การประชุมใหญ่วิชาการประจำปี ครั้งที่ 45
สมาคมโรคติดเชื้อแห่งประเทศไทย
"Bridging science to practice"
ระหว่างวันที่ 11-14 ตุลาคม 2562
ณ โรงแรมรอยัล คลิฟ โฮเต็ล กรุ๊ป พัทยา จังหวัดชลบุรี

PK/PD optimization: Back to Basics

Wichai Santimaleeworagun

B. Pharm, M. Pharm (Clinical Pharmacy),
PhD. (Pharmaceutical Care),
Board Certified Pharmacotherapy (BCP),
Board Certified Infectious Disease Pharmacist (BCIDP)
Faculty of Pharmacy, Silpakorn University

OUTLINES

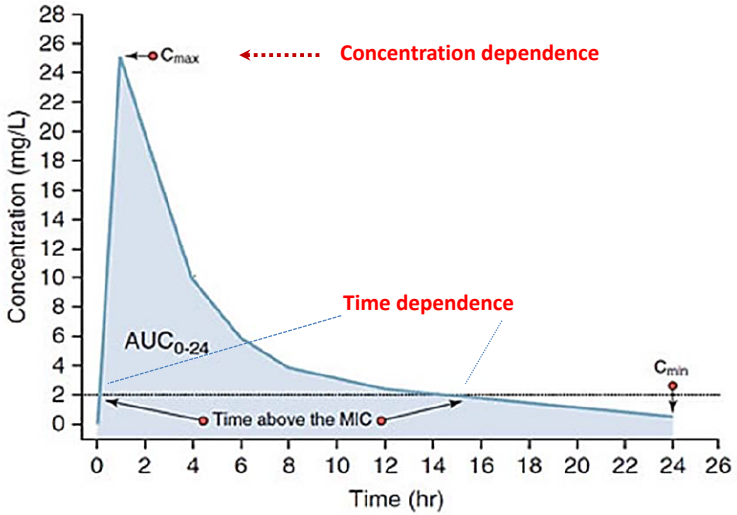
PK/PD optimization: Back to Basics

- Principle of PK/PD relationships
- Update in Antibiotic PK/PD: antibiotic dosing regimens
  - Beta-lactams
  - Aminoglycosides (amikacin, gentamicin)
  - Vancomycin
  - Fluoroquinolones

Principle of pharmacokinetic and pharmacodynamics relationships

- คุณสมบัติต้านเชื้อที่ดี ต้องสัมพันธ์ระหว่าง PK และ PD (PK/PD relationship)
- คุณสมบัติการต้านเชื้อของยาต้านจุลชีพมี 2 ประเภทหลัก คือ

1) ฤทธิ์ของยาขึ้นอยู่กับความเข้มข้นยา (concentration dependent effect)
   - ยิ่งความเข้มข้นยาสูงกว่าค่า MIC ของเชื้อมาก ยิ่งออกฤทธิ์ต้านเชื้อได้มาก
2) ฤทธิ์ของยาขึ้นอยู่กับระยะเวลาที่ความเข้มข้นยาอยู่เหนือค่า MIC (time dependent effect)
   - ระยะเวลาที่ความเข้มข้นยาสูงกว่าค่า MIC ยาวนานมากเท่าใด การออกฤทธิ์ต้านเชื้อจะดียิ่งขึ้นเป็นลำดับ



รูป PK parameter: minimum serum concentration (Cmin), maximum serum concentration (Cmax), 24-h area under the curve (AUC24)

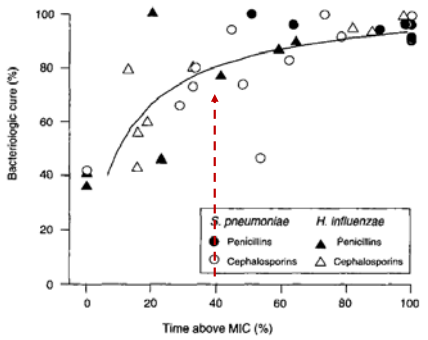
Principle of pharmacokinetic and pharmacodynamics relationships

PK/PD parameters	Antimicrobial class or agents (targeted value)
Time above the MIC (Time dependence)	Penicillins (≥40%, ≥50%) Cephalosporins (≥40%, ≥60-70%) Carbapenems (≥20%, ≥40%) Macrolides, and clindamycin
Cmax/MIC (concentration dependence)	Aminoglycosides (≥8-10 times)
24-hour AUC/MIC (concentration & time dependence)	Fluoroquinolones (Gram pos ≥25, Gram neg ≥125) Vancomycin (≥ 400) Azithromycin Tetracyclines

OUTLINES

PK/PD optimization: Back to Basics

- **Principle of PK/PD relationships**
- **Update in Antibiotic PK/PD: antibiotic dosing regimens**
  - **Beta-lactams**
  - **Aminoglycosides (amikacin, gentamicin)**
  - **Vancomycin**
  - **Fluoroquinolones**



BACK TO BASICS

β-lactam: %Time>MIC

Figure: Bacteriological cure versus time above MIC in otitis media

Craig and Andes. Pediatr Infect Dis J. 1996 ;15(3):255-9

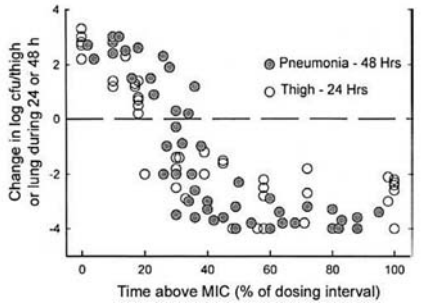


Figure: Relationship between time above MIC and change in bacterial numbers for numerous strains of *S. pneumoniae* at 24 and 48 h in the thighs and lungs, respectively, of mice with neutropenia after they received therapy with amoxicillin or amoxicillin/clavulanate.

