ID ABC'S: ANTIBIOTICS, BACTERIA, AND CORE CONCEPTS

ANGELA LOO, PHARM.D., BCPS-AQ ID, BCIDP
NEWYORK-PRESBYTERIAN/WEILL CORNELL MEDICAL CENTER
JANUARY 8, 2020

DISCLOSURE STATEMENT

- The speaker has no conflicts of interest or relationships with commercial entities that may be referenced in this presentation

AT THE COMPLETION OF THIS ACTIVITY, PHARMACISTS WILL BE ABLE TO:

- Discuss factors to consider in the selection of an antimicrobial regimen
- Interpret an antimicrobial susceptibility report using knowledge of minimum inhibitory concentrations and antimicrobial breakpoints
- Apply pharmacokinetic and pharmacodynamic principles in the selection of appropriate antimicrobial regimens

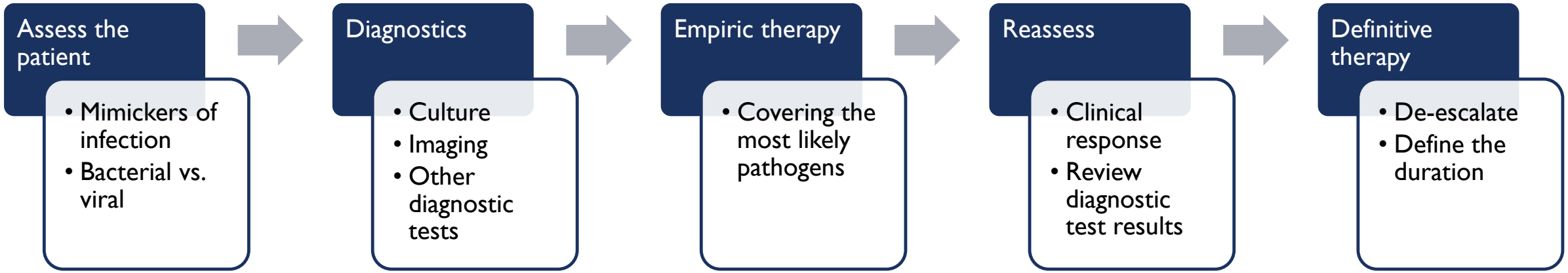
AT THE COMPLETION OF THIS ACTIVITY, PHARMACY TECHNICIANS WILL BE ABLE TO:

- Describe differences between empiric and definitive antimicrobial therapy
- Define minimum inhibitory concentration and antimicrobial breakpoint
- List factors for consideration in the selection of antimicrobial therapy regimen

CASE 1

- EK is a 28-year-old female who presents to the emergency department with fevers, flank pain, and dysuria. She has a leukocytosis (WBC 17) but is hemodynamically stable. The medical intern turns to you and asks what antimicrobial therapy to initiate. What antibiotic would you recommend empirically?

