PK-PD and TDM for Dose Optimization: case-based scenario

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Case 1

- 42 y/o male, wt 64 kg, ht 175 cm Admit:22/06/2563 Consult ID: 1/7/2563
- CC: fever dyspnea
- PI: fever 2 day PTA, cough, white sputum, dyspnea, urine with sediment, diarrhea x2
- PMH:
  - U/D AIHA with cirrhosis child A (Dx 1/2562)
  - Last adm: 11/4/63-6/6/63: active AIHA, ceftriaxone-resistant P. vulgaris/E. coli- UTI tx with ertapenem, XDR-AB,KP colonization in the sputum (20/5/63)
- Current medication: prednisolone (5) 2x1 pc, Azathioprine (50) 1x1 pc

Case 1

- **PE**: **V/S** T 38.5 HR 110 BP 89/56 RR 30 O_2SAT 92 (room air)
  - HEENT, Heart, Abd, neuro: normal
  - Lung: rhonchi, wheezing both lower lungs
- **CXR**: infiltration both lower lobe
- **Lab**:
  - CBC: WBC 14800, PNM 89%, Lym 10%, Mono 1%, Hb 11, Hct 32, plt 267000
  - Electrolyte: Na 143, K 3.5, CL 104, HCO3 20
  - Scr 0.89, BUN 13, AST 90, ALT 55, ALP 130, TB 0.5, DB 0.3, ID 0.2
  - Lactate 2.5
  - Nasal swab for Influenza A/B/RSV-PCR: pending
  - Sputum g/s: moderate gram pos rod, few gram neg rod, PMN numerous, epithelium numerous
  - H/Cx2: pending
  - U/A: WBC 1-2, RBC 3-5
  - U/C: pending
- Dx: severe CAP with septic shock in immunocompromised host

Case 1

- **21/6/2563: ผู้ป่วยใส่ tube admit ICU**
- **Start Empirical Treatment**
  - NE (8:250) rate 10 microdrop/min
  - Meropenem 2 g + nss 100 ml drip in 1 h then 1 g + Nss 100 ml drip in 1 h q 8 h
  - Azithromycin (250) 2x1 ac
  - Oseltamivir (75) 1x2 pc
  - Continue: prednisolone 10 mg/d, Azathioprine 50 mg/day
- Clcr = 97.87 mL/min

Lertwattanachai et al. Journal of Intensive Care (2020) 8:26
https://doi.org/10.1186/s40560-020-00442-7

Journal of Intensive Care

RESEARCH Open Access

Clinical outcomes of empirical high-dose meropenem in critically ill patients with sepsis and septic shock: a randomized controlled trial

Tospon Lertwattanachai[1], Preecha Montakantikul[1], Viratch Tangsujaritvijit[2,3], Pitsucha Sanguanwit[4], Jetjamnong Sueajai[5], Saranya Auparakkitanon[5] and Pitchaya Dilokpattanamongkol[1*]

- n = 79
- high-dose meropenem (2-g infusion over 3 h every 8 h) versus the standard-dose meropenem (1-g infusion over 3 h every 8 h) in sepsis and septic shock patients.

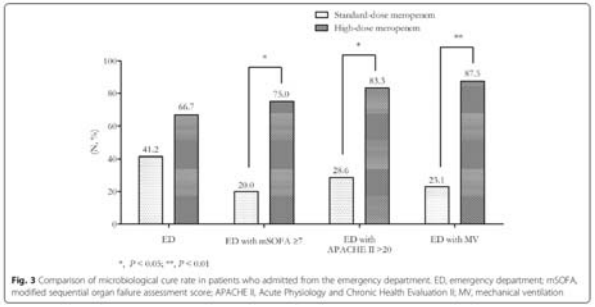


Fig. 3 Comparison of microbiological cure rate in patients who admitted from the emergency department. ED, emergency department; mSOFA, modified sequential organ failure assessment score; APACHE II, Acute Physiology and Chronic Health Evaluation II; MV, mechanical ventilation