Clin Infect Dis. 2001 ;33 Suppl 3:S233-7

Table: Percentage of the dosing interval when the unbound drug concentration in animal infection models

Antibiotic class	$fT > MIC$ (%)	
	Bacteriostasis	Maximal killing
Cephalosporins	40	60–70
Penicillins	30	50
Carbapenems	20	40

Clin Exp Pharmacol Physiol. 2012 ;39(6):489-96

Pharmacokinetics and pharmacodynamics of meropenem in febrile neutropenic patients with bacteremia

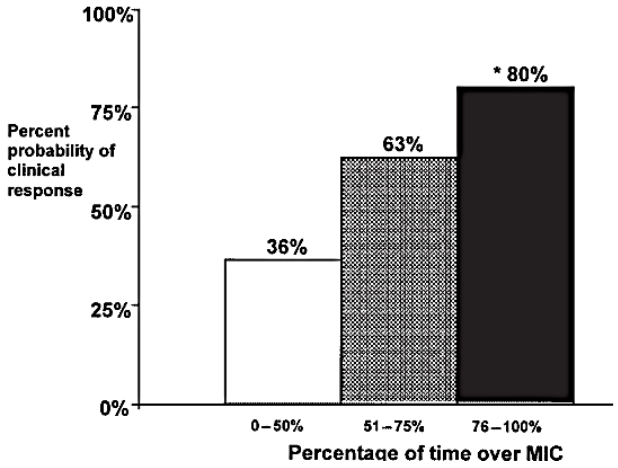


Figure: Probability of clinical response with meropenem as a function of the percentage of T>MIC

Ann Pharmacother. 2005 ;39(1):32-8

Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections

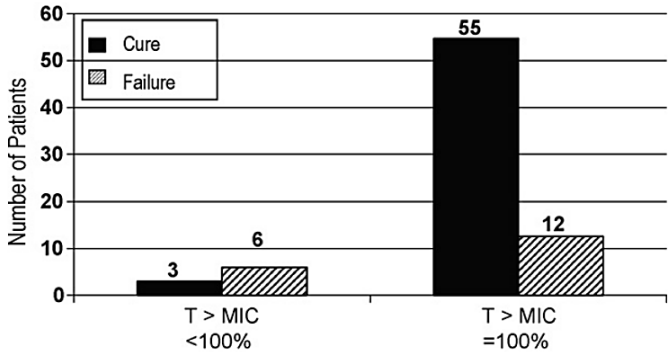


Figure: Clinical cure rates for patients with duration of time that the serum concentration exceeds the minimum inhibitory concentration (T>MIC) of 100% or <100%.

Int J Antimicrob Agents. 2008 ;31(4):345-51

Augmented renal clearance is associated with inadequate antibiotic pharmacokinetic/pharmacodynamic target in Asian ICU population: a prospective observational study