INFECTIOUS DISEASES WORKFLOW



EMPIRIC ANTIMICROBIAL THERAPY

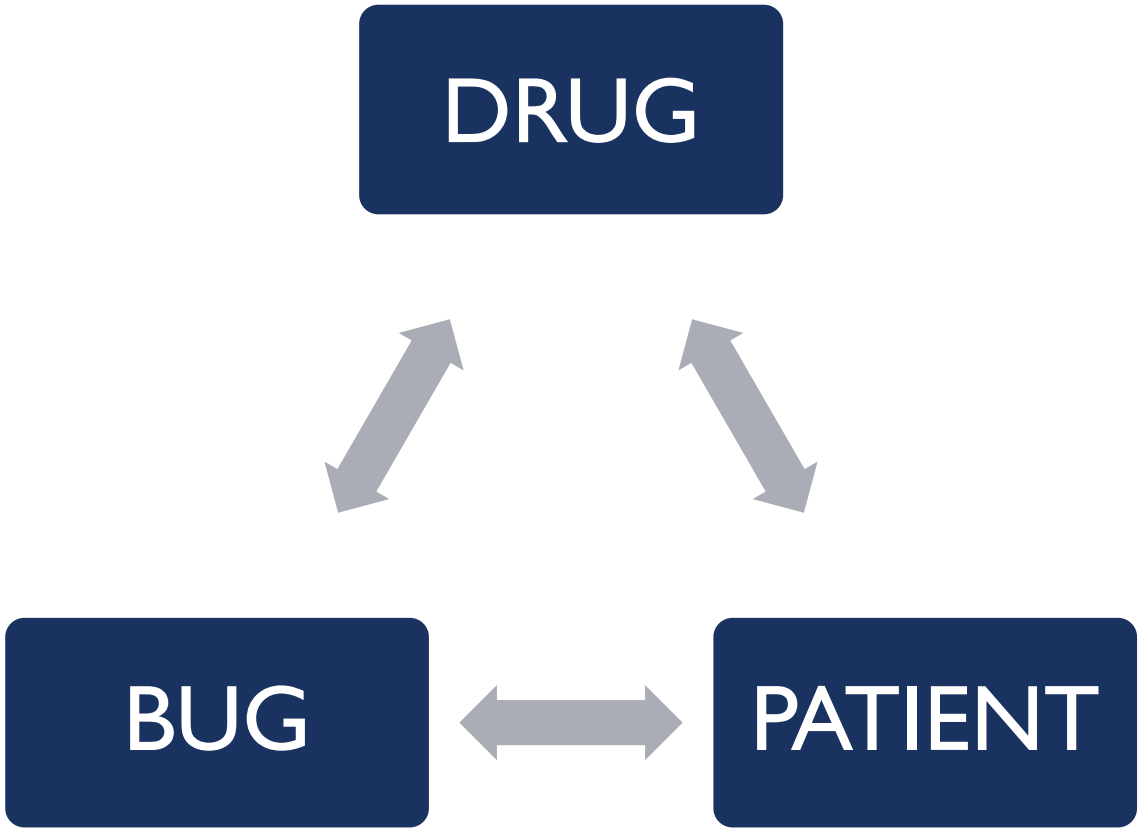
- Empiric therapy = Educated guess, based on clinical diagnosis, clinical evidence/experience
- How do we determine appropriate empiric therapy?

Leekha S et al. Mayo Clin Proc. 2011;86(2):156-167

WHICH OF THE FOLLOWING DOES **NOT** REQUIRE CONSIDERATION IN THE SELECTION OF EMPIRIC ANTIMICROBIAL THERAPY?

A. Suspected site of infection
B. Antimicrobial breakpoint
C. Recent antibiotic exposures
D. Community-acquired vs. hospital acquired

ID TRIAD



EMPIRIC THERAPY: FACTORS FOR CONSIDERATION

BUG	DRUG	PATIENT
Suspected site of infection	Spectrum of activity	Recent antibiotic exposures
Community-acquired vs hospital acquired infection	PK/PD	Allergies
Local susceptibilities	Adverse reactions	Comorbidities
	Drug interactions	Immune status
	Cost	Pregnancy status
		Renal/hepatic function
		Weight (obesity)

COMMON BACTERIAL PATHOGENS BY SITE

Bacterial meningitis

Community-acquired
- Streptococcus pneumoniae
- Neisseria meningitides
- Listeria monocytogenes

Hospital-acquired
- Staphylococcus aureus
- Pseudomonas aeruginosa

Endocarditis
- Staphylococcus aureus
- Staphylococcus epidermidis
- Viridans group streptococci
- Enterococcus species

Urinary tract

Community-acquired
- E. coli
- Proteus mirabilis
- Klebsiella pneumoniae

Hospital-acquired
- E. coli
- Proteus mirabilis
- Klebsiella pneumoniae
- Enterococcus species
- Pseudomonas aeruginosa

