBIDLY OBESE

Kunz Coyne AJ et al. *Open Forum Infect Dis* 2023 Aug 28; 10(9): ofad454

PATIENTS CHARACTERISTICS AND TREATMENT

- 285 patients with HABP (61.4%) and/or VABP (56.1%) were enrolled (morbidly obese, n = 95; non-morbidly obese, n = 190)
- Ceftolozane/tazobactam 170 (59.6%), Ceftazidime/avibactam 73 (25.6%), Meropenem/vaborbactam 42 (14.7%)

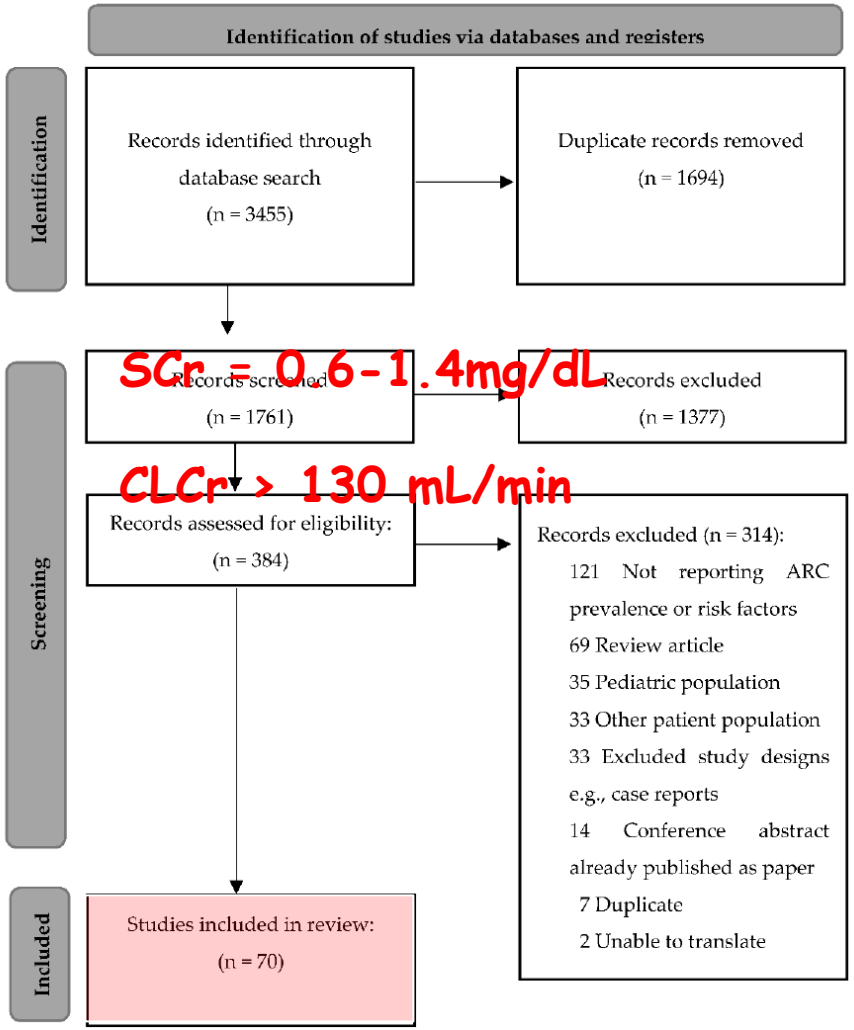
MULTIVARIABLE LOGISTIC REGRESSION MODEL OF PREDICTORS FOR PRESUMED TREATMENT FAILURE

Predictor[a]	aOR	95% CI
Morbid obesity (BMI ≥35 mg/kg^2)	**1.06**	**1.02–1.79**
Time to BL/BLI therapy	**1.47**	**1.28–2.66**
Renal dose-adjusted BL/BLI in the first 48 h of therapy [b]	**1.12**	**1.09–1.75**
CRRT during BL/BLI therapy	**1.35**	**1.06–1.49**
Concomitant antipseudomonal therapy [c]	0.78	.22–1.68

PREVALENCE AND RISK FACTORS OF AUGMENTED RENAL CLEARANCE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Hefny F et al. *Pharmaceutics* 2022; 14: 445

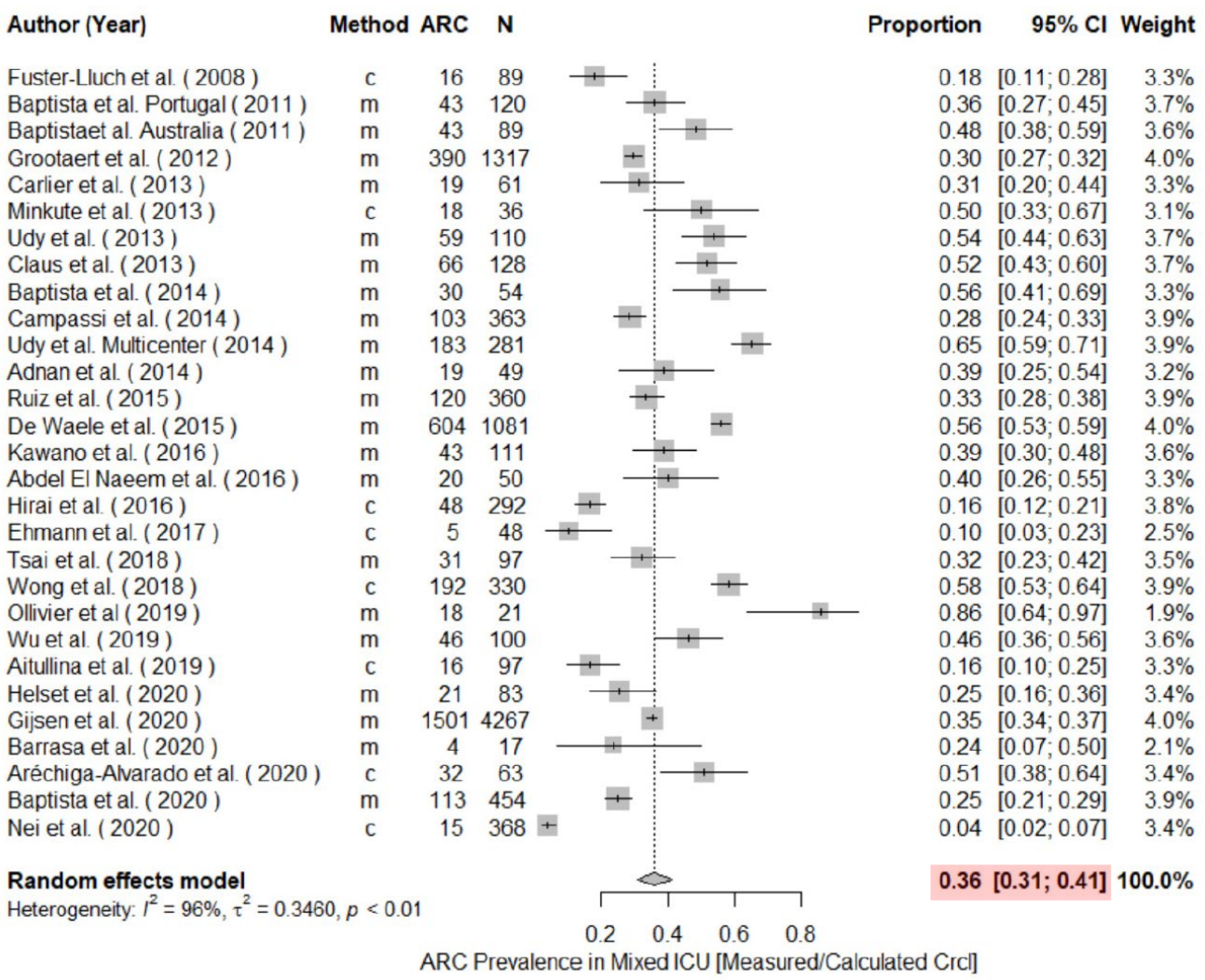
FLOW CHART OF THE STUDY SEARCH AND SCREENING



PREVALENCE AND RISK FACTORS OF AUGMENTED RENAL CLEARANCE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Hefny F et al. *Pharmaceutics* 2022; 14: 445

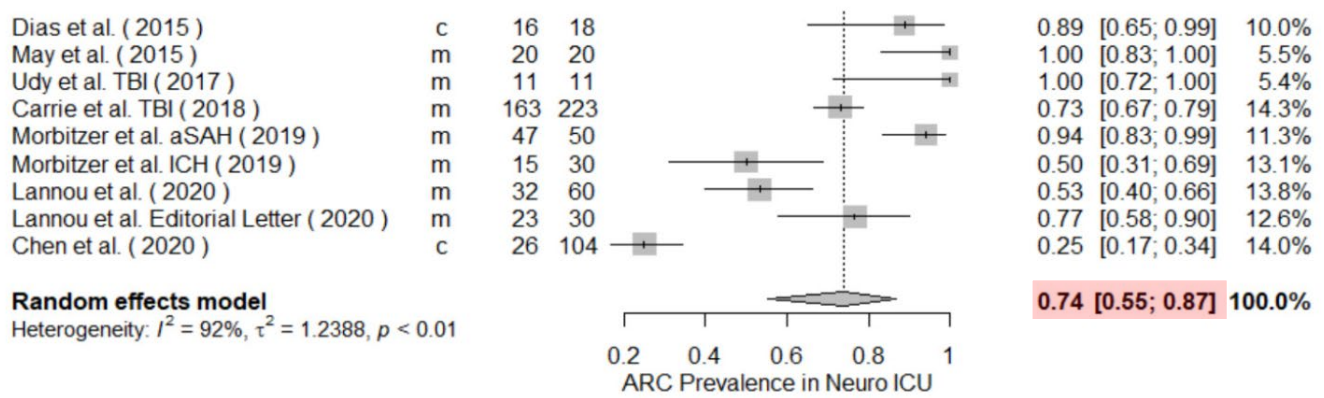
FOREST PLOT OF THE PREVALENCE OF ARC IN MIXED ICU POPULATION (N = 29)



