NOZIONI DI PK/PD PRATICHE

(SOPRATTUTTO SE NON SI DISPONE DEL TDM)

FEDERICO PEA

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

SSD FARMACOLOGIA CLINICA, AZIENDA OSPEDALIERO UNIVERSITARIA DI BOLOGNA

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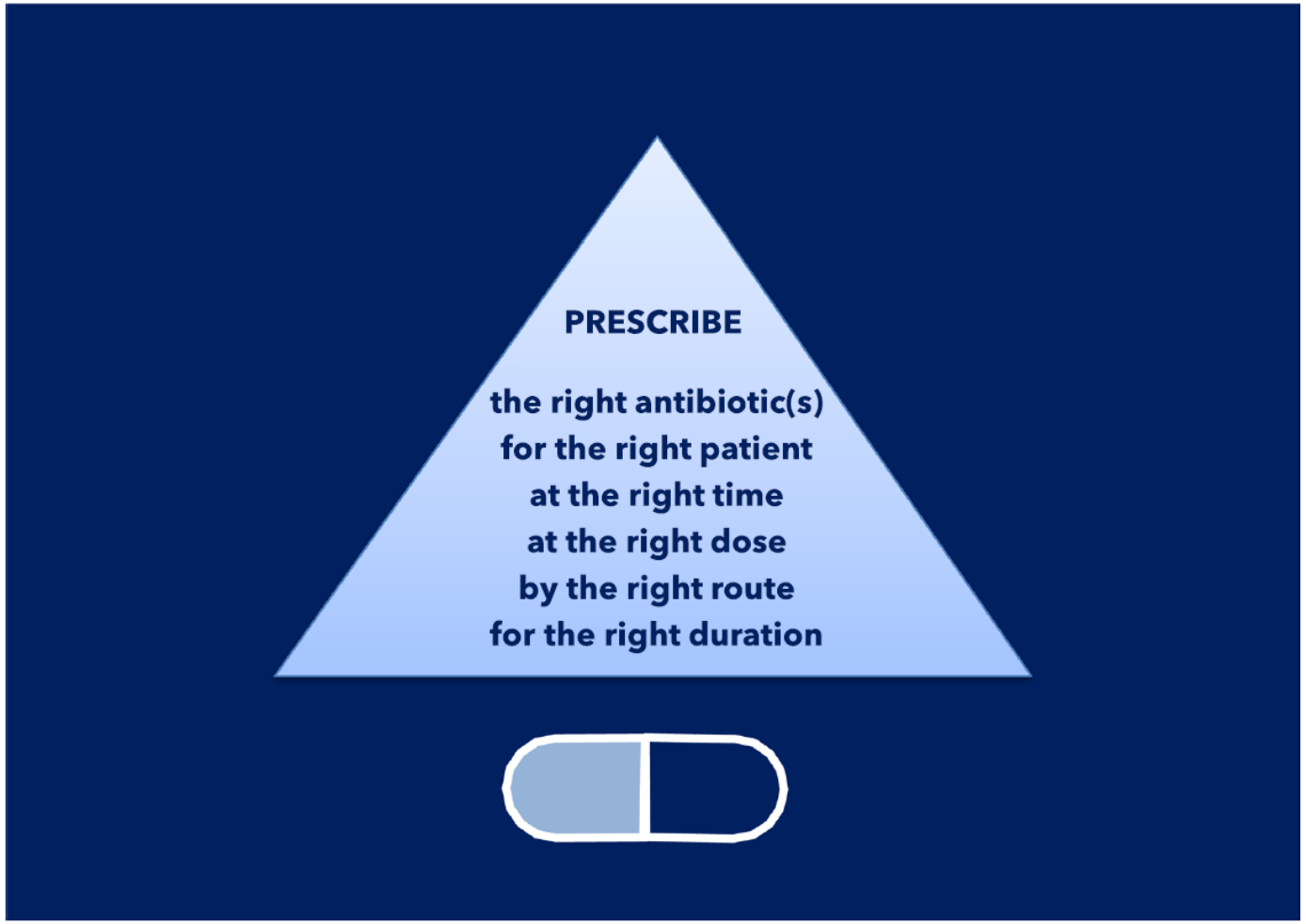
TEN GOLDEN RULES FOR OPTIMAL ANTIBIOTIC USE IN HOSPITAL SETTINGS: THE WARNING CALL TO ACTION

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

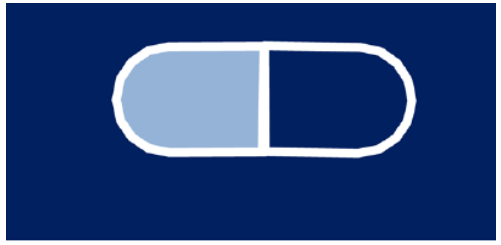
World J Emerg Surg 2023 Oct 16; 18(1):50. doi: 10.1186/s13017-023-00518-3