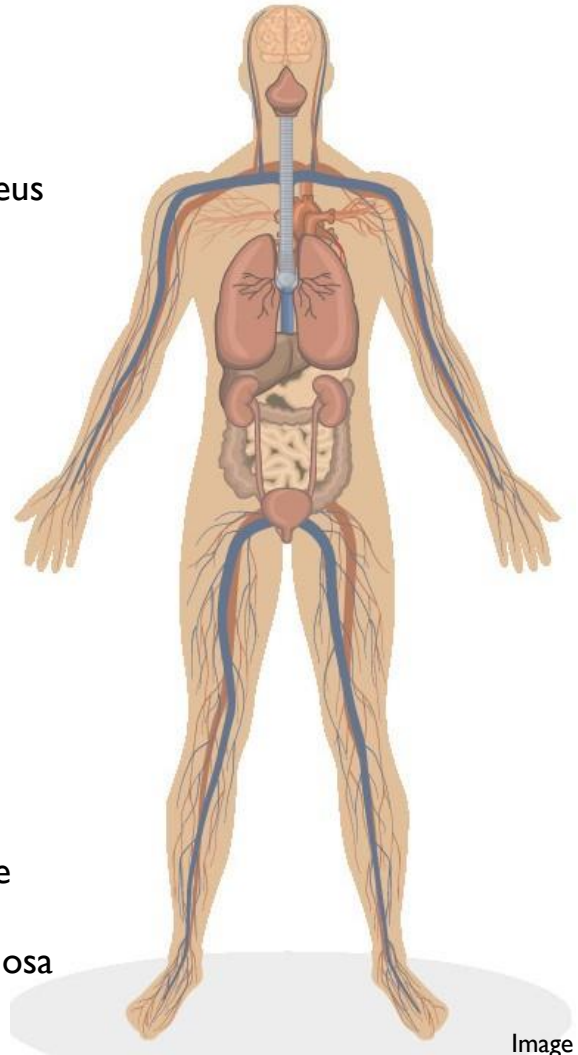


Image from shutterstock.com

Pneumonia

Community-acquired
- Streptococcus pneumoniae
- Haemophilus influenzae
- Atypicals (Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella pneumoniae)

Hospital-acquired
- Staphylococcus aureus
- Pseudomonas aeruginosa
- Enterobacteriaceae

Skin and soft tissue
- Staphylococci (especially Staphylococcus aureus)
- Streptococcus species

Intra-abdominal

Community-acquired
- Enterobacterales
- Streptococcus species
- Anaerobes (Bacteroides)

Hospital-acquired
- Staphylococcus aureus
- Pseudomonas aeruginosa
- Enterobacterales

NATIONAL GUIDELINE RECOMMENDATIONS

- Guidelines from Infectious Diseases Society of America (IDSA) (https://www.idsociety.org/) can assist in selection of empiric therapy

2010 IDSA Recommendations for Acute Pyelonephritis
Microbial spectrum consists mainly *of Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae*
[Ciprofloxacin or levofloxacin] "is an appropriate choice for therapy…where the prevalence of **resistance of community uropathogens is not known to exceed 10%**"
[Trimethoprim-sulfamethoxazole] "is an appropriate choice for therapy **if the uropathogen is known to be susceptible"**
An initial intravenous dose of a long-acting parenteral antimicrobial, such as 1 g of ceftriaxone or a consolidated 24-h dose of an aminoglycoside

Gupta et al. Clin Infect Dis 2011;52(5):e103-120.

LOCAL SUSCEPTIBILITIES ARE KEY

- Cumulative antibiogram—annual summary of local susceptibility rates, specific to each institution

Antibiogram 2018 (% Susceptible) - Adult

		Penicillins		Cephalosporins			Monobactam	Aminoglycosides			Fluoroquinolone	Other
	# tested	Amp/Sulbact A/S	Pip/Tazo P/T	Ceftriaxone CTX	Ceftazidime CEZ	Cefepime[1] CPM	Aztreonam AZM	Gentamicin GEN	Tobramycin TOB	Amikacin AMI	Levofloxacin LVX	Trimeth/Sulfa T/S
Escherichia coli	5163											
In-patients, Non-ICU	528	50%	95%	81%	85%	84%	82%	85%	84%	99%	67%	67%
ICU patients	147	48%	92%	77%	81%	80%	79%	83%	80%	99%	67%	59%
ED patients	1484	55%	98%	86%	90%	88%	86%	87%	87%	99%	73%	70%
Out-patients Only	3004	59%	98%	91%	93%	92%	91%	90%	89%	100%	76%	72%
Klebsiella pneumoniae	1428											
In-patients, Non-ICU	257	68%	88%	86%	85%	87%	87%	91%	87%	97%	89%	73%
ICU patients	99	76%	90%	85%	85%	87%	85%	91%	89%	97%	92%	76%
ED patients	405	81%	95%	91%	91%	91%	90%	95%	91%	99%	94%	79%
Out-patients Only	667	82%	95%	95%	95%	95%	95%	97%	96%	100%	96%	82%

- Can work with your microbiology laboratory to get infection source-specific information and develop local guidelines
  - NYP/WC *E. coli* urine isolates: 72% S Levofloxacin, 69% S TMP/SMX, 87% S Gentamicin

NYP/WC 2018 Antibiogram. Accessed 11/26/19
Hindler JF. Stelling J. *Clin Infect Dis.* 2007;44(6):867-73.