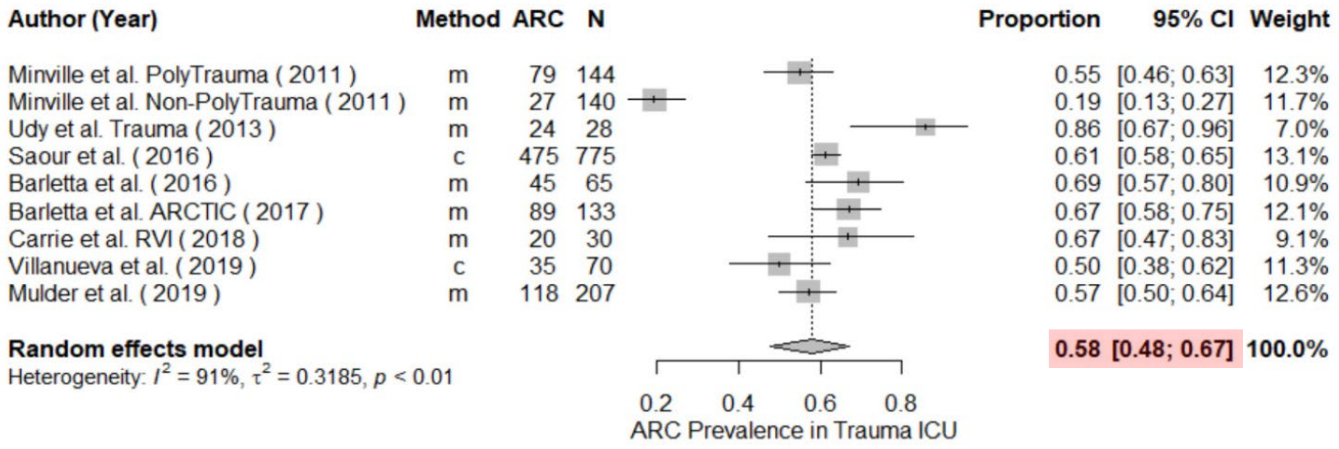
PREVALENCE AND RISK FACTORS OF AUGMENTED RENAL CLEARANCE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Hefny F et al. *Pharmaceutics* 2022; 14: 445

FOREST PLOT OF THE PREVALENCE OF ARC IN NEURO ICU POPULATION (N = 9)



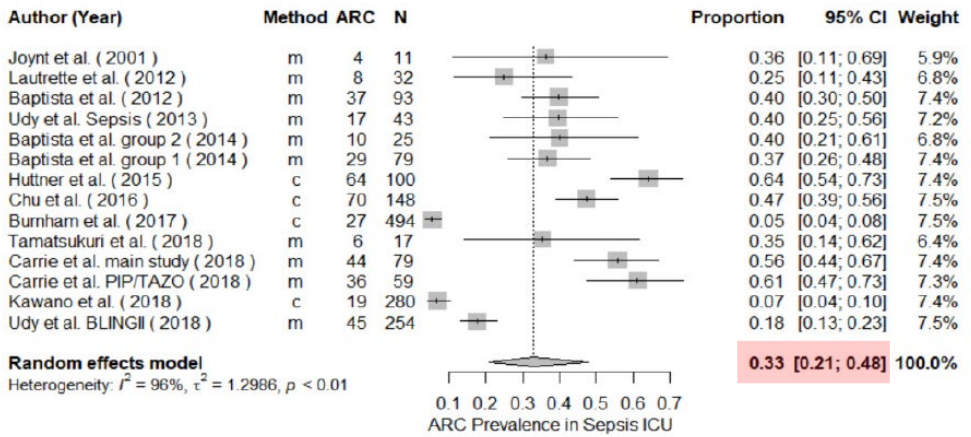
FOREST PLOT OF THE PREVALENCE OF ARC IN TRAUMA ICU POPULATION (N = 9)



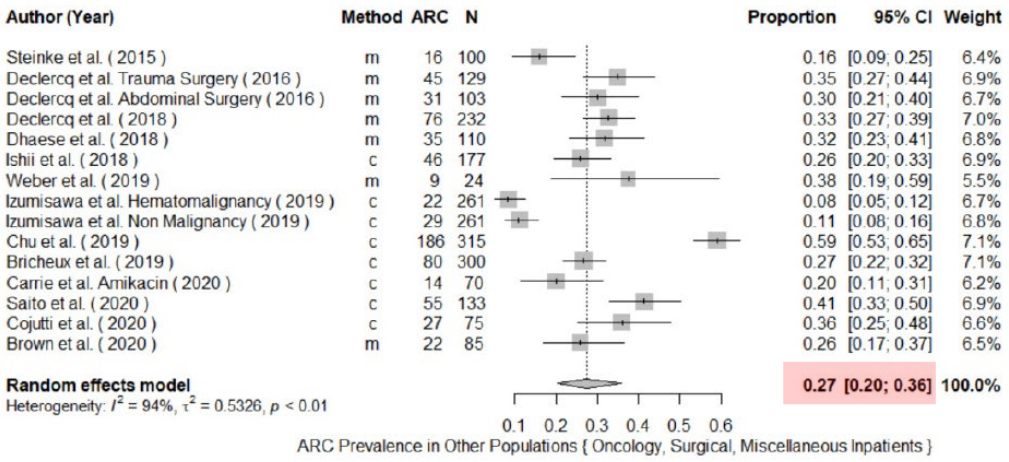
PREVALENCE AND RISK FACTORS OF AUGMENTED RENAL CLEARANCE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Hefny F et al. *Pharmaceutics* 2022; 14: 445

FOREST PLOT OF THE PREVALENCE OF ARC IN SEPSIS ICU POPULATION (N = 14)



FOREST PLOT OF THE PREVALENCE OF ARC IN OTHER POPULATIONS (N = 15)



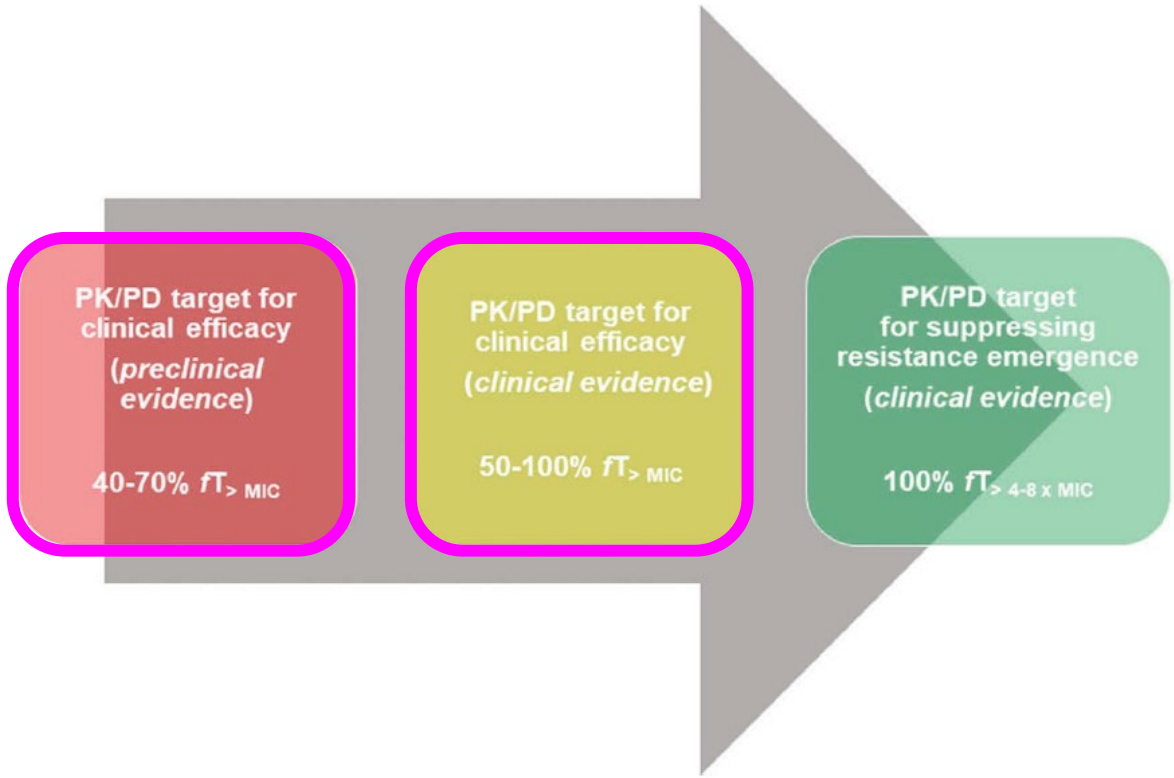
PREVALENCE AND RISK FACTORS OF AUGMENTED RENAL CLEARANCE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Hefny F et al. *Pharmaceutics* 2022; 14: 445

CONCLUSION

- ARC is a prevalent phenomenon in critically ill patients especially neurocritical care and trauma ICU population
- Young age, male sex, and trauma are risk factors for ARC in those with apparently normal renal function
- The estimation of CrCl using mathematical estimates of GFR grossly underestimates the prevalence of ARC in the critical care setting
- therefore measured CrCl through urine collections is prudent