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



1° PK/PD PILL

at the right dose



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)	Preservation of more refracted dosing regimens in renal impairment	Scheduled prolonged infusion
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	✓ Maintained frequency of administration every 8 h except for severe AKI/IHD	✓ Extended infusion in 3 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	✗	✓ Extended infusion in 2 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	✓ Maintained frequency of administration every 8 h	✗ Intermittent infusion in 1 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	✓ Maintained frequency of administration every 6 h	✗ Intermittent infusion in 0.5 h
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	✓ Maintained frequency of administration every 8 h except for severe AKI/IHD	✓ Extended infusion in 3 h

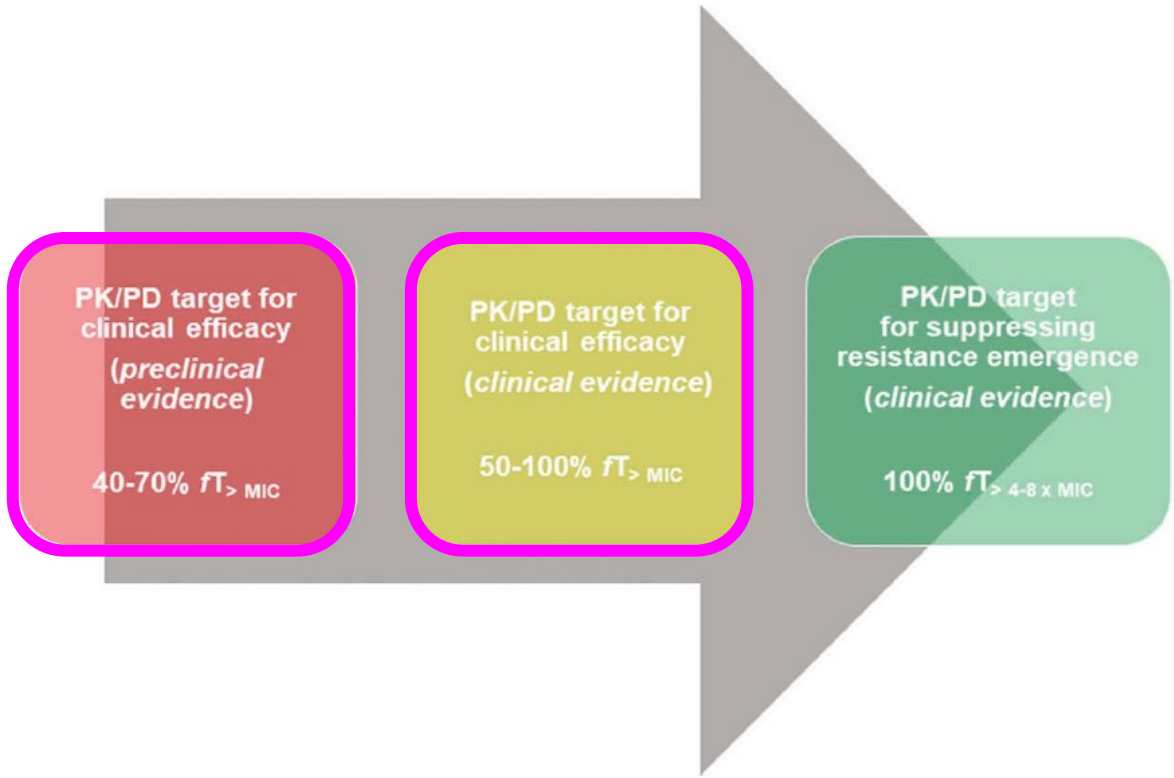
* The doubled dose is indicated for nosocomial pneumonia including ventilator-associated pneumonia

** 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

'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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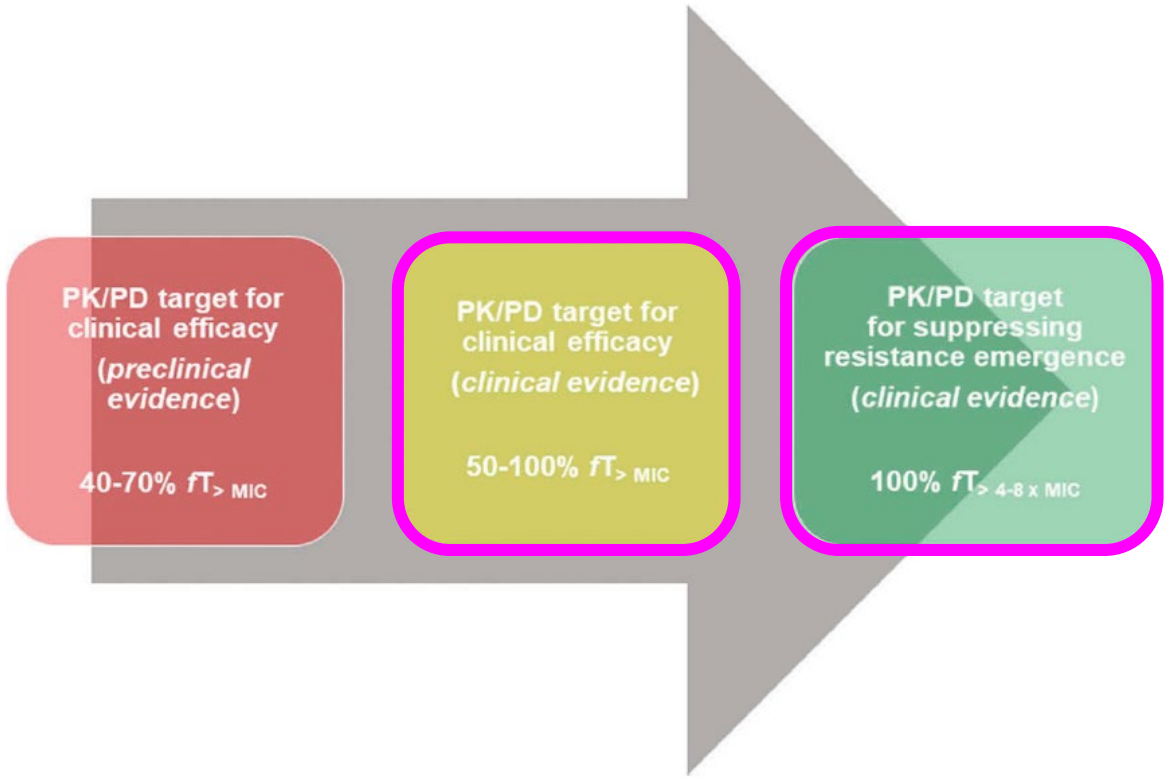