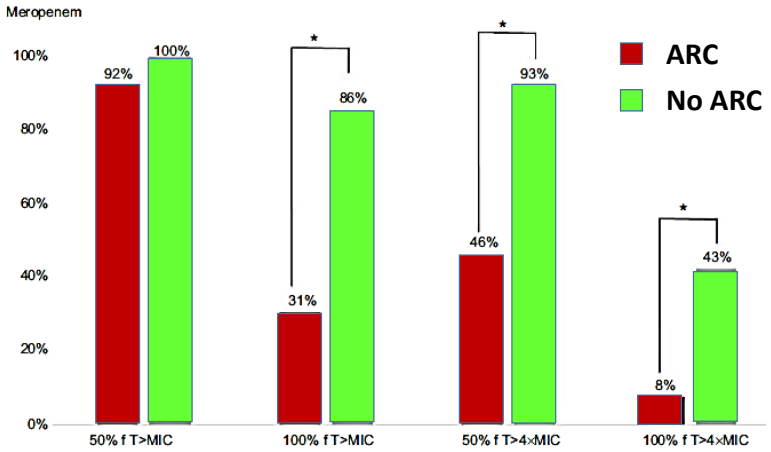


Figure: Targets of pharmacokinetic and pharmacodynamic attainment

Infection and Drug Resistance 2019:12 2531–2541

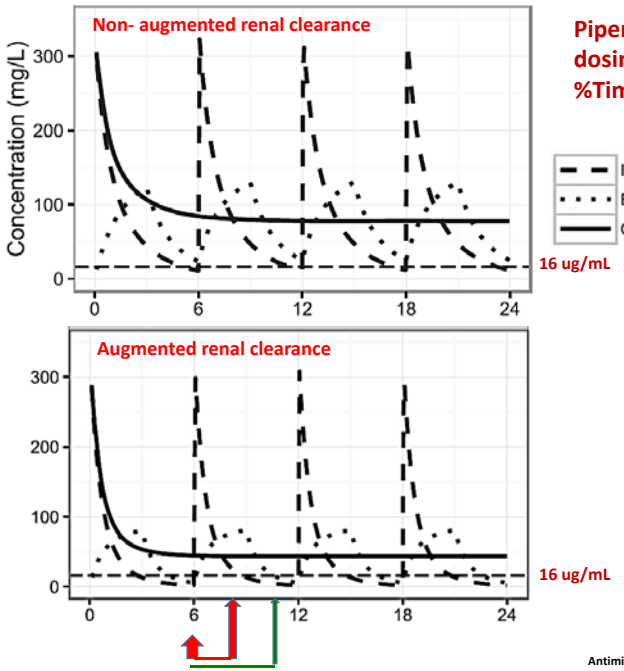
Table: Summary of meropenem dosing regimens providing %Time >MIC

Regimen	%Time >MIC			Reference
Critically ill patient	drip in	0.5 hr		Ther Drug Monit 2013; 35 (1) :63-70.
1 g q 8 hr	MIC = 1	100%		*Enterobacteriaceae* S MIC ≤ 1 μg/mL *P. aerugonisa* S MIC ≤ 2 μg/mL
	MIC = 2	75%		
	MIC = 4	56%		
Sepsis patient	drip in	0.5 hr	3 hr	Antimicrob Agents Chemother 2005; 49 (4) :1337-9
1 g q 8 hr	MIC = 1	75%	93%	
	MIC = 2	-		
	MIC = 4	57%	72%	
Neutropenic patient	drip in	0.5 hr		Ther Drug Monit 2013; 35 (1) :63-70.
1 g q 8 hr	MIC = 1	73%		
	MIC = 2	65%		
	MIC = 4	49%		

Table: Summary of imipenem dosing regimens providing %Time >MIC

Regimen	%Time >MIC			Reference
Critically ill patient	drip in	3 hr		Int J Antimicrob Agents. 2014 ;44(4):358-62
500 mg q 6 hr	MIC = 1	94%		*Enterobacteriaceae* S MIC ≤ 1 µg/mL *P. aerugonisa* S MIC ≤ 2 µg/mL
	MIC = 2	85%		
	MIC = 4	53%		
Sepsis patient	drip in	0.5 hr	2 hr	J Antimicrob Chemother. 2009 Mar;63(3):560-3
500 mg q 6 hr	MIC = 1	100%	100%	
	MIC = 2	100%	100%	

Piperacilin/tazobactam dosing regimens providing %Time >MIC

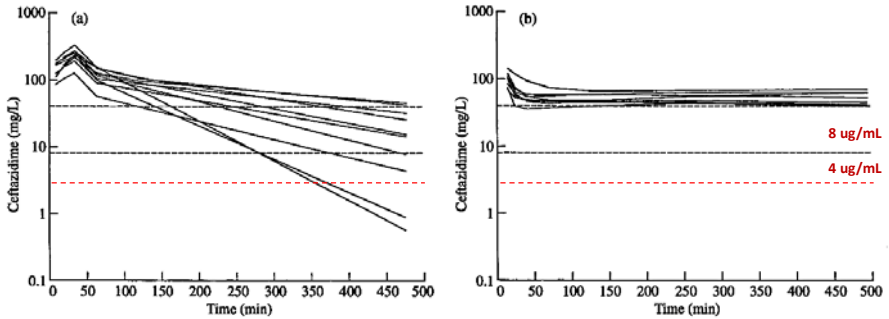


Enterobacteriaceae
P. Aerugonisa
S MIC ≤ 16 µg/mL

Antimicrob Agents Chemother. 2018 26;62(5). pii: e02306-17

Ceftazidime dosing regimens providing %Time >MIC

Enterobacteriaceae
S MIC ≤ 4 µg/mL
P. aerugonisa
S MIC ≤ 8 µg/mL



2 g given as 30 minute-infusion every 8 h

6 g/day by continuous infusion

J Antimicrob Chemother. 1999 ;43(2):309-11.

Table: Stability of beta-lactam antibiotic

Drug	Conditions			Results		References
	Concentration	Condition	Diluent	Time (hr)	Value	
Meropenem	500 mg in 100 mL (5 mg/mL)	Temperature 20 °C	NSS	T =2 hr	1.66%	Southeast Asian J Trop Med Public Health. 2003 ;34(3): 627-9.
				T =4 hr	3.31%	
				T =8 hr	5.80%	
	5 mg/mL	Temperature 34-37 °C	NSS	T =2 hr	3.14%	
				T =4 hr	5.86%	
				T =8 hr	11.85%	
Meropenem	5 mg/mL	Temperature 30 °C	NSS	Time to reach <90%	12 h	Int J Antimicrob Agents. 2011 ;37(2):184-5.
		Temperature 35 °C			8 h	
		Temperature 40 °C			6 h	