'PARADIGM SHIFT IN THE CONCEPT OF DESIRED PK/PD TARGET ATTAINMENT WITH BETA-LACTAMS



Gatti M and Pea F. *Expert Rev Anti Infect Ther* 2023 Jan 31: 1-18

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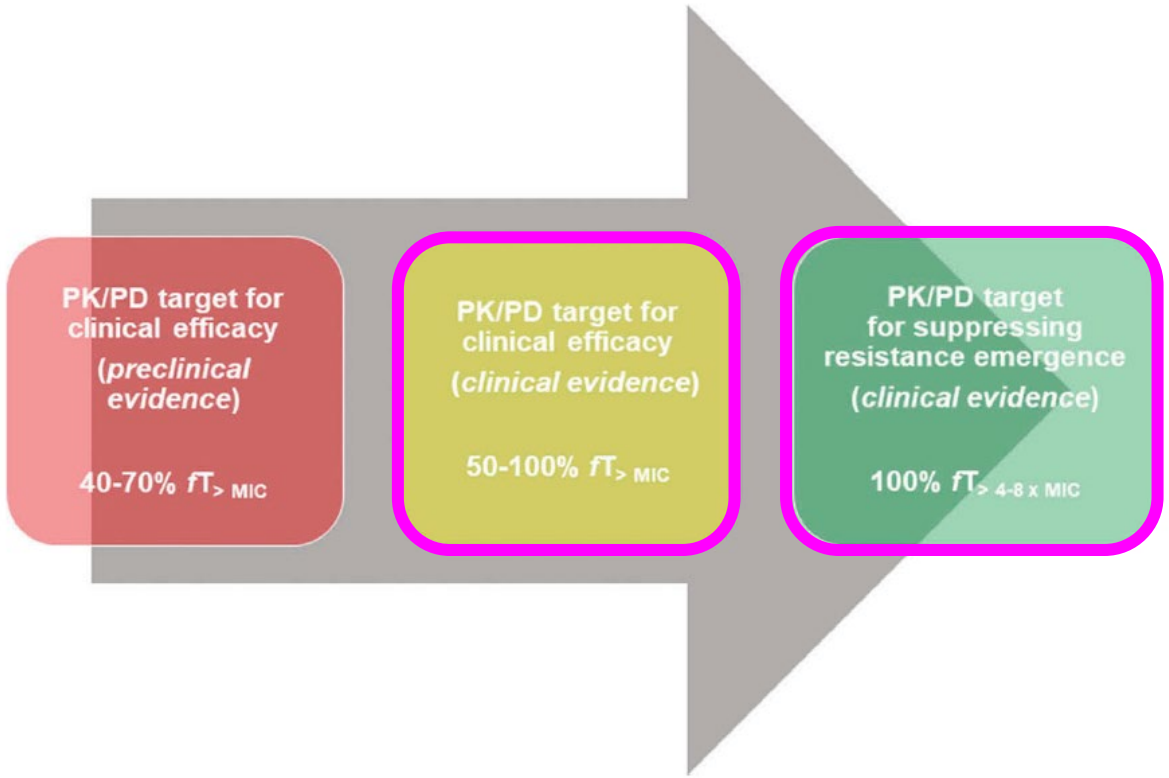
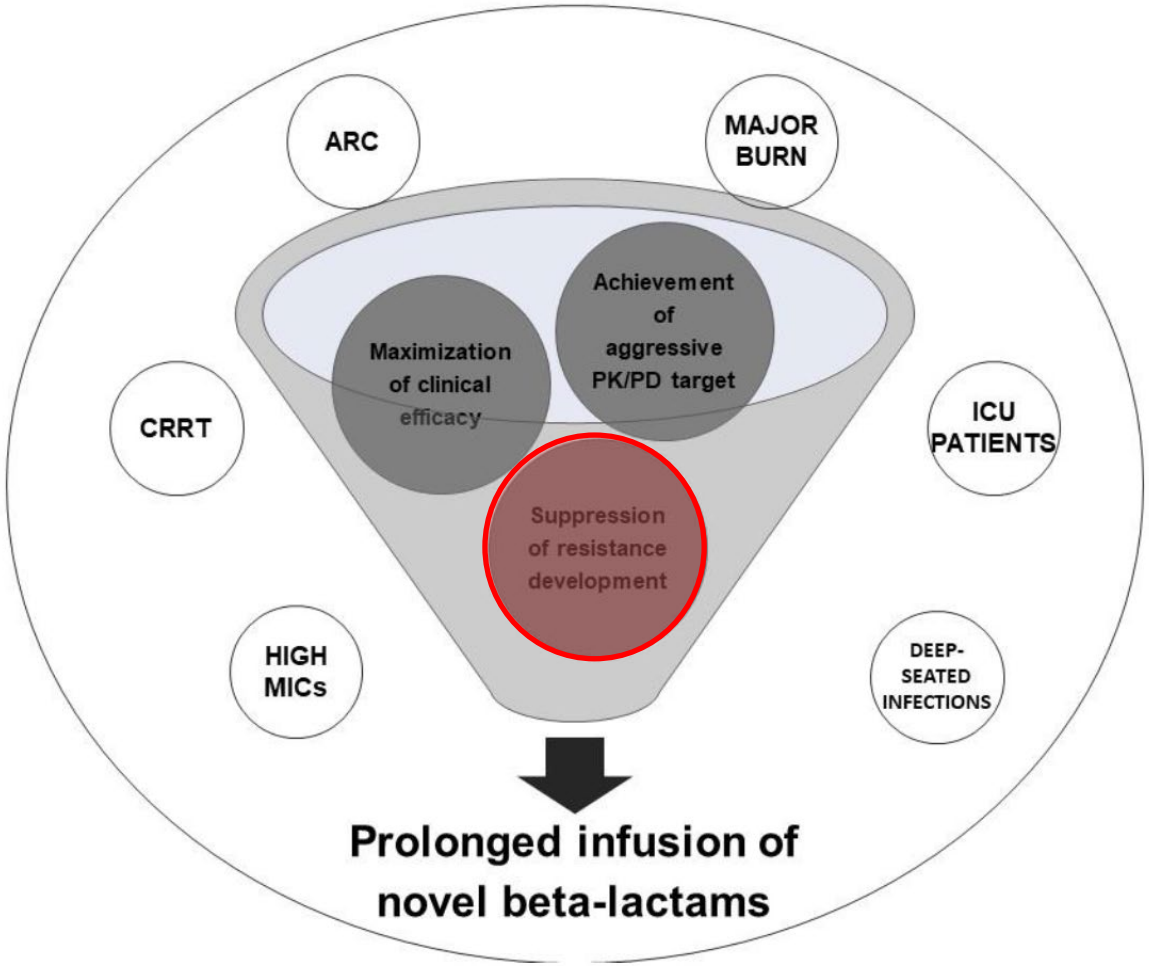


Gatti M and Pea F. *Expert Rev Anti Infect Ther* 2023 Jan 31: 1-18

RATIONALE FOR ADMINISTERING NOVEL BETA-LACTAMS BY PROLONGED INFUSION IN CHALLENGING CLINICAL SCENARIOS



Gatti M and Pea F. *Curr Opin Infect Dis.* 2021 Dec; 34(6): 737-747

A DESCRIPTIVE CASE SERIES OF PK/PD TARGET ATTAINMENT AND MICROBIOLOGICAL OUTCOME IN CRITICALLY ILL PATIENTS WITH DOCUMENTED SEVERE XDR *Acinetobacter baumannii* BSI AND/OR VAP TREATED WITH CEFIDEROCOL

Gatti M, Bartoletti M, Cojutti PG, Gaibani P, Conti M, Giannella M, Viale P, Pea F

J Glob Antimicrob Resist 2021 Dec; 27: 294-29

DEMOGRAPHIC AND CLINICAL FEATURES OF CRITICALLY ILL PATIENTS AFFECTED BY XDR *Acinetobacter baumannii* INFECTIONS RECEIVING CEFIDEROCOL

ID	Age/sex	BMI (kg/m^2)	Type of infection (bacterial load in BAL)	Cefiderocol MIC (mg/L)	Cefiderocol dosage (infused over 3 h)	fC_{min}/MIC [a]	Antibiotic co-treatment	CRRT/ECMO	ME BSI	ME VAP	30-day mortality
#1	55/F	27.1	BSI + VAP ($>10^6$)	0.5	1.5 g q8h	26.71	No	ECMO	Yes	No ($>10^6$)	No
#2	57/M	24.5	BSI	0.5	2 g q8h	3.11	No	ECMO	Yes	NA	Yes
#3	15/M	27.8	VAP ($>10^6$)	1	2 g q8h	6.89	No		NA	No ($>10^6$)	No
#4	75/F	32.7	BSI + VAP ($>10^6$)	0.5	2 g q8h	5.38		ECMO + CVVHDF CVVHDF	Yes	Yes	Yes
#5	54/M	31.6	BSI + VAP ($>10^5$)	1	2 g q8h	0.59	Colistin + SAM Fosfomycin	No	No	No ($>10^6$)	No
#6	67/F	31.3	BSI + VAP (10^6)	1	2 g q8h	2.94	No	No	Yes	No (10^6)	No
#7	65/M	29.4	BSI	0.5	2 g q8h	1.09	SAM	No	Yes	NA	Yes
#8	49/M	37.6	VAP ($>10^6$)	1	2 g q8h	2.39	No	ECMO	NA	No ($>10^5$)	No
#9	76/M	29.4	VAP (10^4)	1	2 g q8h	0.67	No	No	NA	No ($>10^6$)	No
#10	77/M	23.0	VAP ($>10^6$)	1	1.5 g q8h	2.35	No	No	NA	Yes	No
#11	68/F	27.1	BSI + VAP (10^5)	1	2 g q8h	0.63	No	No	Yes	No (10^5)	No
#12	72/F	56.9	BSI + VAP (10^6)	0.5	2 g q8h	28.39	No	No	Yes	Yes	No
#13	78/M	27.8	VAP (10^5)	1	2 g q8h	6.47	No	No	NA	Yes	Yes