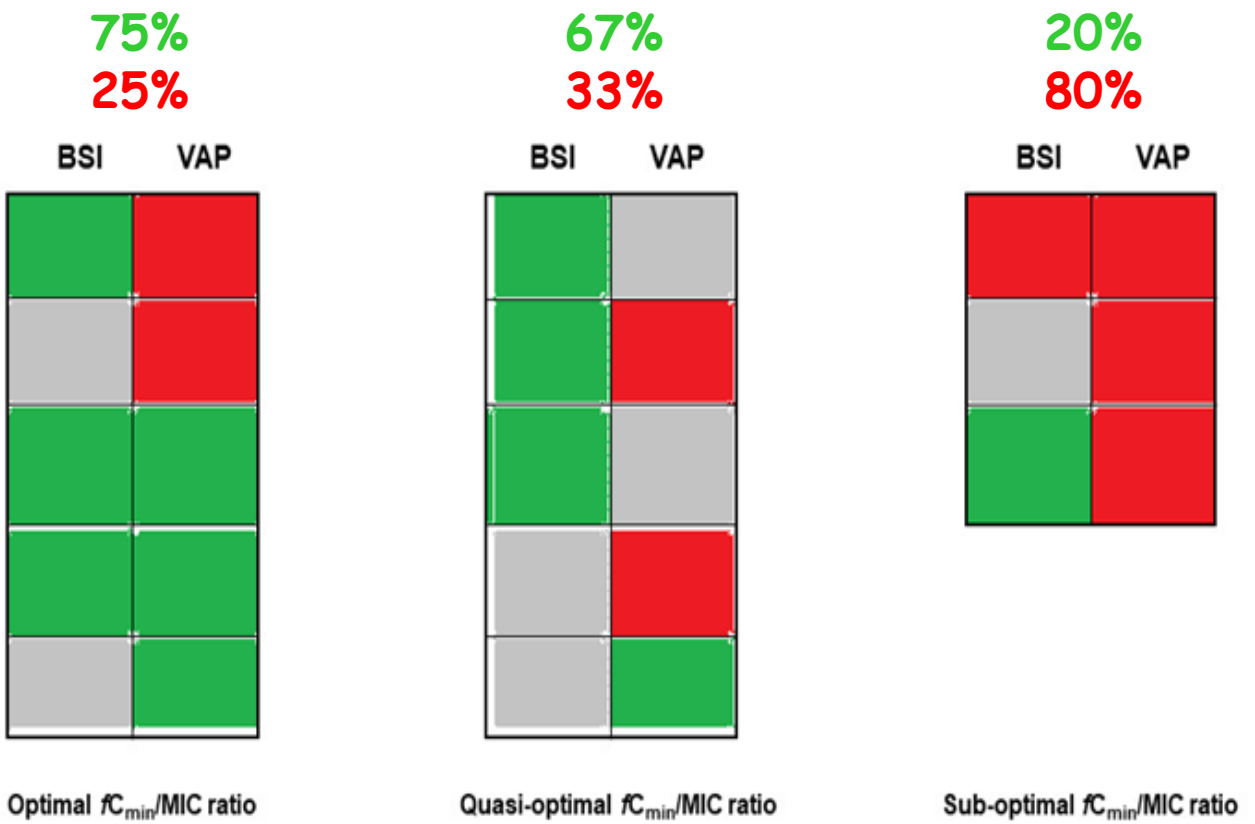
Gatti M and Pea F. *Expert Rev Anti Infect Ther* 2023 Jan 31: 1-18