Table: Stability of beta-lactam antibiotic

Drug	Conditions			Results		References
	Concentration	Condition	Diluent	Time (hr)	Value	
Imipenem	5 mg/mL	Temperature 30 °C	NSS	Time to reach <90%	6 h	Int J Antimicrob Agents. 2011 ;37(2):184-5.
		Temperature 35 °C			4 h	
		Temperature 40 °C			3 h	
Doripenem	5 mg/mL	Temperature 30 °C	NSS	Time to reach <90%	16 h	Int J Antimicrob Agents. 2011 ;37(2):184-5.
		Temperature 35 °C			12 h	
		Temperature 40 °C			8 h	

8 g in 100 mL 12 g in 100 mL

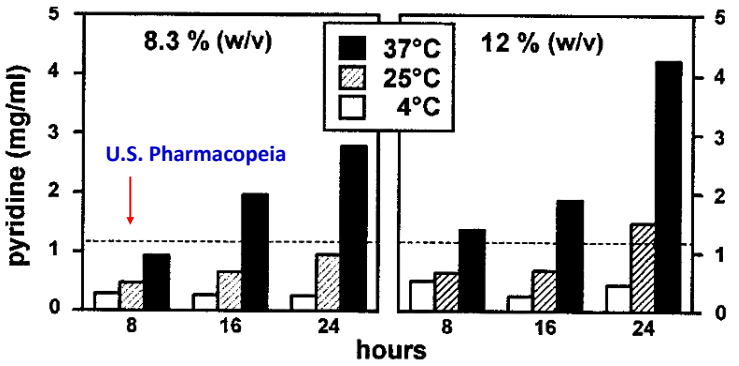
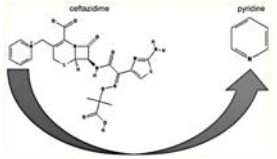


Figure: Release of pyridine from ceftazidime upon incubation at 4°C, 25°C, and 37°C

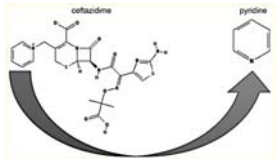


Antimicrob Agents Chemother. 2002 ;46(8):2327-32

Table: Appearance of pyridine in g/ml in four portable infusion devices filled with 40 mg/ml ceftazidime injection (37°C)

40 mg/ml = 4 gram in 100 mL
= 2 gram in 50 mL

Device	Injection	Initial concentration of pyridine (μg/ml)	Concentration of pyridine in μg/ml					
			4 h	8 h	12 h	16 h	20 h	24 h
Baxter	0.9% NaCl	1.8 ± 0.7	119.4 ± 6.0	268.8 ± 14.3	418.2 ± 9.9	567.6 ± 34.9	717.0 ± 4.8	883.5 ± 17.8*
Infusor®	Dextrose 5%	18.6 ± 2.9	199.3 ± 13.9	412.7 ± 58.6	626.1 ± 6.5	839.6 ± 80.9	1052.9 ± 50.9	1266.4 ± 69.7
Braun	0.9% NaCl	16.1 ± 1.7	104.1 ± 4.8	256.7 ± 23.9	409.3 ± 12.4	561.8 ± 46.1	714.4 ± 235.2	866.9 ± 2.8
Easypump®	Dextrose 5%	86.7 ± 1.0	225.5 ± 2.5	378.0 ± 1.7	530.6 ± 10.4	683.2 ± 10.5	835.7 ± 12.1	988.3 ± 5.2
Fresenius	0.9% NaCl	9.2 ± 1.4	166.0 ± 12.9	352.9 ± 26.4	539.8 ± 89.1	726.6 ± 23.7	913.5 ± 17.2	1100.4 ± 162.9
Ultraflow®	Dextrose 5%	90.7 ± 0.7	255.0 ± 2.1	390.5 ± 5.7	525.9 ± 14.6	661.4 ± 21.6	796.8 ± 7.3	932.3 ± 6.2
Zambon	0.9% NaCl	8.6 ± 3.3	133.1 ± 5.8	289.5 ± 2.4	445.8 ± 5.3	602.2 ± 1.9	758.5 ± 0.85	914.9 ± 4.7
Outbound®	Dextrose 5%	19.4 ± 5.7	279.3 ± 3.5	512.4 ± 13.0	745.6 ± 14.9	978.7 ± 11.4	1211.9 ± 146.4	1445.1 ± 71.4