25/6/2563

- **25/6/2563**: ผู้ป่วยย้ายออกจาก **ICU with off ETT** มาที่วอร์ดสามัญ
- **PE**: v/s T 37.3 HR 80 BP 110/75 RR 18 O_2SAT 99 (room air)
- **Lab**
- Nasal swab for Influenza A/B/RSV-PCR: negative
- Sputum
  - G/S: moderate gram pos rod, few gram neg rod, PMN numerous, epithelium numerous
  - C/S: normal flora
- H/Cx2: no growth
- U/C: mix organism

26/9/2563

- ผู้ป่วยมีไข้ ซึมลง ปลุกไม่ตื่น ใส่ ETT ใหม่
- **PE**: V/S T 39 HR 105 BP 96/64 RR 30 O_2SAT 90 (room air)
  - HEENT, Heart, Abd: normal
  - Lung: rhonchi and wheezing at right lower lobe
  - Neuro: E2VTM3, alteration of conscious
- CXR: new infiltration at right middle lobe
- Lab:
  - CBC: WBC 21600, PNM 85%, Lym 13%, Mono 2%, Hb 10, Hct 29, plt 147000
  - Electrolyte: Na 140, K 4.3, CL 105, HCO3 25
  - Scr 1.2, BUN 15, AST 120, ALT 60, ALP 150, TB 1.3, DB 0.8, ID 0.5, Alb 2.4
  - Lactate 1.3
  - Sputum g/s: pending , H/Cx2: pending, U/A: WBC 1-2, RBC 5-10, U/C: pending

26/9/2563

- r/o HAP with sepsis in immunocompromised host
- **Empirical Treatment**:
  - NSS 1000 ml load
  - Meropenem 2 g + nss 100 ml drip in 1 h then 1 g + Nss 100 ml drip in 1 h q 8 h

- CrCl = 72 mL/min

1/7/2563

- **Lab**
- Sputum
  - G/S: moderate gram neg coccobacilli, PMN numerous, epithelium rare
  - C/S: *Acinetobacter baumannii* (XDR)
    - Susceptibility: Tigecycline (MIC = 1)
    - Intermediate: Colistin (MIC ≤ 1)
- H/C
  - ขวดที่ 1: no growth
  - ขวดที่ 2 at 11 h 23 min: *Acinetobacter baumannii* (XDR) (AST – Phoenix®)

ATB	MIC	SIR
Amikacin	>32	R
Ampicillin/sulbactam	>16	R
Cefoperazone/sulbactam		R
Cefepime	>16	R
Ceftazidime	>16	R
Ciprofloxacin	>2	R
Colistin	<=1	I
Gentamicin	>8	R
Fosfomycin	>1024 (E-test)	ไม่มีมาตรฐาน CLSI ในการแปลผล
Imipenem	>8	R
Meropenem	>16	R
Piperacillin/tazobactam	>64	R
Tigecycline	4	R
Sitafloxacin	-	Zone site = 19 mm
Sulbactam	64 (E-test)	ไม่มีมาตรฐาน CLSI ในการแปลผล

Antibiotics for *A. buamannii*

Antibiotics	MIC	CLSI 2020 BP
Colistin	≤ 1	I ≤ 2
Sulbactam	MIC >16, = 64 (E-test)	Amp/sulb R ≥32/16
Meropenem	>16	R ≥ 8
Tigecycline	4	NA
Sitafloxacin	Zone site 19 mm	NA

antibiotics MDPI

Article

In Vitro Activities of Colistin and Sitafloxacin Combinations against Multidrug-, Carbapenem-, and Colistin-Resistant *Acinetobacter baumannii* Using the Broth Microdilution Checkerboard and Time-Kill Methods

Vipavee Rodjun [1], Jantana Houngsaitong [2,*], Preecha Montakantikul [2], Taniya Paiboonvong [3], Piyatip Khuntayaporn [2], Pattareeya Yanyongchaikit [2] and Pusana Sriyant [2]

Table 1. Activity of colistin and sitafloxacin against *A. baumannii* as single agents and in combination.