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 FCMIN/MIC RATIO) ANDMICROBIOLOGICAL OUTCOME



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

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

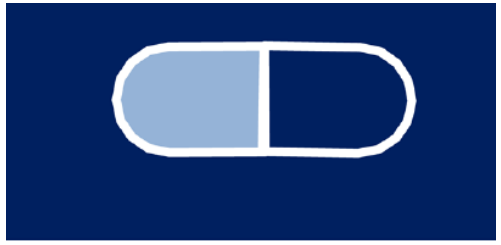
IMPORTANCE

- 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

1° PK/PD PILL

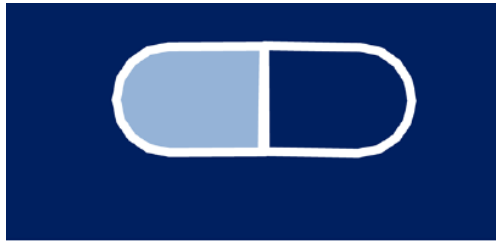
CI ADMINISTRATION IS VALUABLE FOR BETA-LACTAMS

at the right dose



2° PK/PD PILL

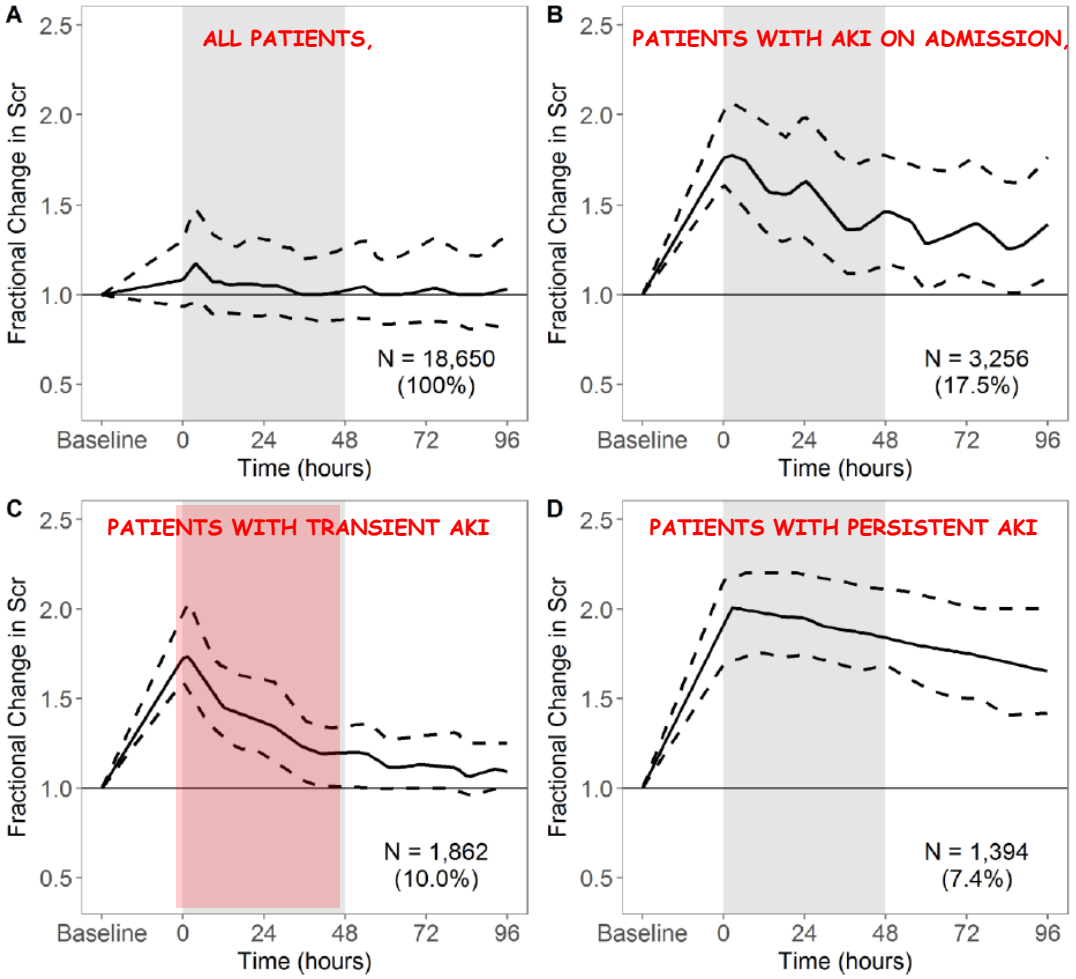
at the right dose



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%)

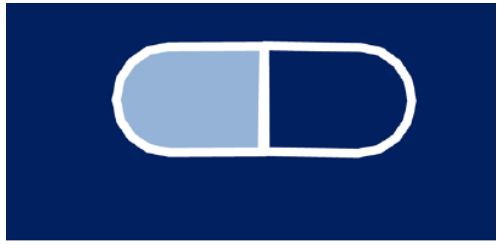
MULTIVARIABLE LOGISTIC REGRESSION MODEL OF PREDICTORS FOR PRESUMED TREATMENT FAILURE