3 gram in 100 mL drip in 12 hr

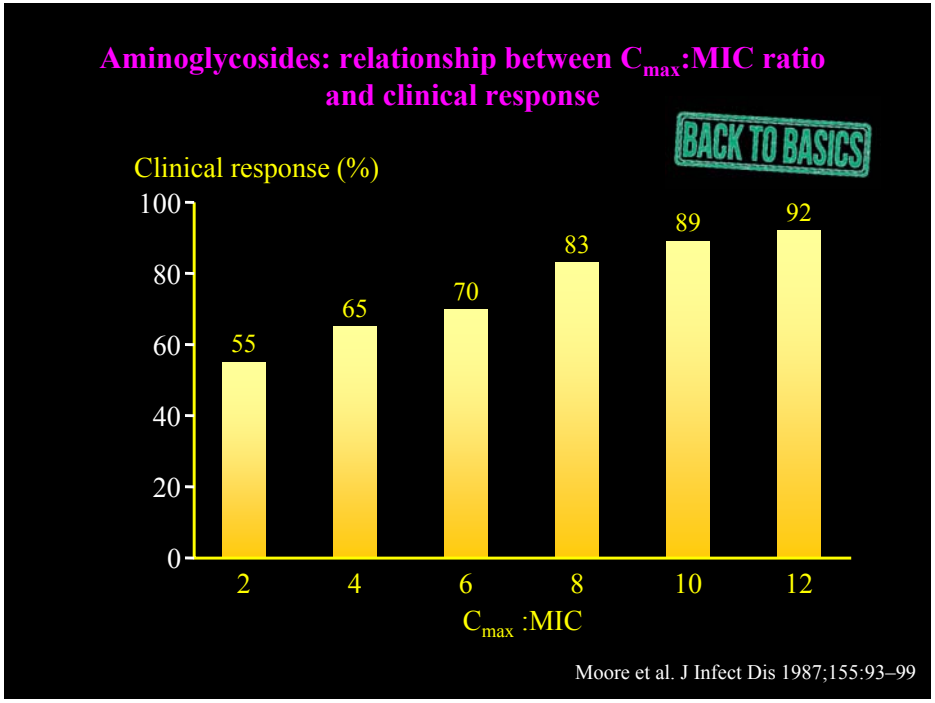
J Pharm Biomed Anal. 2002 ;27(6):873-9.

OUTLINES

PK/PD optimization: Back to Basics

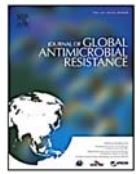
- Principle of PK/PD relationships
- Update in Antibiotic PK/PD: antibiotic dosing regimens
  - Beta-lactams
  - Aminoglycosides (amikacin, gentamicin)
  - Vancomycin
  - Fluoroquinolones

Aminoglycosides: relationship between C_{max}:MIC ratio and clinical response



Moore et al. J Infect Dis 1987;155:93–99

Impact of amikacin pharmacokinetic/pharmacodynamics ratio on treatment response in critically ill patient



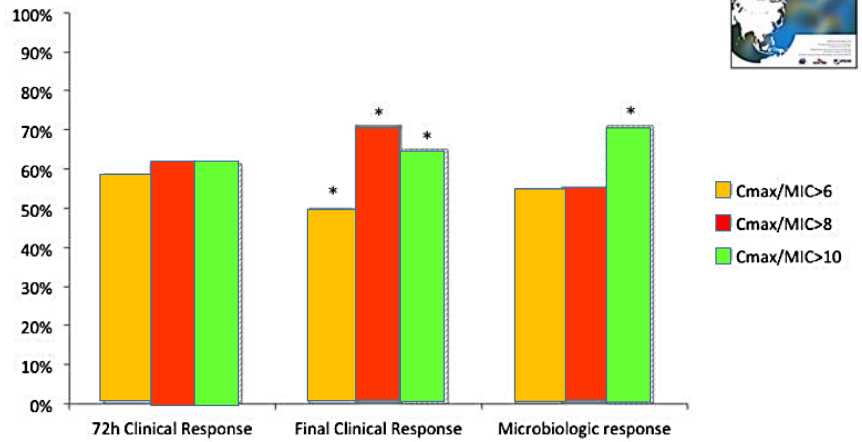


Figure: Clinical and microbiological response to amikacina according to the Cmax/MIC ratio reached (* for statistically significant results)

J Glob Antimicrob Resist. 2018 ;12:90-95

Aminoglycosides (Amikacin และ Gentamicin)

- ยากลุ่ม aminoglycoside เป็นยาที่ออกฤทธิ์ต้านแบคทีเรียแกรมลบ
- ยา amikacin และ gentamicin ในรูปแบบยาฉีด
- ยาขับออกทางไตเป็นหลัก
- เป้าหมายระดับยาในเลือดนั้น เป็นระดับยาสูงสุด (C_{peak}) (Cmax/MIC) อยู่ในช่วง 8-10 ของค่า MIC ของเชื้อ
  - Amikacin C_{peak} 60-80 µg/mL (susceptible breakpoint ≤ 8 µg/mL)
  - Gentamicin C_{peak} 30-40 µg/mL (susceptible breakpoint ≤ 4 µg/mL)

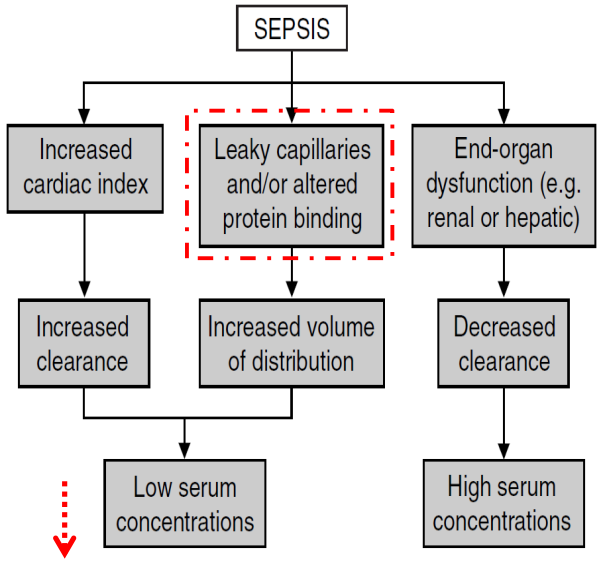
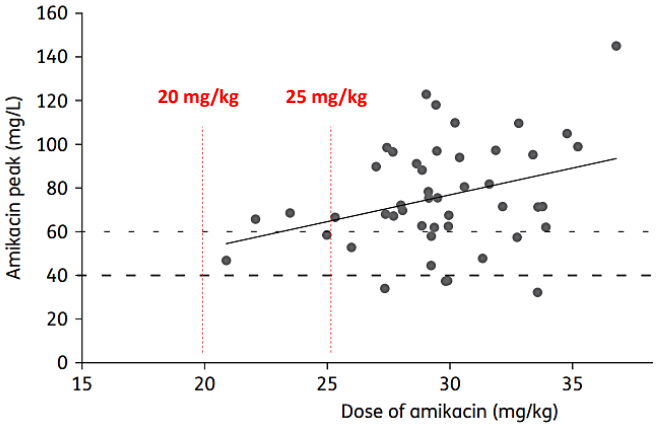