Agent	MDR-AB (263 Isolates)					CRAB (258 Isolates)					CoR-AB (43 Isolates)				
	Alone			In Combination		Alone			In Combination		Alone			In Combination	
	MIC Range (mg/L)	$MIC_{50/90}$ (mg/L)	%S	MIC Range (mg/L)	$MIC_{50/90}$ (mg/L)	%S	MIC Range (mg/L)	$MIC_{50/90}$ (mg/L)	%S	MIC Range (mg/L)	$MIC_{50/90}$ (mg/L)	%S	MIC Range (mg/L)	$MIC_{50/90}$ (mg/L)	%S	MIC Range (mg/L)	$MIC_{50/90}$ (mg/L)	%S
colistin	0.5–16	2/4	86.7	0.06–8	0.5/1	99.6	0.5–16	2/4	87.2	0.06–8	0.5/1	99.6	4–16	8/8	0	0.05–8	1/2	95.4
sitafloxacin	0.02–8	1/2	96.6	0.01–4	0.5/1	99.2	0.02–8	1/2	96.5	0.01–4	0.5/1	99.2	0.02–8	0.5/1	95.4	0.02–2	0.25/1	100

MDR-AB, multidrug-resistant *Acinetobacter baumannii*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CoR-AB, colistin-resistant *Acinetobacter baumannii*; $MIC_{50/90}$, the minimum inhibitory concentration at which 50% and 90% of the isolates are inhibited; mg/L, milligrams per liter; %S, percentage susceptibility; MIC, minimal inhibitory concentration; $MIC_{50/90}$, the minimum inhibitory concentration of the 50th and 90th percentiles.

Antibiotics **2020, 9, 516; doi:10.3390/antibiotics9080516**

Antimicrobial Agents and Chemotherapy®

PHARMACOLOGY

Pharmacokinetics and Penetration of Sitafloxacin into Alveolar Epithelial Lining Fluid in Critically Ill Thai Patients with Pneumonia

Taniya Paiboonvong,[a] Wichit Nosoongnoen,[a] Korbtham Sathirakul,[a] Viratch Tangsujaritvijit,[b] Jaipak Kaemapairoj,[b] Pramote Tragulpiankit,[a] Preecha Montakantikul[a]

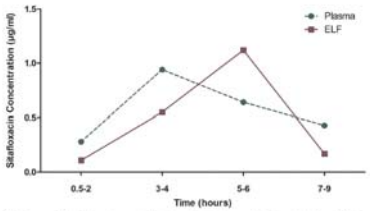


FIG 1 The median of sitafloxacin concentration-time profiles in plasma and ELF after a single dose of 200 mg during 0.5 to 2, 3 to 4, 5 to 6, and 7 to 9 h.

TABLE 3 Concentrations of sitafloxacin in plasma and epithelial lining fluid

	Concentration [mean ± SD (median) μg/ml]			ELF to plasma ratio [mean ± SD (median)]	
Time (h)	Total plasma	Unbound plasma	ELF	Total	Unbound
0.5–2	0.60 ± 0.46 (0.43)	0.39 ± 0.28 (0.28)	0.19 ± 0.20 (0.11)	0.30 ± 0.20 (0.37)	0.45 ± 0.28 (0.59)
3–4	1.37 ± 0.51 (1.56)	0.81 ± 0.34 (0.94)	0.48 ± 0.29 (0.55)	0.32 ± 0.11 (0.35)	0.54 ± 0.17 (0.59)
5–6	1.99 ± 2.34 (1.01)	1.32 ± 1.58 (0.64)	1.07 ± 0.93 (1.12)	0.63 ± 0.42 (0.42)	0.98 ± 0.66 (0.63)
7–9	0.85 ± 0.77 (0.67)	0.55 ± 0.49 (0.43)	0.61 ± 0.77 (0.17)	0.67 ± 0.38 (0.89)	1.02 ± 0.58 (1.33)

Antimicrobial Agents and Chemotherapy 2019;63(10):e00800-19.