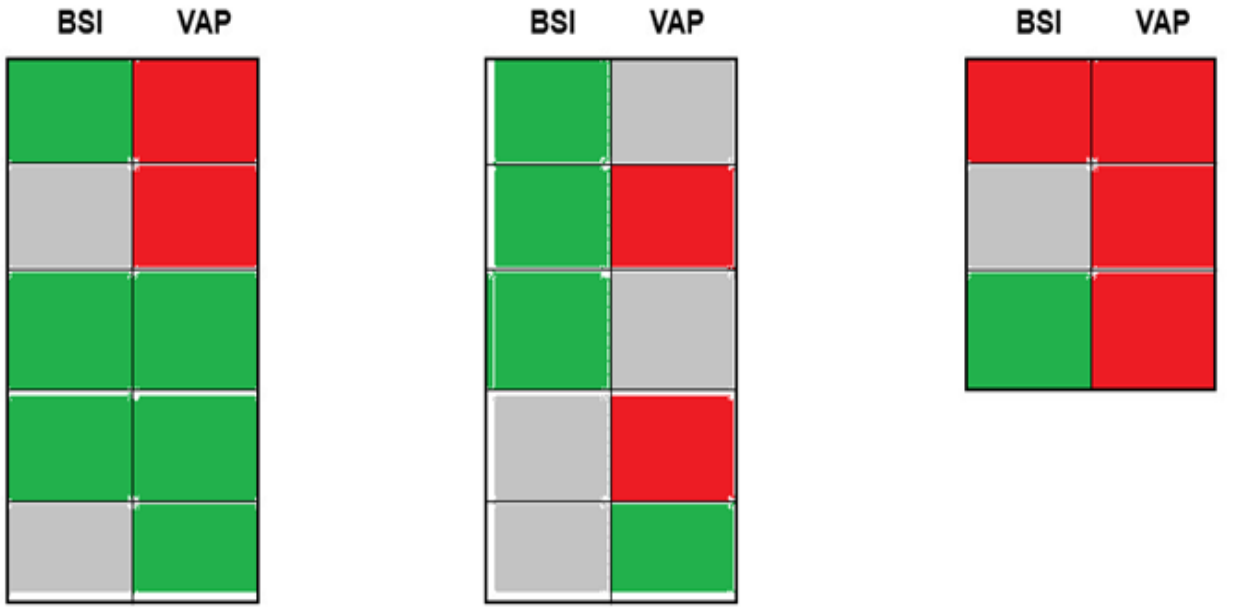
A DESCRIPTIVE CASE SERIES OF PK/PD TARGET ATTAINMENT AND MICROBIOLOGICAL OUTCOME IN CRITICALLY ILL PATIENTS WITH DOCUMENTED SEVERE XDR *Acinetobacter baumannii* BSI AND/OR VAP TREATED WITH CEFIDEROCOL

Gatti M, Bartoletti M, Cojutti PG, Gaibani P, Conti M, Giannella M, Viale P, Pea F

J Glob Antimicrob Resist 2021 Oct 25:S2213-7165(21)00229-0

DESCRIPTION OF PK/PD CEFIDEROCOL TARGET ATTAINMENT (EXPRESSED AS fC_{MIN}/MIC RATIO) ANDMICROBIOLOGICAL OUTCOME

75%	67%	20%
25%	33%	80%



Optimal fC_{min}/MIC ratio	Quasi-optimal fC_{min}/MIC ratio	Sub-optimal fC_{min}/MIC ratio
> 4	1-4	< 1

COMPARISON OF CEFTOLOZANE/TAZOBACTAM INFUSION REGIMENS IN A HOLLOW-FIBER INFECTION MODEL AGAINST XDR *P. aeruginosa* ISOLATES

Montero MM et al. *Microbiol Spectr* 2022 Jun 29; 10(3):e0089222. doi: 10.1128/spectrum.00892-22

OBSERVED VERSUS PREDICTED ANTIBIOTIC CONCENTRATIONS ACHIEVED IN EACH HFIM MODEL

	Free peak concn (mg/L) ± SD		Free trough concn (mg/L)/Css ± SD	
Dosing regimen	Predicted value	Observed value	Predicted value	Observed value
C/T 2/1 g q8h 1-h infusion	74.45	61.96 ± 6.80	14.77	25.67 ± 3.7
C/T 2/1 g q8h 4-h infusion	54.55	53.10 ± 7.92	19.7	27.29 ± 5.63
C/T 6 g q24h CI			45	47.29 ± 5.43

COMPARISON OF CEFTOLOZANE/TAZOBACTAM INFUSION REGIMENS IN A HOLLOW-FIBER INFECTION MODEL AGAINST XDR *P. aeruginosa* ISOLATES

Montero MM et al. *Microbiol Spectr* 2022 Jun 29; 10(3):e0089222. doi: 10.1128/spectrum.00892-22

MEAN OVERALL REDUCTION IN NUMBER OF BACTERIAL COLONIES GROWN WITH ALTERNATIVE C/T INFUSION REGIMENS FOR EACH ST175 ISOLATE

C/T (MIC = 2 mg/L) C/T (MIC = 8 mg/L) C/T (MIC = 16 mg/L)

	P. aeruginosa (10-023)		*P. aeruginosa* (09-012)		*P. aeruginosa* (07-016)	
Infusion regimen	Log diff day 7[a]	LR of AUCFU[b]	Log diff day 7	LR of AUCFU	Log diff day 7	LR of AUCFU
C/T 2/1 g q8h 1-h infusion vs control	−2.26 ± 0.19	−3.37	−2.53 ± 0.04	−3.66	−0.83 ± 0.22	−2.90
C/T 2/1 g q8h 4-h infusion vs control	−3.47 ± 0.10	−3.38	−3.19 ± 0.37	−3.64	−1.7 ± 0.33	−3.15
C/T 6 g q24h CI Css45 vs control	−4.46 ± 0.05	−3.53	−5.45 ± 0.18	3.69	−4.94 ± 0.37	−3.24
C/T 6 g q24h CI Css45 vs C/T 2/1 g q8h 1-h infusion	−2.2 ± 0.1	−1.01	−2.92 ± 0.01	−1.52	−4.11 ± 0.12	−2.1
C/T 6 g q24h CI Css45 vs C/T 2/1 g q8h 4-h infusion	−0.99 ± 0.33	−0.65	−2.26 ± 0.2	−1.23	−3.24 ± 0.05	−1.85
C/T 2/1 g q8h 4-h infusion vs C/T 2/1 g q8h 1-h infusion	−1.21 ± 0.05	−0.87	−0.66 ± 0.15	−0.10	−0.87 ± 0.28	−0.15

[a]Log difference at the end of the assay for each regimen compared with the control.

[b]The log difference is presented as the log ratio (LR), which is used to compare any number of $\log_{10}$ CFU of two regimens (test/reference). AUCFU, area under the curve for CFU; C/T, ceftolozane-tazobactam; CI, continuous infusion; Css, steady-state concentration; q8h, every 8 h.

Css =47.29 ± 5.43 mg/L

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Montero MM et al. *Microbiol Spectr* 2022 Jun 29; 10(3):e0089222. doi: 10.1128/spectrum.00892-22

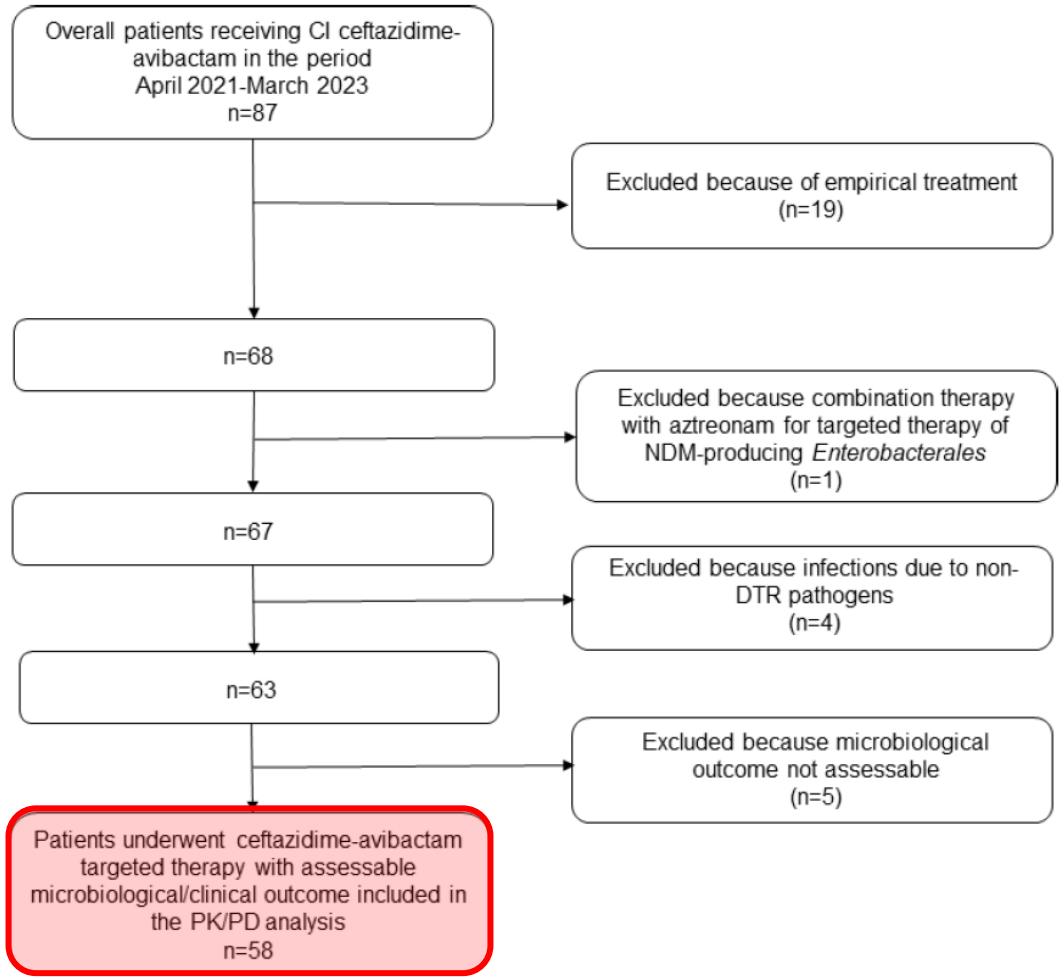
IMPORTANCE

- Given its time-dependent behavior, C/T continuous infusion can improve exposure and therefore the pharmacokinetic/pharmacodynamic target attainment
- We demonstrated that C/T in continuous infusion achieved the largest reduction in bacterial density in the overall treatment arms for both susceptible and resistant isolates
- It was also the only regimen with bactericidal activity against all three isolates
- Through this study, we want to demonstrate that developing individually tailored antimicrobial treatments is becoming essential
- Our results support the role of C/T level monitoring and of dose adjustments for better clinical management and outcomes

COULD AN OPTIMIZED JOINT PK/PD TARGET ATTAINMENT OF CONTINUOUS INFUSION CEFTAZIDIME-AVIBACTAM BE A WAY TO AVOID THE NEED FOR COMBO-THERAPY IN THE TARGETED TREATMENT OF DEEP-SEATED DTR GRAM-NEGATIVE INFECTIONS?