Figure: Pharmacokinetic Principle in Septic Patients

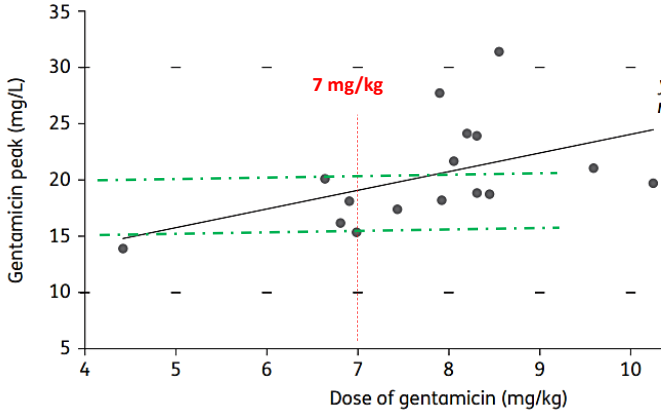
Crit Care Med 2009 37(3); 840-851

Impact of 30 mg/kg amikacin and 8 mg/kg gentamicin on serum concentrations in critically ill patients with severe sepsis



J Antimicrob Chemother 2016; 71: 208 –212

Impact of 30 mg/kg amikacin and 8 mg/kg gentamicin on serum concentrations in critically ill patients with severe sepsis



J Antimicrob Chemother 2016; 71: 208 –212

Adis

What Antibiotic Exposures Are Required to Suppress the Emergence of Resistance for Gram-Negative Bacteria? A Systematic Review

Antibiotics	PK/PD parameter	Target
β-lactam antibiotic	*C*min/MIC	≥ 4
Aminoglycoside	*C*max/MIC	≥ 20
Fluoroquinolones	AUC 24/MIC	300-1400

UPDATE

*Antibiotic exposures required to suppress the emergence of resistance generally exceeded that associated with clinical efficacy

Clin Pharmacokinet. 2019 Jul 20. doi: 10.1007/s40262-019-00791-z

OUTLINES

PK/PD optimization: Back to Basics

- Principle of PK/PD relationships
- Update in Antibiotic PK/PD: antibiotic dosing regimens
  - Beta-lactams
  - Aminoglycosides (amikacin, gentamicin)
  - Vancomycin
  - Fluoroquinolones

Vancomycin: AUC/MIC

BACK TO BASICS

Title	AUC (mg•h/L)	Reference
Impact of Vancomycin Exposure on Outcomes in Patients With Methicillin-Resistant *S. aureus* Bacteremia: Support for Consensus Guidelines Suggested Targets	Patients with AUC_{24} <421 were failure rate, compared with patients with AUC_{24} ≥421 (61.2% vs 48.6%)	Clin Infect Dis. 2011 ;52(8): 975-81
Area under the concentration-time curve to minimum inhibitory concentration ratio as a predictor of vancomycin treatment outcome in methicillin-resistant Staphylococcus aureus bacteraemia	Patients with AUC_{24} <$430_{E\text{-}test}$ were failure rate, compared with patients with AUC_{24} ≥$421_{E\text{-}test}$ (50% vs 25%) Patients with AUC_{24} <398_{BMD} were failure rate, compared with patients with AUC_{24} ≥398_{BMD} (45% vs 23.2%)	Int J Antimicrob Agents. 2014 ;43(2):179-83
Impact of source of infection and vancomycin AUC0–24/MICBMD targets on treatment failure in patients with methicillin-resistant *S. aureus* bacteraemia	Patients with AUC_{24} <398_{BMD} were failure rate, compared with patients with AUC_{24} ≥398_{BMD} (54% vs 23.4%)	Clin Microbiol Infect. 2014 ;20(12):O1098-105
Association between single trough-based area under the curve estimation of vancomycin and treatment outcome among methicillin-resistant *S. aureus* bacteremia patients	Patients with AUC_{24} <421 were failure rate, compared with patients with AUC_{24} ≥421 (78.6% vs 28.5%)	Anaesthesiol Intensive Ther. 2019 ;51(3):218-223. UPDATE

VANCOMYCIN THERAPEUTIC GUIDELINES 2009

Vancomycin Therapeutic Guidelines: A Summary of Consensus Recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists

BACK TO BASICS

- Bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia caused by *S. aureus (MRSA)*
  - C_{trough} 15–20 mg/L are recommended.
  - Achieve an AUC/MIC of > 400 if the MIC is < 1 mg/L.
- Cellulitis , Skin and soft infection : C_{trough} 10–15 mg/L are recommended.