Case 2

- ผู้ป่วยชายไทยคู่ อายุ 82 ปี น้ำหนัก 55 kg ส่วนสูง 170 cm **Admit** 25/04/2563, **Consult ID** 25/04/2563
- CC: ไข้ ซึมลง
- PI: ไข้ ซึมลง ปัสสาวะมีตะกอน หลัง D/C 3 วัน
- PMH: U/D DLBCL CD20+
  - **Last admit** 25/3/2563 – 22/4/2563 มาด้วย prolong fever: 1st diagnosis DLBCL CD20+ Treatment: CHOP regimen cycle 1 (17/4/2563) then dexamethasone 4 mg iv q 6 h (10 -22/4/2563) , fever unknown origin Empiric ATB: meropenem 1 g iv q 8 h (24/3 – 8/4/63)
- Current medication: prednisolone (5) 3x2 pc (22/4 – now), cyclophosphamide (50) 1x1 pc (22/4-now)

Case 2

- **PE**: v/s T 39 HR 80 BP 100/70 RR 22 O_2SAT 95 (room air)
  - HEENT, Heart, Abd, lung: normal
  - Neuro: E3V3M5, motor power grade 4 all
- CXR: no new infiltration
- Lab:
  - CBC: WBC 100, PNM 0%, Hb 8, Hct 26, plt 140000
  - Electrolyte: Na 138, K 3.3, CL 100, HCO3 18
  - Scr 0.72, BUN 14, AST 45, ALT 50, ALP 100, TB 0.4, DB 0.3, ID 0.1
  - H/Cx2: pending
  - U/A: WBC 2-3, RBC 3-5
  - U/C: pending
- Dx: fever with UTI in immunocompromised host

Case 2

- **Empirical Treatment**:
  - Meropenem 2 g + nss 100 ml drip in 1 h then 1 g + Nss 100 ml drip in 1 h q 8 h
  - Continue: prednisolone 15 mg/d
- 27/4/2563
  - H/C (25/4)
    - ขวดที่ 1: at 14 h 8 min: gram negative bacilli
    - ขวดที่ 2 at 11 h 51 min: gram negative bacilli
  - U/C (25/4): *Klebsiella pneumoniae*

ATB	MIC	SIR
Amikacin	<=8	S
Ampicillin/sulbactam	>16	R
Ampicillin	>16	R
Cefepime	>16	R
Ceftazidime	>16	R
Ceftriaxone	>4	R
Ciprofloxacin	>2	R
Ertapenem	>1	R
Gentamicin	<=2	S
Imipenem	>8	R
Meropenem	>16	R
Piperacillin/tazobactam	>64	R
Cotrimoxazole	>4	R
Ceftazidime/avibactam	>8	R
Colistin	<=1	I

Dx: *Klebsiella pneumoniae* (CRE) UTI with GNB bacteremia in immunocompromised host

28/4/2563

- H/C (25/4)
  - ขวดที่ 1: at 14 h 8 min: *Klebsiella pneumoniae* (CRE)
  - ขวดที่ 2 at 11 h 51 min: *Klebsiella pneumoniae* (CRE)

ATB	MIC	SIR
Amikacin	>32	R
Ampicillin/sulbactam	>16	R
Ampicillin	>16	R
Cefepime	>16	R
Ceftazidime	>16	R
Ceftriaxone	>4	R
Ciprofloxacin	>2	R
Ertapenem	>1	R
Gentamicin	<=2	S
Imipenem	>8	R
Meropenem	>16	R
Piperacillin/tazobactam	>64	R
Cotrimoxazole	>4	R
Ceftazidime/avibactam	>8	R
Colistin	<=1	I
Tigecycline	<=4	ไม่มีมาตรฐาน CLSI ในการแปลผล
Fosfomycin	48	