Gatti M, Rinaldi M, Bonazzetti C, Gaibani P, Giannella M, Viale P, Pea F. *Antimicrob Agents Chemother* 2023 Oct 16: e0096923

FLOWCHART OF PATIENT INCLUSION AND EXCLUSION CRITERIA FOR PK/PD ANALYSIS



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Gatti M, Rinaldi M, Bonazzetti C, Gaibani P, Giannella M, Viale P, Pea F. *Antimicrob Agents Chemother* 2023 Oct 16: e0096923

DEMOGRAPHICS AND CLINICAL CHARACTERISTICS OF PATIENTS TREATED WITH CI CEFTAZIDIME-AVIBACTAM TARGETED THERAPY

Variables	Overall included patients (n = 58)
Demographics	
Age (median [IQR])	62.5 (55.5–73.8)
Gender (male/female; *n* [%])	36/22 (62.1/37.9)
Body mass index (median [IQR])	24.7 (22.2–28.4)
Baseline eGFR (mL/min/1.73 m^2; median [IQR])	86.5 (41.3–109.8)
ICU admission (*n* [%])	31 (53.4)
Augmented renal clearance (*n* [%])	6 (10.3)
Continuous renal replacement therapy (*n* [%])	15 (25.9)
Immunosuppression (*n* [%])	16 (27.6)
Underlying disease (*n* [%])	
Severe COVID-19	8 (13.8)
Febrile neutropenia	8 (13.8)
Hepatic cirrhosis	8 (13.8)
Solid organ transplantation	8 (13.8)
Bowel perforation	6 (10.3)
Acute cholecystitis	4 (6.9)
Cancer	3 (5.2)
Other	13 (22.4)

Variables	Overall included patients (n = 58)
BSI	24 (41.4)
HAP/VAP	11 (19.0)
HAP/VAP + BSI	10 (17.2)
IAI + BSI	7 (12.1)
IAI	3 (5.2)
SSTI	1 (1.7)
CNS	1 (1.7)
CNS + BSI	1 (1.7)
CAZ-AVI treatment	
Initial full maintenance dosing (*n* [%])	54 (93.1)
Length of treatment (days; median [IQR])	13.5 (7.75–19)
Combination therapy	22 (37.9)
Ceftazidime fC_{ss}/MIC ratio (median [IQR])	23.5 (13.4–39.1)
Avibactam fC_{ss}/C_T ratio (median [IQR])	3.5 (2.2–6.2)
PK/PD joint target attainment (*n* [%])	
Optimal	53 (91.4)
Quasi-optimal	4 (6.9)
Suboptimal	1 (1.7)
Outcome	
Microbiological eradication	53 (91.4)
Clinical cure	46 (79.3)
Resistance development	2 (3.4)
30-day mortality rate	15 (25.9)

COULD AN OPTIMIZED JOINT PK/PD TARGET ATTAINMENT OF CONTINUOUS INFUSION CEFTAZIDIME-AVIBACTAM BE A WAY TO AVOID THE NEED FOR COMBO-THERAPY IN THE TARGETED TREATMENT OF DEEP-SEATED DTR GRAM-NEGATIVE INFECTIONS?

Gatti M, Rinaldi M, Bonazzetti C, Gaibani P, Giannella M, Viale P, Pea F. *Antimicrob Agents Chemother* 2023 Oct 16: e0096923

JOINT PK/PD TARGETS OF CAZ-AVI

CAZ → Css/MIC 4 -8

AVI → Css/C_T > 1

OPTIMAL: 2/2

QUASI-OPTIMAL: 1/2

SUBOPTIMAL: 0/2

COULD AN OPTIMIZED JOINT PK/PD TARGET ATTAINMENT OF CONTINUOUS INFUSION CEFTAZIDIME-AVIBACTAM BE A WAY TO AVOID THE NEED FOR COMBO-THERAPY IN THE TARGETED TREATMENT OF DEEP-SEATED DTR GRAM-NEGATIVE INFECTIONS?

Gatti M, Rinaldi M, Bonazzetti C, Gaibani P, Giannella M, Viale P, Pea F. *Antimicrob Agents Chemother* 2023 Oct 16: e0096923

UNIVARIATE ANALYSIS COMPARING PATIENTS RECEIVING MONO- VS COMBO-THERAPY WITH CI CAZ-AVI FOR TARGETED THERAPY OF DTR GRAM-NEGATIVE INFECTIONS

Variables	Monotherapy (*n* = 36)	Combination therapy (*n* = 22)	*P* value
Demographics			
Age (median [IQR])	62 (54.75–72.5)	63 (58.75–75.25)	0.39
Gender (male/female; *n* [%])	20/16 (55.6/44.4)	16/6 (72.7/27.3)	0.19
Body mass index (median [IQR])	23.9 (21.0–28.0)	26.3 (23.7–29.5)	0.12
Baseline eGFR (mL/min/1.73 m^2; median [IQR])	88.0 (46.0–110.0)	81.0 (32.7–103.0)	0.43
ICU admission (*n* [%])	15 (41.7)	16 (72.7)	0.023
Continuous renal replacement therapy (*n* [%])	8 (22.2)	7 (31.8)	0.42
Augmented renal clearance (*n* [%])	5 (13.9)	1 (4.5)	0.39
Site of infection (*n* [%])			
BSI	18 (50.0)	6 (27.3)	0.09
HAP/VAP	2 (5.6)	9 (40.9)	0.001
HAP/VAP + BSI	7 (19.4)	3 (13.7)	0.73
IAI + BSI	7 (19.4)	0 (0.0)	0.04
IAI	1 (2.8)	2 (9.1)	0.55
SSTI	0 (0.0)	1 (4.5)	0.38
CNS + BSI	1 (2.8)	0 (0.0)	0.99
CNS	0 (0.0)	1 (4.5)	0.38

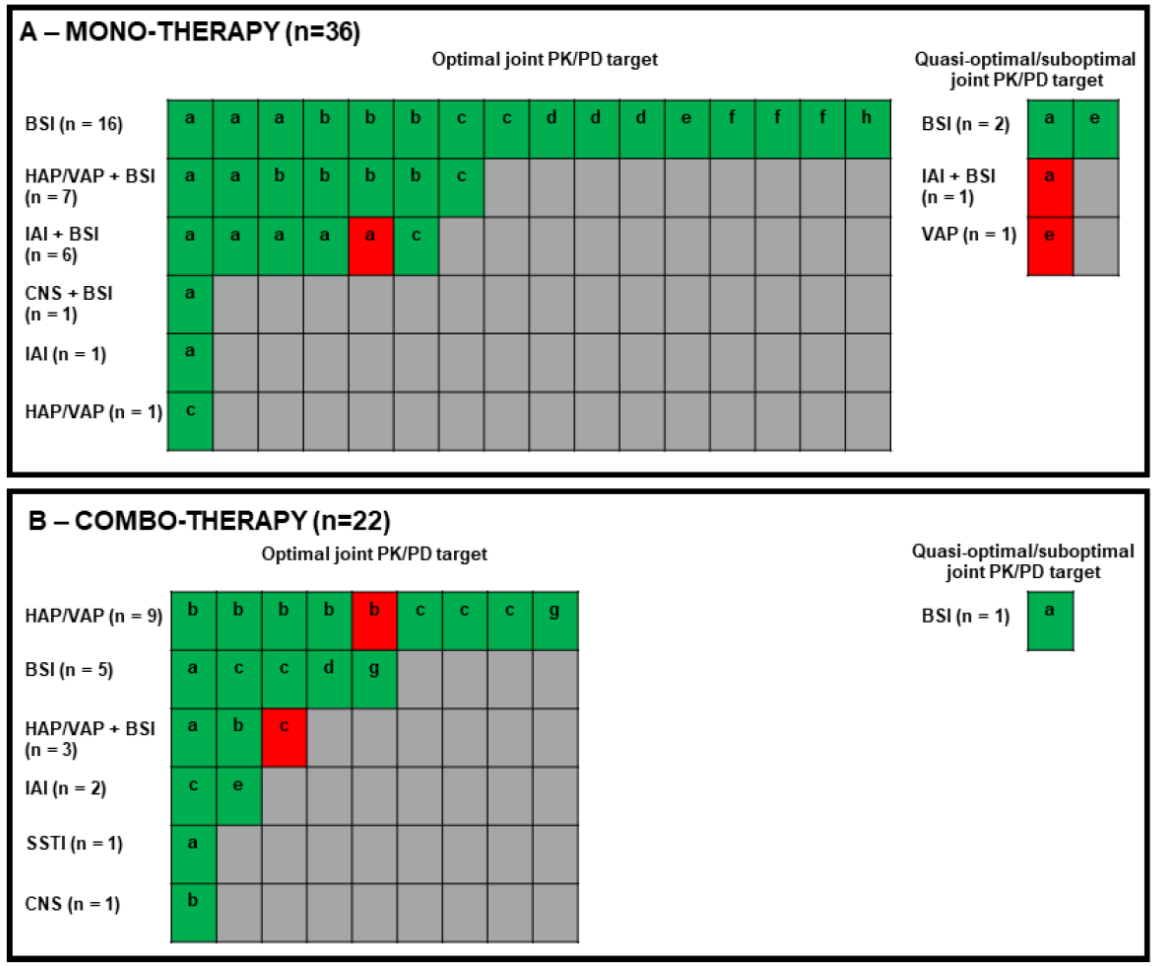
Variables	Monotherapy (*n* = 36)	Combination therapy (*n* = 22)	*P* value
Pathogens (*n* [%])			
KPC-producing *K. pneumoniae*	14 (38.9)	4 (18.2)	0.14
DTR *P. aeruginosa*	7 (19.4)	7 (31.8)	0.29
OXA-48-producing *K. pneumoniae*	5 (14.0)	7 (31.8)	0.18
OXA-48-producing *Escherichia coli*	3 (8.3)	1 (4.5)	0.99
Carbapenem-resistant *Klebsiella aerogenes* (non-CPE)	3 (8.3)	1 (4.5)	0.99
Carbapenem-resistant *K. pneumoniae* (non-CPE)	3 (8.3)	0 (0.0)	0.28
KPC/OXA-48-coproducing *K. pneumoniae*	0 (0.0)	2 (9.1)	0.14
AmpC-producing *Enterobacter cloacae*	1 (2.8)	0 (0.0)	0.99
PK/PD joint target attainment (*n* [%])			
Optimal	32 (88.9)	21 (95.5)	0.64
Quasi-optimal/suboptimal	4 (11.1)	1 (4.5)	0.64
Outcome (*n* [%])			
Microbiological eradication	33 (91.7)	20 (90.9)	0.99
Clinical cure	28 (77.8)	18 (81.8)	0.99
Resistance occurrence	1 (2.8)	1 (4.5)	0.99
30-day mortality rate	7 (19.4)	8 (36.4)	0.16

[a]BSI, bloodstream infection; CAZ-AVI, ceftazidime-avibactam; CNS, central nervous system; CPE, carbapenemase-producing *Enterobacterales*; eGFR, estimated glomerular filtration rate; ESBL, extended-spectrum beta-lactamase; HAP, hospital-acquired pneumonia; IAI, intra-abdominal infection; ICU, intensive care unit; IQR, interquartile range; PK/PD, pharmacokinetic/pharmacodynamic; SSTI, skin and soft tissue infection; VAP, ventilator-associated pneumonia.