EMPIRIC THERAPY: FACTORS FOR CONSIDERATION

BUG	DRUG	PATIENT
Suspected site of infection	Spectrum of activity	Recent antibiotic exposures
Community-acquired vs hospital acquired infection	PK/PD	Allergies
Local susceptibilities	Adverse reactions	Comorbidities
	Drug interactions	Immune status
	Cost	Pregnancy status
		Renal/hepatic function
		Weight (obesity)

ANTIMICROBIAL SPECTRUM OF ACTIVITY

- Cover the most likely pathogens while considering risk of future resistance

Sepsis requires appropriate therapy

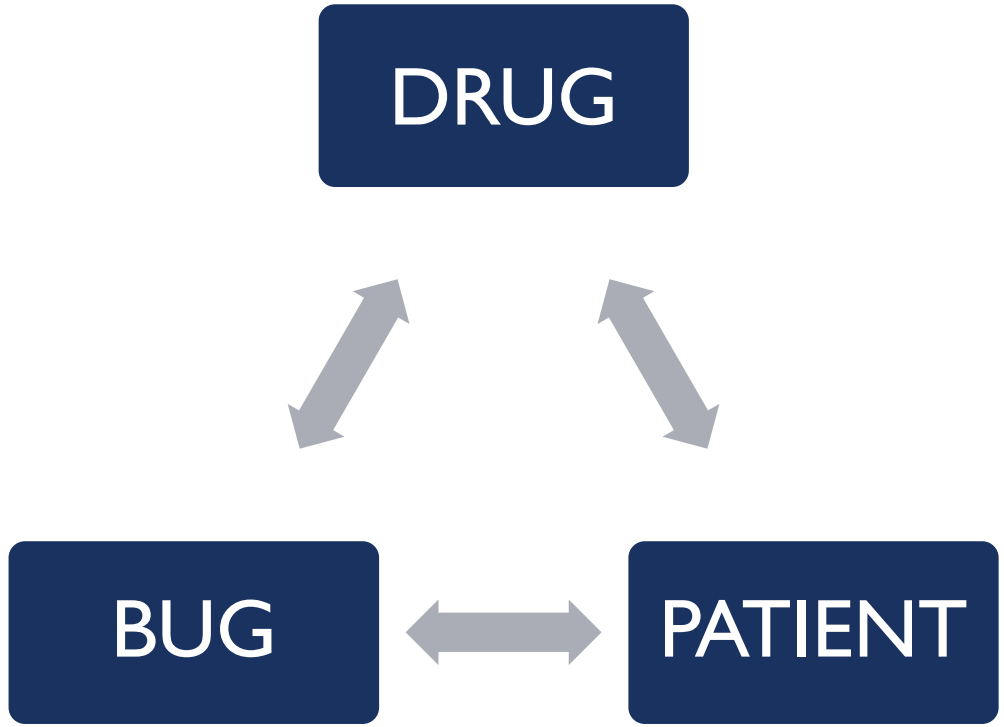
Inappropriate use of antimicrobials increases risk of resistance

- Vancomycin → Vancomycin-resistant enterococci
- Carbapenems → Carbapenem-resistant Enterobacterales, Pseudomonas aeruginosa
- Fluoroquinolones → Fluoroquinolone-resistant Gram-negative organisms, MRSA

Kumar A et al. Crit Care Med. 2006 Jun;34(6):1589-96
Cetinkaya Y et al. Clin Micr Rev 2000;686-707
Dalhoff A. Interdiscip Perspect Infect Dis 2012 https://doi.org/10.1155/2012/976273
Richter SE et al. Open Forum Infect Dis 2019;6(3). https://doi.org/10.1093/ofid/ofz027

PHARMACOKINETICS (PK) AND PHARMACODYNAMICS (PD)