ATB	MIC	SIR
Amikacin	>32	R
Ampicillin/sulbactam	>16	R
Ampicillin	>16	R
Cefepime	>16	R
Ceftazidime	>16	R
Ceftriaxone	>4	R
Ciprofloxacin	>2	R
Ertapenem	>1	R
Gentamicin	<=2	S
Imipenem	>8	R
Meropenem	>16	R
Piperacillin/tazobactam	>64	R
Cotrimoxazole	>4	R
Ceftazidime/avibactam	>8	R
Colistin	<=1	I
Tigecycline	<=4	ไม่มีมาตรฐาน CLSI ในการแปลผล
Fosfomycin	48	

Treatment

- **Off**: meropenem
- **Add** colistin 300 mg in nss 100 ml drip in 30 min then 150 mg in nss 100 ml drip in 30 min q 12 h
- **Add** fosfomycin 6 g in D5W 200 ml drip in 4 h q 8 h
- **Continue**: prednisolone 15 mg/d

- Crcl = 61.54 mL/min

Dosage regimens of colistin for CRE

- Empirically predict the right dosage regimen for the whole population and specific dosage regimen for each MIC

Article

Pharmacokinetic/Pharmacodynamic (PK/PD) Simulation for Dosage Optimization of Colistin Against Carbapenem-Resistant *Klebsiella pneumoniae* and Carbapenem-Resistant *Escherichia coli*

Kamonchanok Jitaree [1], Korbtham Sathirakul [1], Jantana Houngsaitong [1], Orarik Asuphon [2], Weerayuth Saelim [3], Visanu Thamlikitkul [4,*] and Preecha Montakantikul [5,*]

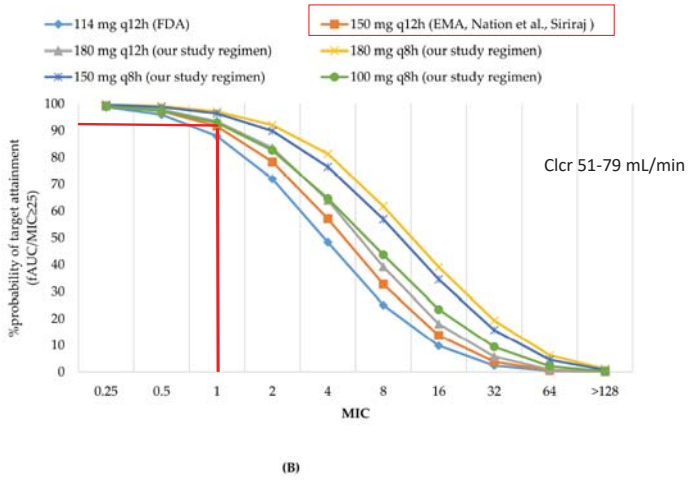
Jitaree K. Antibiotics **2019**, 8, 125; doi:10.3390/antibiotics8030125

MIC Distribution of CRE at Siriraj Hospital

Table 4. Minimum inhibitory concentrations (MICs) distribution of colistin.

MIC (mcg/mL)	0.25	0.5	1	2	4	8	16	32	64	>128	MIC_{50} (mcg/mL)	MIC_{90} (mcg/mL)
All isolates (n = 116)	3	55	19	14	4	5	10	4	1	1	1	16
%	2.58	47.41	16.38	12.07	3.45	4.31	8.6	3.45	0.86	0.86	CoRO = 21.53%	
Colistin-Susceptible Isolates (MIC ≤ 2 mcg/mL)												
K. pneumoniae (n = 74)	3	40	18	13	-	-	-	-	-	-	0.5	2
E. coli (n = 17)	-	15	1	1	-	-	-	-	-	-	0.5	0.5
Colistin-Resistant Isolates (MIC > 2 mcg/mL)												
K. pneumoniae (n = 22)	-	-	-	-	3	4	10	3	1	1	16	32
E. coli (n = 3)	-	-	-	-	1	1	-	1	-	-	8	32