Clinical Infectious Diseases 2009;49:325–7

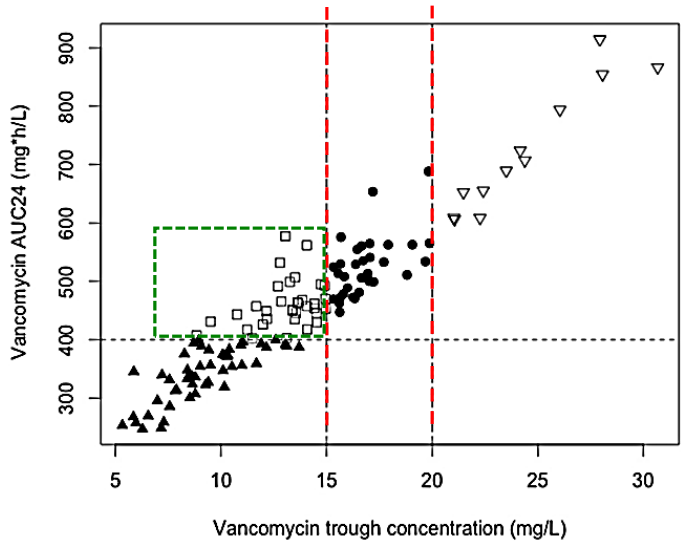


Figure: Scatterplot of vancomycin measured trough concentrations and AUC0 –24.

Antimicrob Agents Chemother 2017 24;61(5).

UPDATE

Title	AUC (mg•h/L)	Reference
Are Vancomycin Trough Concentrations of 15 to 20 mg/L Associated With Increased Attainment of an AUC/MIC 400 in Patients With Presumed MRSA Infection?	C_{trough} 10-14.9 µg/mL: 51.6% of patient achieve ≥ AUC_{24} 400	J Pharm Pract. 2017 ;30(3):329-335.
Is Trough Concentration of Vancomycin Predictive of the Area Under the Curve? A Clinical Study in Elderly Patients	C_{trough} < 15 µg/mL: 37% of patient achieve ≥ AUC_{24} 400	Ther Drug Monit 2017 ;39(1):83-87.
Establishment of an AUC0 –24 Threshold for Nephrotoxicity Is a Step towards Individualized Vancomycin Dosing for Methicillin-Resistant *S. aureus* Bacteremia	C_{trough} < 15 µg/mL: 26.7% of patient achieve ≥ AUC_{24} 400	Antimicrob Agents Chemother 2017 24;61(5).
Vancomycin Trough Concentration Poorly Characterizes AUC: Is It Time to Transition to AUC-Based Vancomycin Monitoring?	C_{trough} 15-19.9 µg/mL: 80% of patient achieve > AUC_{24} 600	Ann Pharmacother. 2017 ;51(10):926-927

Vancomycin Therapeutic guidelines 2019

Therapeutic monitoring of vancomycin: A revised consensus guideline and review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society and the Society of Infectious Diseases Pharmacists

Rybak, MJ,[1-3] Le J,[4] Lodise, TP,[5,6] Levine DP,[2,3] Bradley, JS,[7,8] Liu, C,[9,10] Mueller, BA,[11] Pai, MP,[11] Wong-Beringer, A,[12] Rotschafer, JC,[13] Rodvold, KA,[14] Maples, HD,[15] Lomaestro, B.[16]

UPDATE

Vancomycin Therapeutic guidelines 2019

UPDATE

SUMMARY OF RECOMMENDATIONS

AUC/MIC ratio of 400 to 600

- **This can be accomplished in two ways**

- Collection of two concentrations

(one near steady state, post-distributional C_{max} at 1-2 hours post infusion and trough) during the same dosing interval

(Level of evidence, I ; grade of recommendation, B+)

- Bayesian software programs : preferred to obtain two PK samples (shortly after the end of infusion and at end of dosing interval)

(Level of evidence, II ; grade of recommendation, C+)

- Targeted exposure should be achieved early during the course of therapy, preferably within the first 24 to 48 hours.

OUTLINES

PK/PD optimization: Back to Basics

- **Principle of PK/PD relationships**
- **Update in Antibiotic PK/PD: antibiotic dosing regimens**
  - Beta-lactams
  - Vancomycin
  - Aminoglycoside (amikacin, gentamicin)
  - **Fluoroquinolones**

BACK TO BASICS

Fluoroquinolone therapy for nosocomial pneumonia: correlation between drug exposure and clinical outcome

AUIC range	Total no. of patients	Result for the following cure:			
		Clinical		Microbiologic	
		No. of patients	%	No. of patients	%
0–62.5	9	4	44	2	22
62.5–125	10	4	40	3	30
125–250	16	14	88	13	81
250–500	7	5	71	6	86
500–5,541	22	17	77	18	82