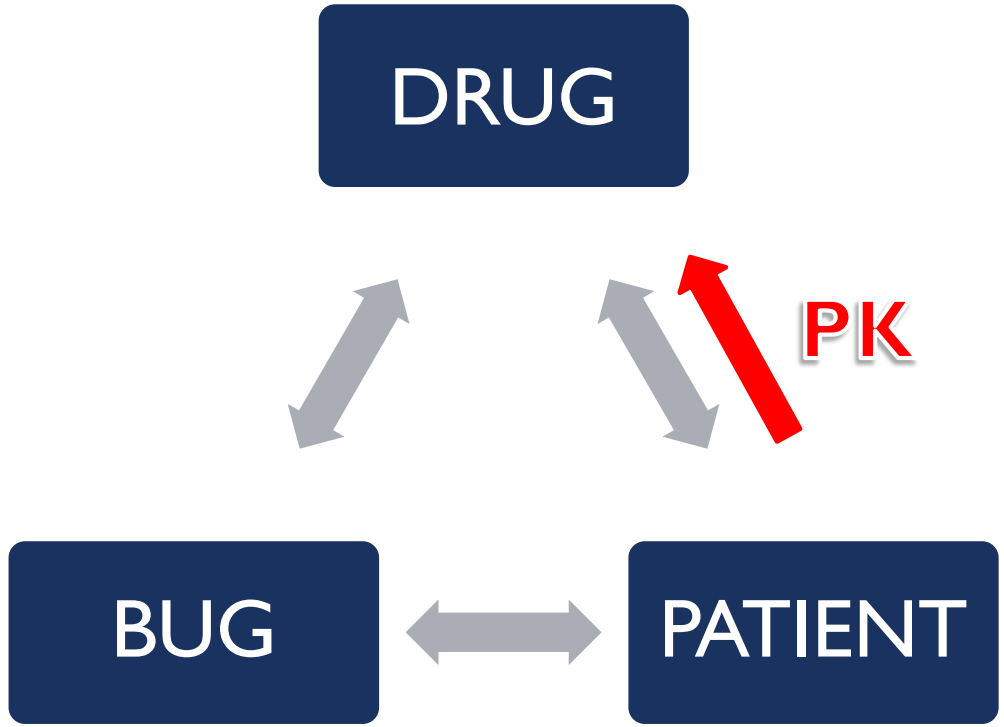
- Achieving PK/PD targets not only increases likelihood of clinical success but also chance of bacterial eradication and limits the emergence of resistance



Craig WA. Clin Infect Dis. 1998;26:1-12.

PHARMACOKINETICS (PK) AND PHARMACODYNAMICS (PD)

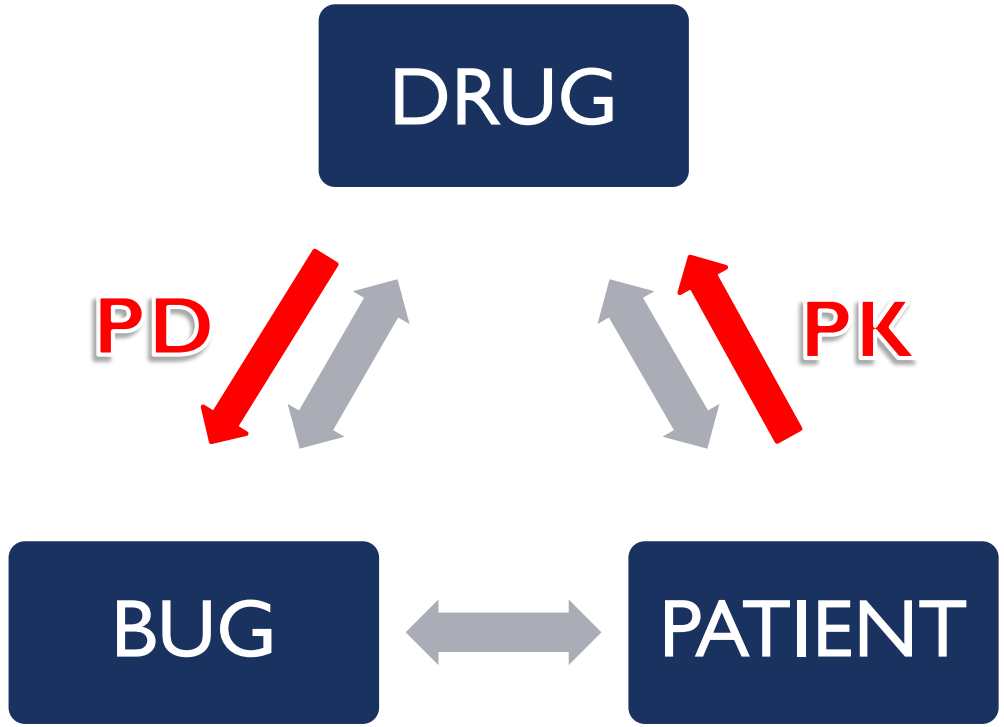
- Achieving PK/PD targets not only increases likelihood of clinical success but also chance of bacterial eradication and limits the emergence of resistance



Craig WA. Clin Infect Dis. 1998;26:1-12.