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

2° PK/PD PILL

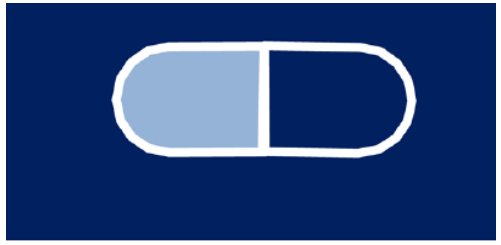
DO NOT REDUCE BETA-LACTAM DOSAGES IN THE FIRST 48H IN PATIENTS WITH SEPSIS-RELATED AKI

at the right dose

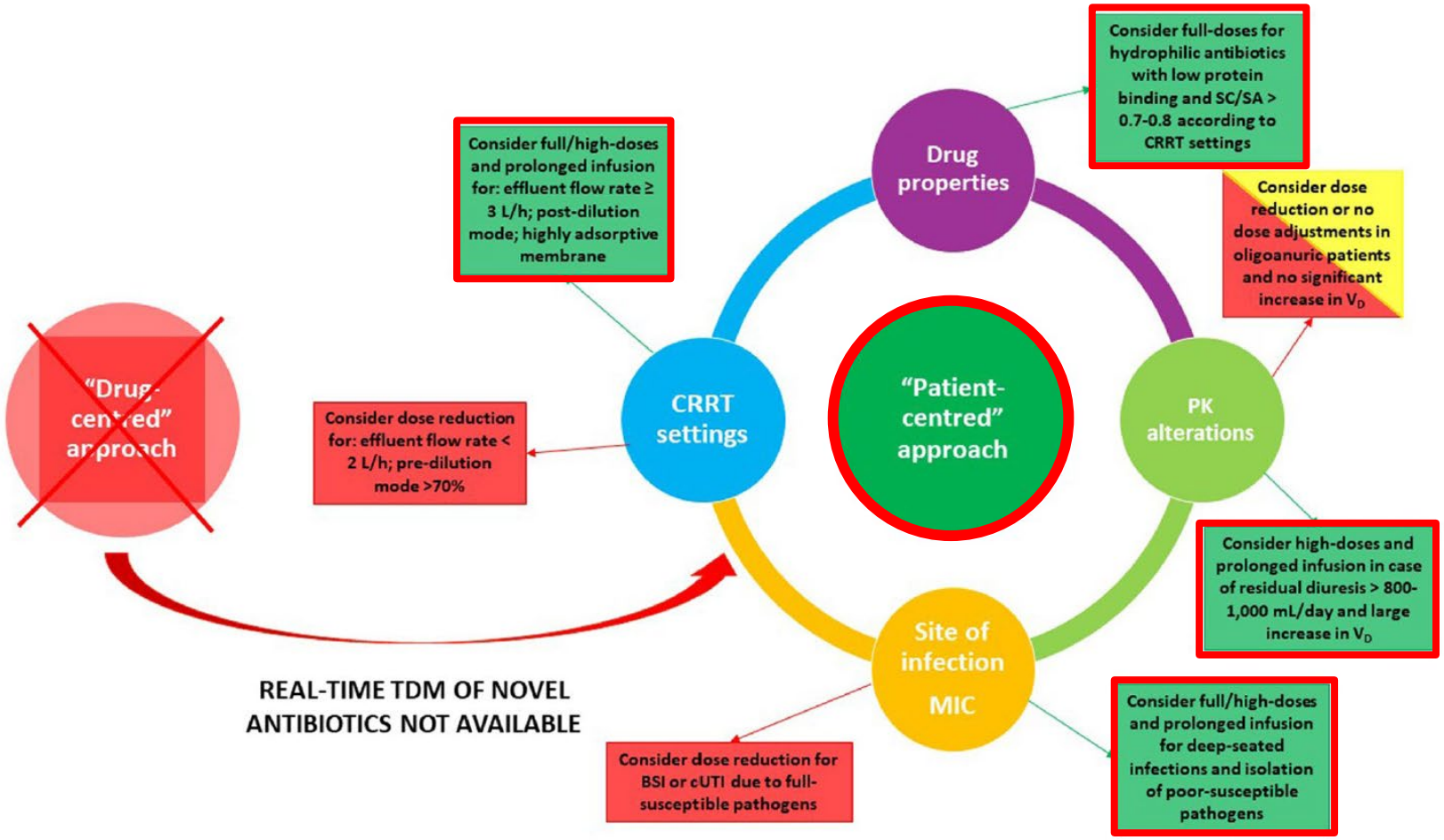


3° PK/PD PILL

at the right dose



'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

A DESCRIPTIVE PK/PD ANALYSIS OF CONTINUOUS INFUSION CEFTAZIDIME-AVIBACTAM FOR TREATING DTR GRAM-NEGATIVE INFECTIONS IN A CASE SERIES OF CRITICALLY ILL PATIENTS UNDERGOING CVVHDF

Gatti M, Rinaldi M, Gaibani P, Siniscalchi A, Tonetti T, Giannella M, Viale P, Pea F