Forrest et al. Antimicrob Agents Chemother 1993;37:1073–1081

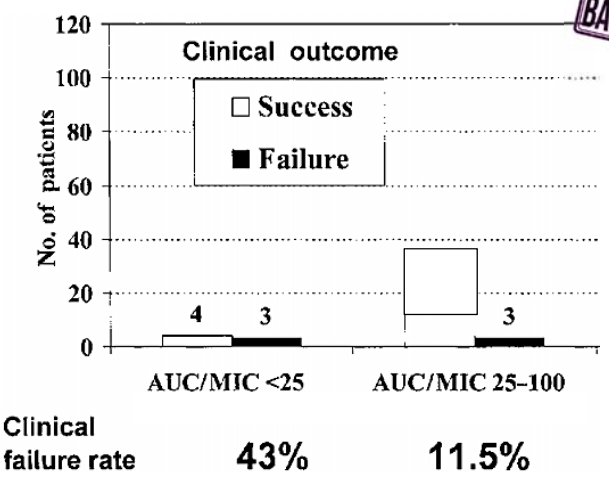


Figure: Correlation of AUC/MIC in hospitalized patients with respiratory tract, skin and soft tissue, and urinary tract infection treated with levofloxacin.

Clin Microbiol Infect. 2001 ;7(11):589-96

Pharmacodynamics of Intravenous Ciprofloxacin in Seriously Ill Patients

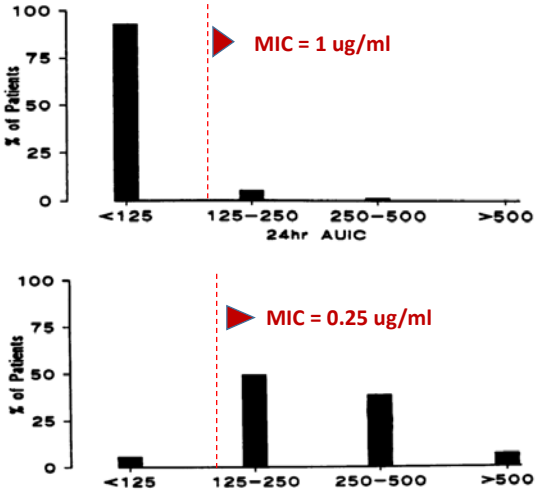


Figure: Frequency distributions of AUC/MIC given doses based on traditional dosing guidelines. Top and bottom panels are for hypothetical MICs of 0.25 and 1.0 ug/ml, respectively.

Antimicrob Agents Chemother. 1993 ;37(5):1073-81

Don't Get Wound Up: Revised Fluoroquinolone Breakpoints for *Enterobacteriaceae* and *Pseudomonas aeruginosa*

Gram-negative organism and FQ	MIC breakpoints (μg/ml)[a] 2019 CLSI breakpoints (4)	2018 CLSI breakpoints (48)
Enterobacteriaceae		
Ciprofloxacin	S, ≤0.25; I, 0.5; R, ≥1	S, ≤1; I, 2; R, ≥4
Levofloxacin	S, ≤0.5; I, 1; R, ≥2	S, ≤2; I, 4; R, ≥8
P. aeruginosa		
Ciprofloxacin	S, ≤0.5; I, 1; R, ≥2	S, ≤1; I, 2; R, ≥4
Levofloxacin	S, ≤1; I, 2; R, ≥4	S, ≤2; I, 4; R, ≥8

[a]S, susceptible; I, intermediate; R, resistant.

Table: Summary of ciprofloxacin dosing regimens providing %Time >MIC

Regimen	AUC (mg•h/L)	AUC/MIC$_{2019}$ *Enterobacteriaceae* ≤ 0.25 µg/mL	AUC/MIC$_{2019}$ *P. aeruginosa* ≤ 0.5 µg/mL	Reference
Critically ill patient				
400 mg q 8 hr	53	212	106	Br J Clin Pharmacol. 2013 ; 75 (1) :180-5
Non-critically ill patient				
400 mg q 12 hr	48	192	96	Antimicrob Agents Chemother. 2001 ;45 (12) :3468-73.
400 mg q 8 hr	72	288	144	

Fluoroquinolones: AUC/MIC
Gram negative bacteria >125

Table: Summary of levofloxacin dosing regimens providing %Time >MIC

Regimen	AUC (mg•h/L)	AUC/MIC$_{2019}$		Reference
Critically ill patient		*Enterobacteriaceae* ≤ 0.5 μg/mL	*P. aeruginosa* ≤ 1 μg/mL	
500mg twice daily	68	136	68	Clin Pharmacokinet 2003; 42 (6): 589-598
500mg once daily	66	132	66	Pharmacotherapy 2002; 22 (10):1216–1225
Non-critically ill patient				
500mg once daily	75	150	75	J Antimicrob Chemother. 2003 ; 51 (1):101-6

Fluoroquinolones: AUC/MIC
Gram negative bacteria >125

Adis

What Antibiotic Exposures Are Required to Suppress the Emergence of Resistance for Gram-Negative Bacteria? A Systematic Review

Antibiotics	PK/PD parameter	Target
β-lactam antibiotic	*C*min/MIC	≥ 4
Aminoglycoside	*C*max/MIC	≥ 20
Fluoroquinolones	AUC 24/MIC	300-1400

*Antibiotic exposures required to suppress the emergence of resistance generally exceeded that associated with clinical efficacy

Clin Pharmacokinet. 2019 Jul 20. doi: 10.1007/s40262-019-00791-z