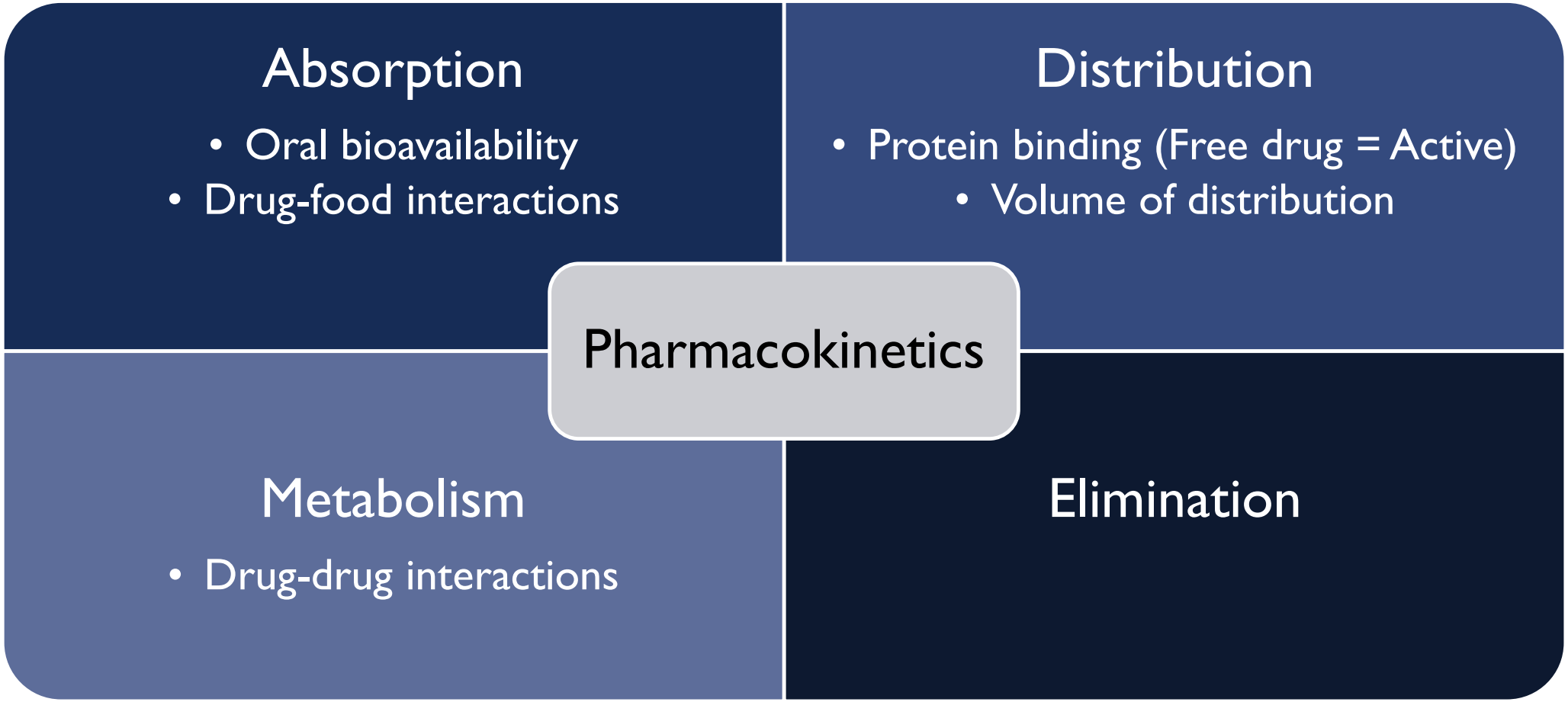
PHARMACOKINETICS (PK) AND PHARMACODYNAMICS (PD)

- Achieving PK/PD targets not only increases likelihood of clinical success but also chance of bacterial eradication and limits the emergence of resistance



Craig WA. Clin Infect Dis. 1998;26:1-12.