J Crit Care 2023 Apr 12; 76: 154301

KEY FINDINGS

- A loading dose of 2.5 g over 2h was shown to grant initial adequate concentrations but the subsequent maintenance doses by CI should depend on the RRT dose and on the residual renal function of the patient, and should be hopefully TDM-guided
- In centers where real-time TDM is unfeasible, we believe that, by taking into account that in our case series the joint PK/PD targets were even more than optimal during the 2.5 q8h CI dosing regimen, a maintenance dosing regimen of 1.25 g q8h CI could be a valuable approach for ensuring optimal joint PK/PD targets against susceptible pathogens with an MIC value for ceftazidime-avibactam up to the EUCAST clinical breakpoint of 8 mg/L

REAL-TIME TDM-BASED EXPERT CLINICAL PHARMACOLOGICAL ADVICE PROGRAM FOR ATTAINING AGGRESSIVE PK/PD TARGET OF CONTINUOUS INFUSION MEROPENEM IN THE TREATMENT OF CRITICALLY ILL PATIENTS WITH DOCUMENTED GRAM- INFECTIONS UNDERGOING CVVHDF

Gatti M, Rinaldi M, Tonetti T, Siniscalchi A, Viale P, Pea F

Antibiotics 2023, 12, 1524. https://doi.org/10.3390/antibiotics12101524

MEROPENEM DOSING ECPA PROVIDED IN OUR STUDY

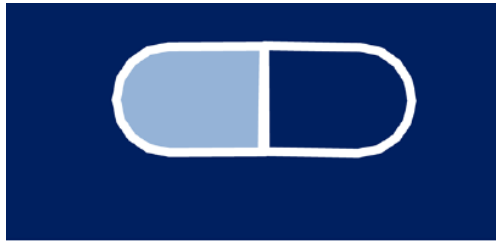
Optimal PK/PD Target	MIC of Isolated Pathogen (mg/L)	TDM-Based Meropenem Dosing ECPA Recommendation
fC_{ss}/MIC > 4	0.12	125 mg q6h over 6 h
fC_{ss}/MIC > 4	0.25–1	250 mg q6h over 6 h
fC_{ss}/MIC > 4	2	500 mg q6h over 6 h

CI: continuous infusion; C_{ss}: steady-state concentration; MIC: minimum inhibitory concentration; PK/PD: pharmacokinetic/pharmacodynamic

3° PK/PD PILL

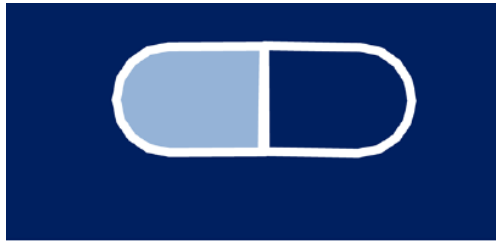
DO NOT REDUCE TOO MUCH BETA-LACTAM DOSAGES IN PATIENTS UNDERGOING HIGH-FLUX CVVHDF AND HAVING RRF

at the right dose



4° PK/PD PILL

at the right dose



LINEZOLID POPULATION PHARMACOKINETICS TO IMPROVE DOSING IN CARDIOSURGICAL PATIENTS: FACTORING A NEW DRUG-DRUG INTERACTION PATHWAY.

Pai MP, Cojutti PG, Gerussi V, Della Siega P, Tascini C, Pea F. Clin Infect Dis. 2023 Apr 3; 76(7): 1173-1179

DEMOGRAPHICS AND CLINICAL CHARACTERISTICS (N = 150)

Variable	Median or Count	Interquartile Range or Percentage
Age, years	66	58–75
Gender (male/female)	119/31	79.3/20.7
Body weight, kg	76.0	67.0–85.8
BMI, kg/m^2	25.9	23.2–28.7
BSA, m^2	1.9	1.8–2.0
Serum creatinine,[a] mg/dL	1.47	1.02–2.24
eGFR,[a] mL/minute/1.73 m^2	46.8	27.5–66.4
CRP,[a] mg/dL	147.3	70.7–236.1
Reason for linezolid use		
HAP/CAP	71	46.7
Sepsis/septic shock	38	25.0
Sternal wound infections	20	13.2
Mediastinitis	6	3.9
IAI	3	2.0
Others	14	9.2
Linezolid treatment		
Dose, mg/day	1200	600–1200
C_{trough}, mg/L	5.55	3.49–8.58
C_{peak}, mg/L	16.30	12.69–20.50
No. of TDM instances	3.0	2.0–5.0
Treatment duration, days	12.5	7.0–19.0
Linezolid tolerability		
PLT count at baseline, $\times 10^9$ cells/L	144.0	89.0–214.8
PLT count at end of treatment, $\times 10^9$ cells/L	148.0	90.0–234.0
Co-medications		
Amiodarone	73	48.7
Carvedilol, bisoprolol	42	28.0
Cyclosporine	26	17.3
Omeprazole, pantoprazole	72	48.0