COULD AN OPTIMIZED JOINT PK/PD TARGET ATTAINMENT OF CONTINUOUS INFUSION CEFTAZIDIME-AVIBACTAM BE A WAY TO AVOID THE NEED FOR COMBO-THERAPY IN THE TARGETED TREATMENT OF DEEP-SEATED DTR GRAM-NEGATIVE INFECTIONS?

Gatti M, Rinaldi M, Bonazzetti C, Gaibani P, Giannella M, Viale P, Pea F. *Antimicrob Agents Chemother* 2023 Oct 16: e0096923

RELATIONSHIP BETWEEN PHARMACOKINETIC/PHARMACODYNAMIC JOINT TARGET ATTAINMENT AND THE MICROBIOLOGICAL OUTCOME



a – Kp-KPC (n =18)
b – DTR-PA (n =14)
c – Kp OXA-48 (n = 12)
d – E. coli OXA-48 (n =4)
e – non-CP K. aerogenes (n = 4)
f – non-CP Kp (n = 3)
g – Kp KPC/OXA-48-co-producer (n =2)
h – E. cloacae AmpC (n = 1)

COULD AN OPTIMIZED JOINT PK/PD TARGET ATTAINMENT OF CONTINUOUS INFUSION CEFTAZIDIME-AVIBACTAM BE A WAY TO AVOID THE NEED FOR COMBO-THERAPY IN THE TARGETED TREATMENT OF DEEP-SEATED DTR GRAM-NEGATIVE INFECTIONS?

Gatti M, Rinaldi M, Bonazzetti C, Gaibani P, Giannella M, Viale P, Pea F. *Antimicrob Agents Chemother* 2023 Oct 16: e0096923

UNIVARIATE AND MULTIVARIATE ANALYSES COMPARING PATIENTS SHOWING MICROBIOLOGICAL ERADICATION VS MICROBIOLOGICAL FAILURE

Variables	Microbiological eradication (n = 53)	Microbiological failure (n = 5)	Univariate analysis P value	Multivariate analysis (OR; 95% CI)	Multivariate analysis P value
Demographics					
Age (median [IQR])	63.0 (55.0–74.0)	60.0 (57.0–61.0)	0.26		
Gender (male/female; n [%])	34/19 (64.2/35.8)	2/3 (40.0/60.0)	0.36		
Body mass index (median [IQR])	24.7 (22.2–28.6)	23.1 (20.8–27.5)	0.40		
Baseline eGFR (mL/min/1.73 m^2; median [IQR])	85.0 (38.9–107.0)	120.0 (84.5–124.0)	0.18		
ICU admission (n [%])	28 (52.8)	3 (60.0)	0.99		
Continuous renal replacement therapy (n [%])	14 (26.4)	1 (20.0)	0.99		
Augmented renal clearance (n [%])	4 (7.5)	2 (40.0)	0.08		
Site of infection (n [%])					
BSI	24 (45.3)	0 (0.0)	0.07		
HAP/VAP	9 (17.0)	2 (40.0)	0.24		
HAP/VAP + BSI	9 (17.0)	1 (20.0)	0.99		
IAI + BSI	5 (9.4)	2 (40.0)	0.11		
IAI	3 (5.6)	0 (0.0)	0.99		
SSTI	1 (1.9)	0 (0.0)	0.99		
CNS + BSI	1 (1.9)	0 (0.0)	0.99		
CNS	1 (1.9)	0 (0.0)	0.99		
Pathogens (n [%])					
KPC-producing *K. pneumoniae*	16 (30.2)	2 (40.0)	0.64		
DTR *P. aeruginosa*	13 (24.5)	1 (20.0)	0.99		
OXA-48-producing *K. pneumoniae*	11 (20.7)	1 (20.0)	0.99		
OXA-48-producing *E. coli*	4 (7.5)	0 (0.0)	0.99		
Carbapenem-resistant *K. aerogenes* (non-CPE)	3 (5.7)	1 (20.0)	0.31		
Carbapenem-resistant *K. pneumoniae* (non-CPE)	3 (5.7)	0 (0.0)	0.99		
KPC/OXA-48-coproducing *K. pneumoniae*	2 (3.8)	0 (0.0)	0.99		
AmpC-producing *E. cloacae*	1 (1.9)	0 (0.0)	0.99		
CAZ-AVI treatment and PK/PD joint target attainment (n [%])					
Quasi-optimal/suboptimal joint PK/PD target attainment	3 (5.7)	2 (40.0)	0.05	11.11 (1.31–93.98)	0.027
Combination therapy	20 (37.7)	2 (40.0)	0.99		

Our findings suggest that optimizing joint PK/PD target attainment of CI ceftazidime-avibactam monotherapy could represent a way forward for allowing microbiological eradication in the targeted treatment of DTR Gram-negative infections

PK/PD ANALYSIS OF CONTINUOUS-INFUSION FOSFOMYCIN IN COMBINATION WITH EXTENDED-INFUSION CEFIDEROCOL OR CONTINUOUS-INFUSION CEFTAZIDIME-AVIBACTAM IN A CASE SERIES OF DTR-*P. aeruginosa* BSI AND/OR HAP

Gatti M, Giannella M, Rinaldi M, Gaibani P, Viale P, Pea F. *Antibiotics (Basel)* 2022 Dec; 11(12): 1739

DEMOGRAPHIC AND CLINICAL FEATURES OF PATIENTS WITH SEVERE INFECTIONS CAUSED BY DTR-PA TREATED WITH COMBINATION THERAPY INCLUDING FOSFOMYCIN PLUS NOVEL BETA-LACTAMS

ID Cases	Age/Sex	Ward	Type of Infection	Fosfomycin MIC (mg/L)	Fosfomycin Dosage	AUC/MIC Ratio (mg/L·h)	Fosfomycin Dosing Adjustment	Beta-Lactam Co-Treatment	Beta-Lactam MIC (mg/L)	Average fC_{SS}/MIC Ratio or fC_{min}/MIC Ratio	Beta-Lactam Dosing Adjustment	Joint PK/PD Target	Microbiological Eradication	30-Day Mortality
DTR *Pseudomonas aeruginosa*														
#1	27/F	Infectious disease unit	HAP	64	8 g LD 16 g/day CI	92.0	No	Cefiderocol 2 g q8h (EI)	1	19.7	No	Optimal	Yes	No
#2	61/F	ICU	VAP	256	8 g LD 16 g/day CI	32.4	No	CAZ-AVI 2.5 g q8h CI	8	5.9 (avibactam fC_{SS} 8.4 mg/L)	No	Quasi-optimal	No	Yes
#3	75/M	ICU	BSI + VAP	32	8 g LD 16 g/day CI	471.4	Reduction (12 g/day CI)	Cefiderocol 2 g q8h (EI)	2	23.2	Reduction 1 g q8h (EI 3h)	Optimal	Yes	No
#4	35/M	Haematology + ICU	BSI	64	8 g LD 24 g/day CI	180.2	No	Cefiderocol 2 g q6h (EI)	8	0.9	Increase 2 g q6h CI	Quasi-optimal	Yes	No
#5	69/M	ICU	BSI + VAP	32	8 g LD 16 g/day CI	626.6	Reduction (12 g/day CI)	Cefiderocol 2 g q8h (EI)	2	6.3	No	Optimal	Yes	No
#6	79/M	ICU	VAP	32	8 g LD 16 g/day CI	458.3	No	CAZ-AVI 2.5 g q8h CI	8	14.9 (avibactam fC_{SS} 27.6 mg/L)	Reduction 1.25 g q8h CI	Optimal	Yes	Yes

AUC: area-under-the-curve; CAZ-AVI: ceftazidime-avibactam; CI: continuous infusion; C_{min}: trough concentrations; C_{ss}: steady-state concentration; EI: extended infusion; HAP: hospital-acquired pneumonia; ICU: intensive care unit; LD: loading dose; MIC: minimum inhibitory concentration; PK/PD: pharmacokinetic/pharmacodynamic; VAP: ventilator-associated pneumonia. Green box: achievement of optimal PK/PD targets (or microbiological eradication for microbiological outcome); yellow box: achievement of quasi-optimal PK/PD targets; red box: achievement of suboptimal PK/PD targets (or microbiological failure for microbiological outcome).