PHARMACOKINETIC FACTORS



Levison ME, Levison JH. Infect Dis Clin N Am .2009;23:791-815
Meagher AK, Ambrose PG, Grasela TH, Grosse JE. Clin Infect Dis. 2005;41(suppl 5):S333-S340

PHARMACOKINETIC FACTORS—DRUG PENETRATION

	"Lower" concentration examples	"Higher" concentration examples
Blood	• Tigecycline Cmax ~0.6 – 0.8 mcg/mL	
CNS	• Beta-lactamase inhibitors (eg Tazobactam 10% CSF:Serum)	• Metronidazole 86% CSF:Serum • Ceftriaxone ~10% CSF:Serum
Lung	• Gentamicin 20% ELF:Serum	• Cefepime 100% ELF:Serum
Urine	• Moxifloxacin	• Levofloxacin, Ciprofloxacin • Aminoglycosides, Vancomycin, Beta-lactams • Nitrofurantoin (urine but not kidney parenchyma)

ELF=Epithelial lining fluid

- Note: must consider absolute concentration at site of infection, not just % penetration

Boselli et al. Intensive Care Med. 2004;30*5):989-991
Craig WA. Clin Infect Dis. 1997;24(Suppl 2):S266-75
Drusano GL. J. Antimicrob Chemother. 2011;66(suppl 3):iii61-iii67
Frasca D et al. Antimicrob Agents Chemother. 2014;58(2):1024-1027
Nau R, Sorgel F, Eiffert H. Clin Microbiol Rev. 2010;23(4):858-883
Nicolau DP et al. J. Antimicrob Chemother. 2015;70(10):2862-2869
Tigecycline prescribing information. Wyeth Pharmaceuticals. Sept 2013.

EMPIRIC THERAPY: FACTORS FOR CONSIDERATION

BUG	DRUG	PATIENT
Suspected site of infection	Spectrum of activity	Recent antibiotic exposures
Community-acquired vs hospital acquired infection	PK/PD	Allergies
Local susceptibilities	Adverse reactions	Comorbidities
	Drug interactions	Immune status
	Cost	Pregnancy status
		Renal/hepatic function
		Weight (obesity)

CASE 1

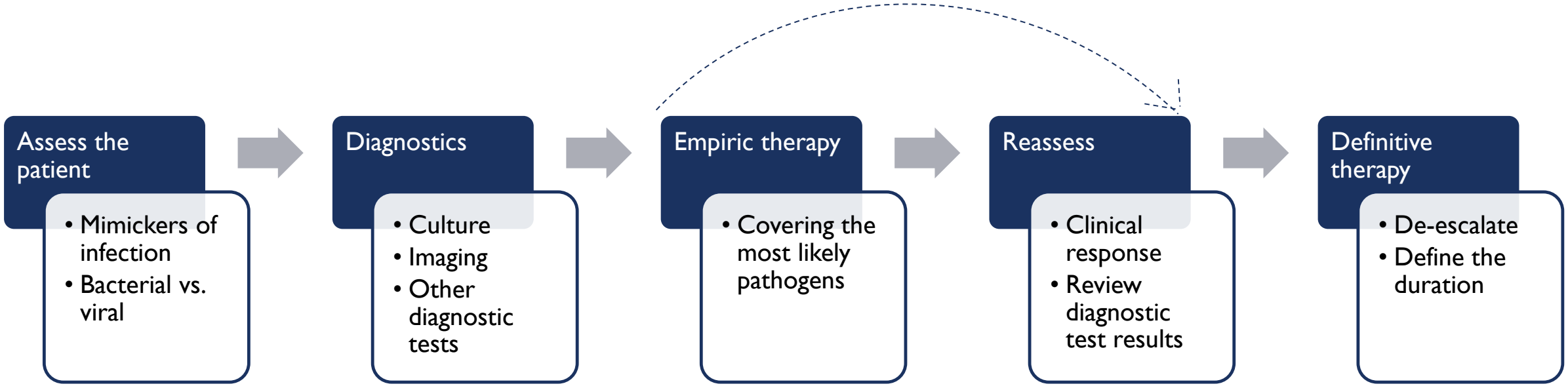
- EK is a 28-year-old female who presents to the ER with fevers, flank pain, and dysuria. She has a leukocytosis (WBC 17) but is hemodynamically stable. The medical intern turns to you and asks what antibiotic therapy to initiate. You, the astute pharmacist, ask several clarifying questions and learn the following information:
- PMH: Recently completed levofloxacin course for sinusitis, No recent hospitalizations
- Allergy: Penicillin (anaphylaxis 2 years ago)
- Presumed diagnosis: Pyelonephritis

WHICH OF THE FOLLOWING ANTIBIOTICS IS MOST APPROPRIATE TO RECOMMEND?