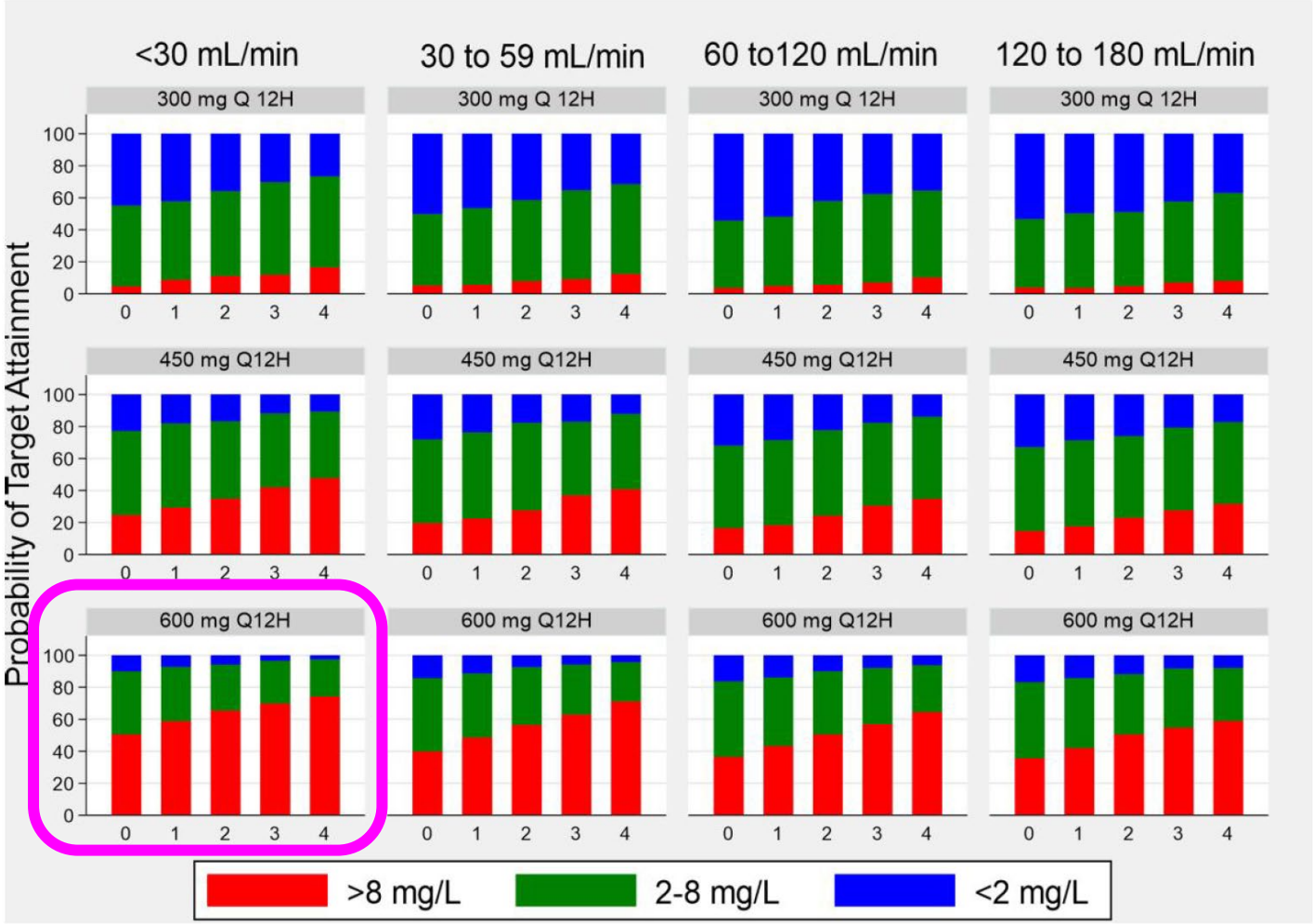
Abbreviations: BMI, body mass index; BSA, body surface area; CAP, community-acquired pneumonia; C_{peak}, peak concentration; CRP, C-reactive protein; C_{trough}, trough concentration; eGFR, estimated glomerular filtration rate; HAP, hospital-acquired pneumonia; IAI, intra-abdominal infection; PLT, platelet; TDM, therapeutic drug monitoring.

[a]Values at baseline.

LINEZOLID POPULATION PHARMACOKINETICS TO IMPROVE DOSING IN CARDIOSURGICAL PATIENTS: FACTORING A NEW DRUG-DRUG INTERACTION PATHWAY.