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Gatti M, Giannella M, Rinaldi M, Gaibani P, Viale P, Pea F. *Antibiotics (Basel)* 2022 Dec; 11(12): 1739

SUSCEPTIBILITY PROFILE OF EACH DTR-PA CLINICAL ISOLATE AND RATIONALES FOR SELECTING COMBINATION THERAPY

ID Cases (Combo)	Susceptibility Profile (MIC in mg/L)	Criteria for Combination Therapy
#1 CID + FOS	AMI ≤ 8; CEP > 8; CTZ 16; CTV > 8; CTT ≤ 1; CIP 1; IMI > 8; MER 32; PIT > 16; FOS 64; CID 1	(1) Ceftolozane-tazobactam supply shortage (2) Ceftazidime-avibactam resistance (3) Potential synergism of combination therapy (4) HAP
#2 CTV + FOS	AMI ≤ 8; CEP > 8; CTZ 16; CTV 8; CTT ≤ 1; CIP 1; IMI > 8; MER 32; PIT > 16; COL 2; FOS 256	(1) Ceftolozane-tazobactam supply shortage (2) Potential synergism of combination therapy according to in vitro evidence (3) VAP
#3 CID + FOS	AMI ≤ 8; CEP > 8; CTZ > 32; CTV > 8; CTT 4; CIP 0.5; IMI > 8; MER 32; PIT > 16; COL 2; FOS 32; CID 2	(1) Ceftolozane-tazobactam supply shortage (2) Ceftazidime-avibactam resistance (3) Potential synergism of combination therapy (4) VAP
#4 CID + FOS	AMI 16; CEP > 8; CTZ > 32; CTV > 8; CTT > 4; CIP > 1; IMI > 8; MER 16; PIT > 16; COL 1; FOS 64; CID 8	(1) Ceftolozane-tazobactam resistance (2) Ceftazidime-avibactam resistance (3) Potential synergism of combination therapy
#5 CID + FOS	AMI 16; CEP > 8; CTZ > 32; CTV > 8; CTT ≤ 1; CIP 1; IMI > 8; MER 32; PIT > 16; COL 1; FOS 32; CID 2	(1) Ceftolozane-tazobactam supply shortage (2) Ceftazidime-avibactam resistance (3) Potential synergism of combination therapy (4) VAP
#6 CTV + FOS	AMI > 16; CEP > 8; CTZ > 32; CTV 8; CTT > 4; CIP > 1; IMI 8; MER 8; PIT > 16; FOS 32	(1) Ceftolozane-tazobactam resistance (2) Potential synergism of combination therapy according to in vitro evidence (3) VAP

AMI: amikacin; CEP; cefepime; CID: cefiderocol; CTZ; ceftazidime; CTV: ceftazidime-avibactam; CTT: ceftolozane-tazobactam; CIP: ciprofloxacin; FOS: fosfomycin; HAP: hospital-acquired pneumonia; IMI: imipenem; MER: meropenem; PIT: piperacillin-tazobactam; VAP: ventilator-acquired pneumonia.

PK/PD ANALYSIS OF CONTINUOUS-INFUSION FOSFOMYCIN IN COMBINATION WITH EXTENDED-INFUSION CEFIDEROCOL OR CONTINUOUS-INFUSION CEFTAZIDIME-AVIBACTAM IN A CASE SERIES OF DTR-*P. aeruginosa* BSI AND/OR HAP

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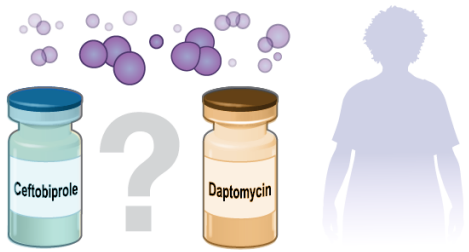
#3	75/M	ICU	BSI + VAP	32	8 g LD 16 g/day CI	471.4	Reduction (12 g/day CI)	Cefiderocol 2 g q8h (EI)	2	23.2	Reduction 1 g q8h (EI 3h)	Optimal	Yes	No
#4	35/M	Haematology + ICU	BSI	64	8 g LD 24 g/day CI	180.2	No	Cefiderocol 2 g q6h (EI)	8	0.9	Increase 2 g q6h CI	Quasi-optimal	Yes	No
#5	69/M	ICU	BSI + VAP	32	8 g LD 16 g/day CI	626.6	Reduction (12 g/day CI)	Cefiderocol 2 g q8h (EI)	2	6.3	No	Optimal	Yes	No
#6	79/M	ICU	VAP	32	8 g LD 16 g/day CI	458.3	No	CAZ-AVI 2.5 g q8h CI	8	14.9 (avibactam fC_{SS} 27.6 mg/L)	Reduction 1.25 g q8h CI	Optimal	Yes	Yes

AUC: area-under-the-curve; CAZ-AVI: ceftazidime-avibactam; CI: continuous infusion; C_{min}: trough concentrations; C_{ss}: steady-state concentration; EI: extended infusion; HAP: hospital-acquired pneumonia; ICU: intensive care unit; LD: loading dose; MIC: minimum inhibitory concentration; PK/PD: pharmacokinetic/pharmacodynamic; VAP: ventilator-associated pneumonia. Green box: achievement of optimal PK/PD targets (or microbiological eradication for microbiological outcome); yellow box: achievement of quasi-optimal PK/PD targets; red box: achievement of suboptimal PK/PD targets (or microbiological failure for microbiological outcome).

RESEARCH SUMMARY

Ceftobiprole for Treatment of Complicated *Staphylococcus aureus* Bacteremia

Holland TL et al. DOI: 10.1056/NEJMoa2300220



CLINICAL TRIAL

Design: A phase 3, multinational, double-blind, double-dummy, randomized trial assessed whether ceftobiprole would be noninferior to daptomycin for the treatment of complicated *S. aureus* bacteremia.

Intervention: 390 adults hospitalized with complicated *S. aureus* bacteremia were assigned to receive either ceftobiprole (500 mg) intravenously every 6 hours during the first 8 days and then every 8 hours thereafter or daptomycin (6–10 mg per kilogram of body weight) intravenously every 24 hours with optional aztreonam, plus matching placebo infusions. Maximum treatment durations ranged from 28 to 42 days. The primary efficacy outcome was overall treatment success at 70 days after randomization; success was defined as survival, a reduction in symptoms, *S. aureus* bloodstream clearance, absence of new *S. aureus* bacteremia–related complications, and no receipt of other potentially effective antibiotics.

RESULTS

Efficacy: Among evaluable patients, ceftobiprole was found to be noninferior to daptomycin with respect to overall treatment success.

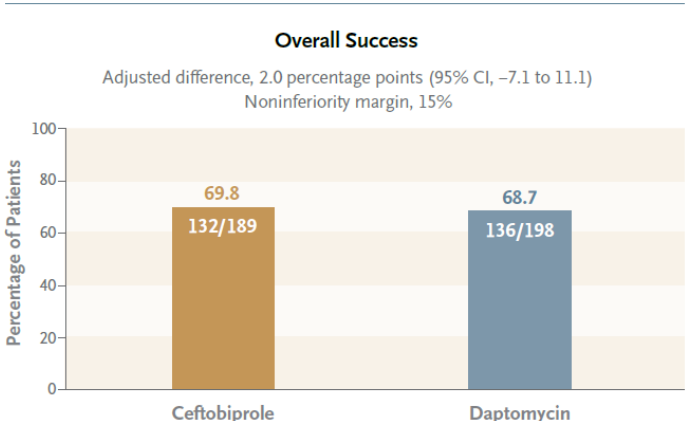
Safety: The proportion of patients with adverse events or with serious adverse events was similar in the two groups. Gastrointestinal adverse events occurred more often with ceftobiprole than with daptomycin.

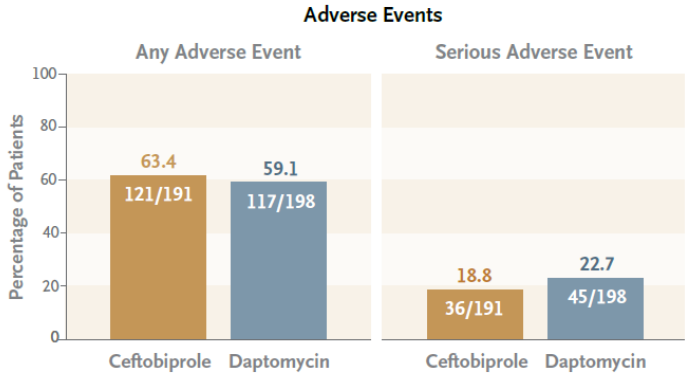
CONCLUSIONS

In patients with complicated *S. aureus* bacteremia, ceftobiprole was noninferior to daptomycin with respect to overall treatment success at 70 days.

LIMITATIONS AND REMAINING QUESTIONS

- Definitive conclusions could not be made about the efficacy of ceftobiprole in patients with MRSA bacteremia, who accounted for approximately one fourth of the trial patients.
- More than 95% of the patients were White.
- Daptomycin was administered primarily at the FDA-approved dose of 6 mg/kg/day, which is lower than the dose sometimes used in clinical practice.

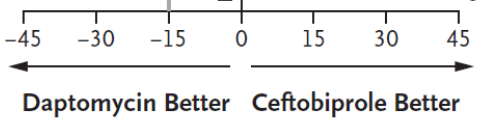




N Engl J Med 2023 Oct 12; 389(15): 1390-1401

OVERALL TREATMENT SUCCESS AT THE POST-BASELINE EVALUATION VISIT, ACCORDING TO PATIENT CHARACTERISTICS AT BASELINE (MODIFIED INTENTION-TO-TREAT ANALYSIS POPULATION).