Jitaree K. Antibiotics **2019**, 8, 125; doi:10.3390/antibiotics8030125



Jitaree K. Antibiotics **2019**, 8, 125; doi:10.3390/antibiotics8030125

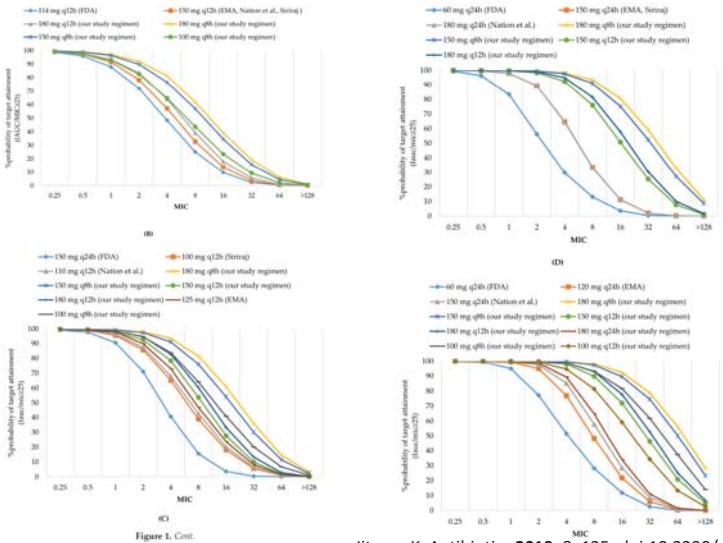


Figure 1. Cont.

Jitaree K. Antibiotics **2019**, 8, 125; doi:10.3390/antibiotics8030125

Colistin Dosage Regimens

Table 5. The recommended dose based on the ability to achieve PTA target at various MICs.

Creatinine Clearance (mL/min)	MIC 0.5 mcg/mL Daily Dose (CBA)	MIC 2 mcg/mL Daily Dose (CBA)	MIC 8 mcg/mL Daily Dose (CBA)
≥80	150 mg every 12 h (EMA, FDA)	Not recommended	Not recommended
51–79	114 mg every 12 h (FDA)	180 mg every 8 h (our study)	Not recommended
30–50	150 mg every 24 h (FDA)	150 mg every 12 h (our study)	Not recommended
11–29	60 mg every 24 h (FDA)	150 mg every 12 h (our study)	150 mg every 8 h (our study)
≤10	60 mg every 24 h (FDA)	120 mg every 24 h (EMA)	180 mg every 12 h (our study)

Jitaree K. Antibiotics **2019**, 8, 125; doi:10.3390/antibiotics8030125

Fosfomycin

- Empirical dosage regimen and specific dosage regimen for each MIC
- MIC distribution: CRE from King Chulalonkorn Memorial Hospital 2016-2018.

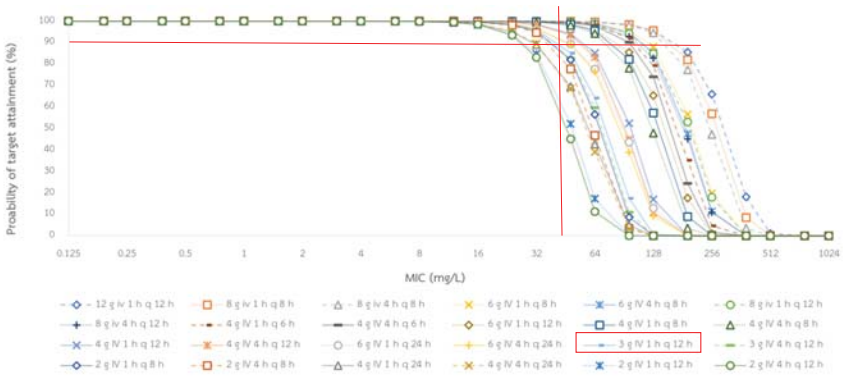
antibiotics

MDPI

Article

Evaluation of Intravenous Fosfomycin Disodium Dosing Regimens in Critically Ill Patients for Treatment of Carbapenem-Resistant Enterobacterales Infections Using Monte Carlo Simulation