Pai MP, Cojutti PG, Gerussi V, Della Siega P, Tascini C, Pea F. Clin Infect Dis. 2023 Apr 3; 76(7): 1173-1179

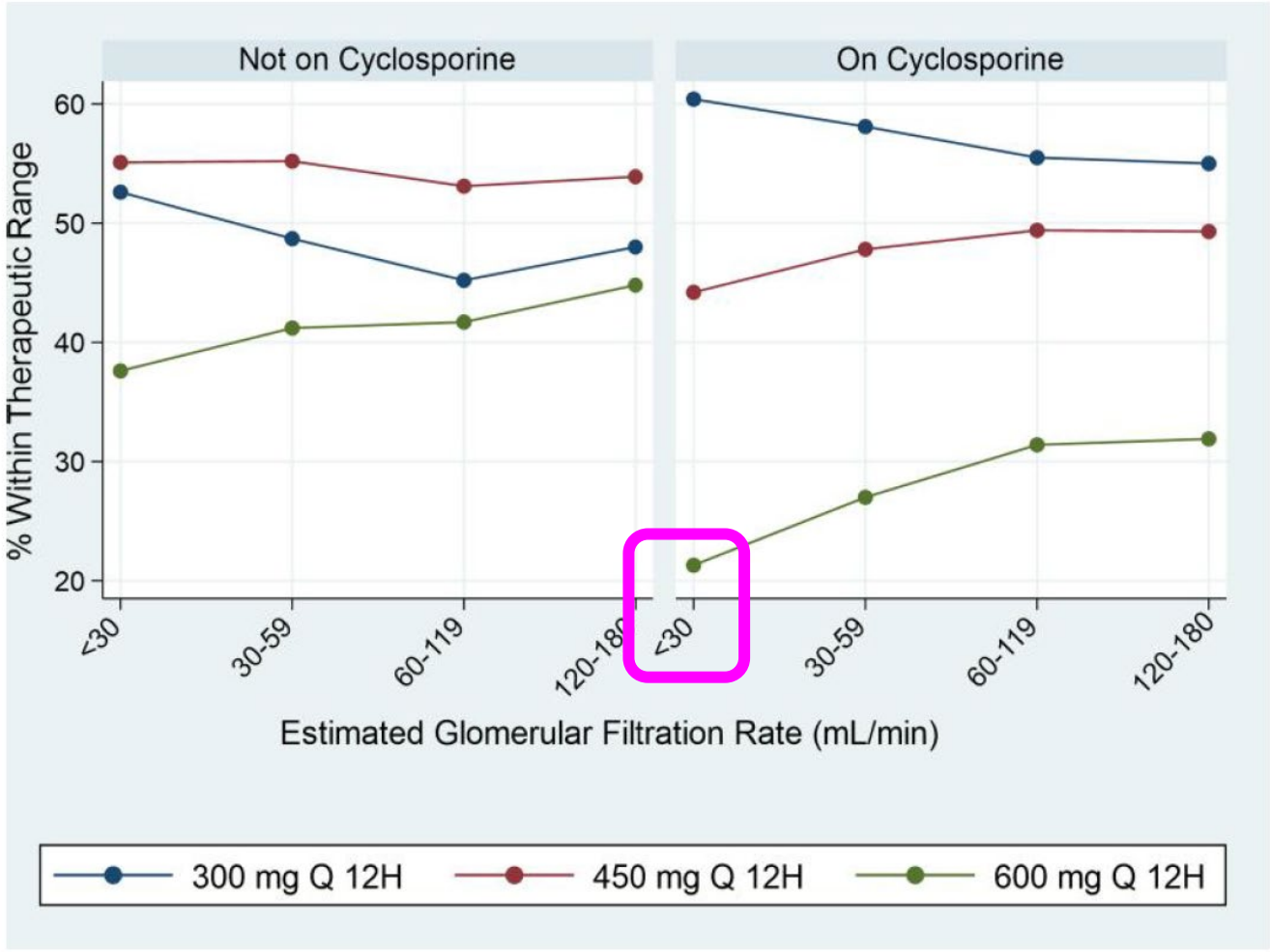
STACKED BAR GRAPH OF THE PROBABILITY OF TROUGH CONCENTRATIONS BEING IN THE TOXIC RANGE (>8 MG/L), SUBTHERAPEUTIC (<2 MG/L), OR WITHIN RANGE (2-8 MG/L) BY ESTIMATED GLOMERULAR FILTRATION RATE (IN COLUMN) AND DOSAGE REGIMEN (IN ROW) OVER THE NUMBER OF INTERACTING MEDICATIONS (X-AXIS).



LINEZOLID POPULATION PHARMACOKINETICS TO IMPROVE DOSING IN CARDIOSURGICAL PATIENTS: FACTORING A NEW DRUG-DRUG INTERACTION PATHWAY.

Pai MP, Cojutti PG, Gerussi V, Della Siega P, Tascini C, Pea F. Clin Infect Dis. 2023 Apr 3; 76(7): 1173-1179

PERCENTAGE OF SIMULATED PATIENTS WITHIN THE THERAPEUTIC RANGE (TROUGH: 2-8 MG/L) BASED ON THE LINEZOLID DOSE AND ESTIMATED GLOMERULAR FILTRATION RATE WITH AND WITHOUT CONCURRENT USE OF CYCLOSPORINE



4° PK/PD PILL

REDUCE LINEZOLID DOSE TO 300-450 MG BID IN CARDIOSURGICAL PATIENTS RECEIVING CYCLOSPORIN AND HAVING RENAL DYSFUNCTION

at the right dose