Subgroup	Ceftobiprole	Daptomycin	Percentage-Point Difference (95% CI)
	no. of patients/total no. (%)		
All patients	132/189 (69.8)	136/198 (68.7)	2.0 (–7.1 to 11.1)
Age at written informed consent			
18 to <65 yr	98/131 (74.8)	101/135 (74.8)	0.6 (–9.8 to 10.9)
≥65 yr	34/58 (59)	35/63 (56)	6.9 (–10.5 to 24.3)
Sex			
Male	93/128 (72.7)	92/140 (65.7)	8.0 (–2.8 to 18.8)
Female	39/61 (64)	44/58 (76)	–11.3 (–27.7 to 5.1)
Baseline category of complicated *S. aureus* bacteremia			
Soft-tissue infection	81/116 (69.8)	80/121 (66.1)	4.5 (–7.3 to 16.3)
S. aureus bacteremia excluding soft-tissue infection	51/73 (70)	56/77 (73)	–1.7 (–15.9 to 12.6)
Osteoarticular infection	23/32 (72)	24/35 (69)	2.9 (–19.7 to 25.6)
Abdominal abscess	18/26 (69)	22/29 (76)	–9.7 (–33.3 to 13.9)
Hemodialysis	13/24 (54)	15/25 (60)	–4.6 (–32.5 to 23.3)
Persistent *S. aureus* bacteremia	8/16 (50)	8/16 (50)	–0.0 (–35.9 to 35.9)
Infective endocarditis on right side of heart	10/15 (67)	7/10 (70)	–6.6 (–40.1 to 27.0)
Baseline *S. aureus* infection			
Methicillin-susceptible	100/141 (70.9)	97/146 (66.4)	4.8 (–5.9 to 15.5)
Methicillin-resistant	31/45 (69)	38/49 (78)	–8.3 (–25.3 to 8.6)
Previous antibiotic use			
Yes	92/139 (66.2)	85/134 (63.4)	2.9 (–8.4 to 14.2)
No	40/50 (80)	51/64 (80)	–0.2 (–15.0 to 14.6)
Trial cohort			
Cohort 1	68/97 (70)	62/96 (65)	7.6 (–5.6 to 20.8)
Cohort 2	64/92 (70)	74/102 (72.5)	–3.4 (–16.1 to 9.3)



N Engl J Med 2023 Oct 12; 389(15): 1390-1401

MIC distributions for Ceftobiprole, 2023-11-20

Antimicrobial: Ceftobiprole (Method: MIC)

	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	Distributions	Observations	(T)ECOFF	Confidence interval
Staphylococcus aureus	0	0	0	1	0	95	313	10356	7881	5781	2262	119	1	3	0	0	0	0	0	10	26812	1	1 - 2
Staphylococcus aureus ATCC 29213	0	0	0	0	0	0	0	1	14	1	0	0	0	0	0	0	0	0	0	1	16	ID	
Staphylococcus aureus MRSA	0	0	0	0	0	9	12	105	4276	8914	2398	147	1	3	0	0	0	0	0	14	15865	1	1 - 2
Staphylococcus aureus MSSA	0	0	0	0	4	73	383	10118	5132	205	8	0	0	0	0	0	0	0	0	15	15923	1	1 - 2
Staphylococcus capitis	0	0	0	4	31	40	52	16	17	24	2	0	0	0	0	0	0	0	0	4	186	(0.25)	0.25 - 1
Staphylococcus epidermidis	0	0	0	1	2	44	304	318	615	657	116	51	0	0	0	0	0	0	0	9	2108	1	0.25 - 1

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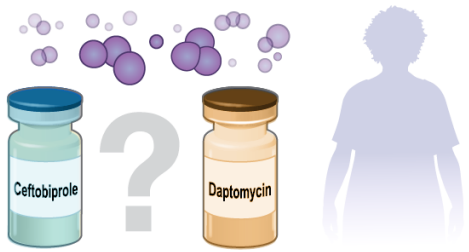
The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Ceftobiprole for Treatment of Complicated *Staphylococcus aureus* Bacteremia

Holland TL et al. DOI: 10.1056/NEJMoa2300220



CLINICAL TRIAL

Design: A phase 3, multinational, double-blind, double-dummy, randomized trial assessed whether ceftobiprole would be noninferior to daptomycin for the treatment of complicated *S. aureus* bacteremia.

Intervention: 390 adults hospitalized with complicated *S. aureus* bacteremia were assigned to receive either ceftobiprole (500 mg) intravenously every 6 hours during the first 8 days and then every 8 hours thereafter or daptomycin (6–10 mg per kilogram of body weight) intravenously every 24 hours with optional aztreonam, plus matching placebo infusions. Maximum treatment durations ranged from 28 to 42 days. The primary efficacy outcome was overall treatment success at 70 days after randomization; success was defined as survival, a reduction in symptoms, *S. aureus* bloodstream clearance, absence of new *S. aureus* bacteremia–related complications, and no receipt of other potentially effective antibiotics.

RESULTS

Efficacy: Among evaluable patients, ceftobiprole was found to be noninferior to daptomycin with respect to overall treatment success.

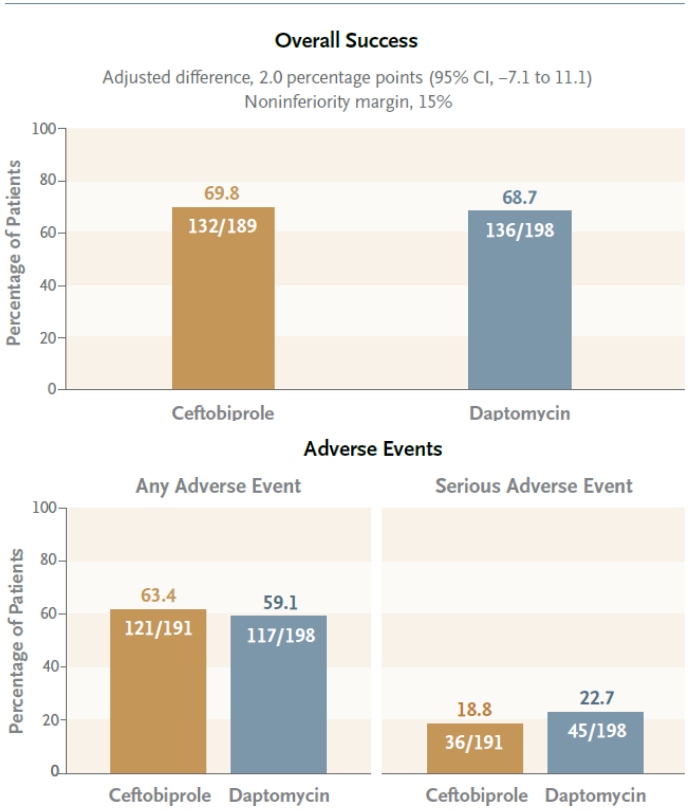
Safety: The proportion of patients with adverse events or with serious adverse events was similar in the two groups. Gastrointestinal adverse events occurred more often with ceftobiprole than with daptomycin.

CONCLUSIONS

In patients with complicated *S. aureus* bacteremia, ceftobiprole was noninferior to daptomycin with respect to overall treatment success at 70 days.

LIMITATIONS AND REMAINING QUESTIONS

- Definitive conclusions could not be made about the efficacy of ceftobiprole in patients with MRSA bacteremia, who accounted for approximately one fourth of the trial patients.
- More than 95% of the patients were White.
- Daptomycin was administered primarily at the FDA-approved dose of 6 mg/kg/day, which is lower than the dose sometimes used in clinical practice.



N Engl J Med 2023 Oct 12; 389(15): 1390-1401

POP PK/PD ANALYSIS FOR MAXIMIZING THE EFFECTIVENESS OF CEFTOBIPROLE IN THE TREATMENT OF SEVERE METHICILLIN-RESISTANT STAPHYLOCOCCAL INFECTIONS

Cojutti PG, Giuliano S, Pascale R, Angelini J, Tascini C, Viale P, Pea F. *Microorganisms* under review

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS (N=132)

Characteristic	Value
Age (years)	71.0 (61.8 – 79.0)
Gender (male/female)	86/46
Body weight (kg)	73.5 (65.0 – 89.0)
BMI (kg/m²)	25.7 (22.5 – 30.1)
Serum creatinine (mg/dL)	0.90 (0.68 – 1.36)
eGFR (mL/min/1.73 m²)	83.7 (50.5 – 101.7)
Serum albumin (g/L)	3.1 (2.7 – 3.4)
Type of infection, n (%)	
Hospital-acquired pneumonia	38 (28.8)
Endocarditis	27 (20.5)
Bloodstream infection	22 (16.6)
Community-acquired pneumonia	20 (15.2)
Bone and joint infections	9 (6.8)
Skin and soft tissue infections	9 (6.8)
Device-related infections	4 (3.0)
CNS infections	3 (2.3)

Characteristic	Value
Patients with identified microbiological isolates, n (%)	80 (60.6)
Ceftobiprole treatment	
Median dose (mg daily)	1500 (1000 – 1500)
Trough concentration (mg/L)	7.6 (4.9 – 11.7)
Length of treatment (days)	10.0 (2.0 – 81.0)
Patients with co-administered antibiotics, n(%)	88 (66.7)
Treatment outcome in assessable patients (n=126)	
N. of patients with microbiological eradication	118 (96.7)
N. of patients with clinical cure	88 (69.8)

Data are presented as median (IQR) for continuous variables and as number (%) for dichotomous variables.
eGFR, estimated glomerular filtration rate

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CUMULATIVE FRACTION OF RESPONSE AGAINST THE EUCAST MIC DISTRIBUTION OF MRSA (N = 15865)

Optimal PK/PD target
fCmin/MIC (EI) or fCss/MIC (CI) ratio ≥4

Ceftobiprole dosages and classes of eGFR	MRSA	
	Quasi-optimal PK/PD target	Optimal PK/PD target
eGFR <30 mL/min/1.73m²		
250 q12h EI	95.9	58.2
250 q12h CI	99.7	79.1
250 q8h EI*	98.8	8[illegible]7
250 q8h CI*	100	91.4
eGFR 30-50 mL/min/1.73m²		
500 q12h EI	98.6	78.4
500 q12h CI	99.9	94.5
500 q8h EI*	99.7	92.6
500 q8h CI*	100	98.4
eGFR 51-80 mL/min/1.73m²		
500 q8h EI	99.5	83.2
500 q8h CI	100	96.8
500 q6h EI*	99.4	93.4
500 q6h CI*	100	98.9

Ceftobiprole dosages and classes of eGFR	MRSA	
	Quasi-optimal PK/PD target	Optimal PK/PD target
eGFR 81-130 mL/min/1.73m²		
500 q8h EI	97.2	66.0
500 q8h CI	100	90.5
500 q6h EI*	99.4	8[illegible]5
500 q6h CI*	100	96.5
eGFR >130 mL/min/1.73m²		
500 q8h EI	75.2	22.2
500 q8h CI	99.2	66.7
500 q6h EI*	89.2	[illegible]1
500 q6h CI*	99.8	[illegible]3
500 q4h EI*	98.4	72.2
500 q4h CI*	100	92.5

*Intensified dosages tested in different classes of eGFR

CI, 24h-continuous infusion; EI, 2h-extended infusion

TAKE HOME MESSAGES

- PK/PD is the most relevant factor for addressing correct use of the new antibiotics
- Deep-seated infections and/or challenging clinical conditions may require more aggressive PK/PD target attainment
- Critical illness may significantly alter the pharmacokinetics of the new hydrophilic antibiotics
- Renal function must be evaluated daily in the critically ill patients for choosing the correct dosage