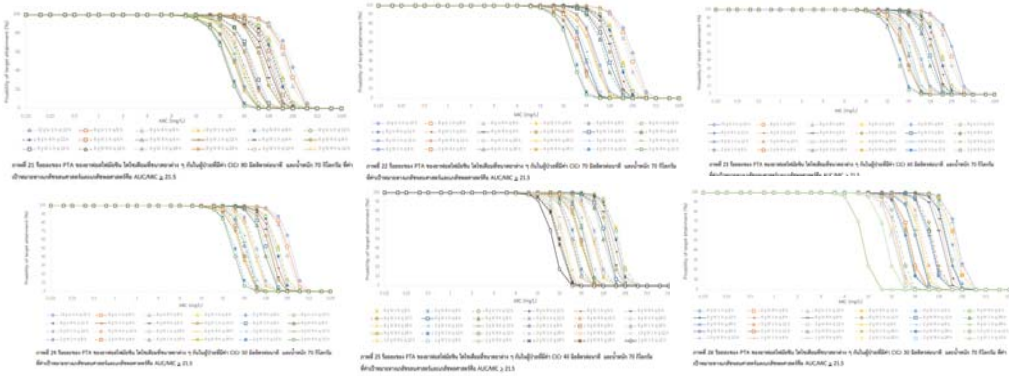
Pannee Leelawattanachai [1,2], Thitima Wattanavijitkul [3], Taniya Paiboonvong [4], Rongpong Plongla [5,6], Tanittha Chatsuwan [6,7], Sang Usayaporn [3], Wichit Nosoongnoen [1] and Preecha Montakantikul [1,*]



ภาพที่ 12 ร้อยละของ PTA ของยาฟอสโฟมัยซิน ไดโซเดียมที่ขนาดยาต่าง ๆ กันในผู้ป่วยที่มีค่า CICr 60 มิลลิลิตรต่อนาที และน้ำหนัก 50 กิโลกรัม ที่ค่าเป้าหมายทางเภสัชจลนศาสตร์และเภสัชพลศาสตร์คือ AUC/MIC ≥ 21.5

Antibiotics **2020**, 9, 615; doi:10.3390/antibiotics9090615

Fosfomycin



Antibiotics **2020**, 9, 615; doi:10.3390/antibiotics9090615

Table 2. Daily dosing suggestions for intravenous fosfomycin disodium to treat carbapenem-resistant Enterobacterales infections, according to CLSI and EUCAST breakpoints.

CLCr (mL/min) [a]	Daily Doses Suggestion		Dosage Adjustments
	CLSI Breakpoints [b]	EUCAST Breakpoints [c]	
≥80	16 g per day (in 2 or 4 divided doses) (1 h or 4 h infusion)	8 g per day (in 2 divided doses) (1 h or 4 h infusion)	Initial dosage
50 to <80	12 g per day (in 2 to 3 divided doses) (1 h or 4 h infusion)	6 g per day (in 1 to 3 divided doses) (1 h or 4 h infusion)	Reduce maintenance dosage by 25%
30 to <50	8 g per day (in 2 divided doses) (1 h or 4 h infusion)	4 g per day (in 1 to 2 divided doses) (1 h or 4 h infusion)	Reduce maintenance dosage by 50%
15 to <30	6 g per day (in 1 to 2 divided doses) (1 h or 4 h infusion)	3 g per day (in 1 to 2 divided doses) (1 h or 4 h infusion)	Reduce maintenance dosage by 62.5%
<15	4 g per day (in 1 divided doses) (1 h infusion)	2 g per day (in 1 divided doses) (1 h infusion)	Reduce maintenance dosage by 75%

[a] Creatinine clearance (CLCr) estimated by Cockcroft-Gault Equation. [b] Clinical and Laboratory Standards Institute (CLSI) breakpoints (MICs ≤ 64 mg/L) to treat urinary tract infection caused by carbapenem-resistant *Escherichia coli*. [c] European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints (MICs ≤ 32 mg/L) to treat carbapenem-resistant Enterobacterales infection.

Antibiotics **2020**, 9, 615; doi:10.3390/antibiotics9090615

Conclusion

- PKPD is a useful tool to help predict the appropriate dosage regimens for MDR to enhance efficacy and reduce side effects