- 28 year old female presents to the ER with fevers, flank pain, and dysuria
- PMH: Recently completed levofloxacin course for sinusitis, No recent hospitalizations
- Allergy: Penicillin (anaphylaxis 2 years ago)
- Presumed diagnosis: Pyelonephritis

A. Cephalexin
B. Ciprofloxacin
C. Gentamicin
D. Nitrofurantoin

INFECTIOUS DISEASES WORKFLOW



DEFINITIVE ANTIMICROBIAL THERAPY

- Once pathogen identified and susceptibility results available, therapy should be de-escalated from empiric regimen to a narrower, targeted antibiotic
- Culture information useful to guide antibiotic choice

Organism		Methicillin-Susceptible Staphylococcus aureus	
Organism			[ug/mL]
Methicillin-Susceptible Staphylococcus aureus			
Method		Minimum Inhibitory Concentration	
Clindamycin		<=0.25 S	[ug/mL]
This organism does not demonstrate inducible clindamycin resistance in vitro.			
Erythromycin		>8 R	[ug/mL]
Oxacillin		0.5 S	[ug/mL]
Oxacillin-susceptible staphylococci are susceptible to penicillinase-stable penicillins, beta-lactamase inhibitor combinations, cephalosporins and carbapenems.			
Penicillin G		>8 R	[ug/mL]
Rifampin		<=1 S	[ug/mL]
Tetracycline		<=2 S	[ug/mL]
Trimeth/Sulfamethoxazole		>2/38 R	[ug/mL]
Vancomycin		1 S	[ug/mL]

CASE 2

- A 60-year-old male with a history of meningioma and hydrocephalus requiring ventriculoperitoneal shunt placement 2 months ago was transferred from an OSH with nausea, emesis, increased lethargy, and low-grade fever.
- A shunt tap revealed 150 nucleated cells and low glucose in CSF. Vancomycin and cefepime are initiated.
- 48 hours later, both blood and CSF cultures reveal *Staphylococcus aureus*.
- Which antimicrobial therapy would you recommend?

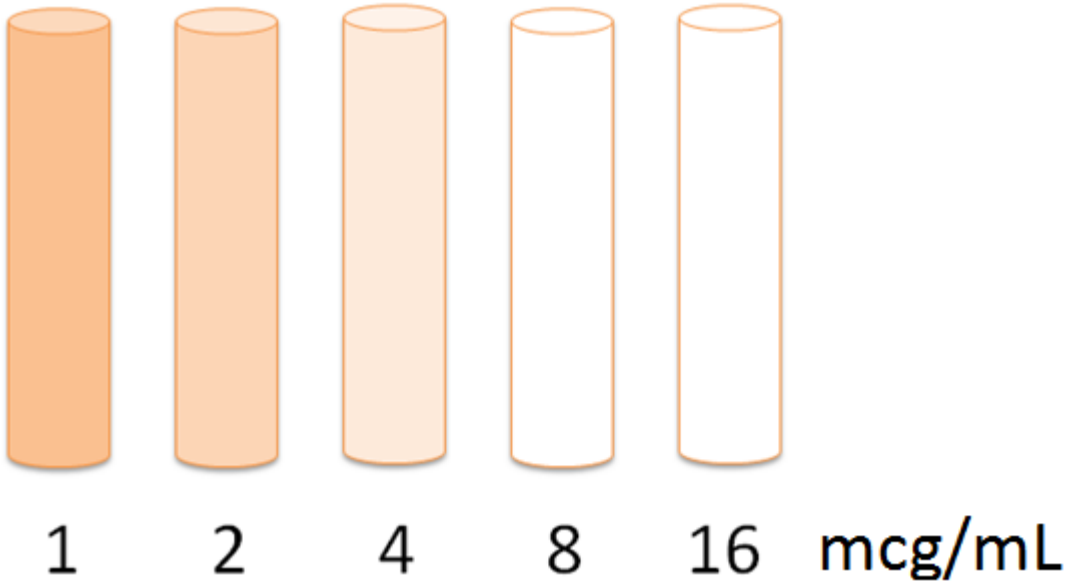
Organism H	Methicillin-Susceptible Staphylococcus aureus		
Organism H			[ug/mL]
Methicillin-Susceptible Staphylococcus aureus			
Method H	Minimum Inhibitory Concentration		
Clindamycin		<=0.25 S	[ug/mL]
This organism does not demonstrate inducible clindamycin resistance in vitro.			
Erythromycin		>8 R	[ug/mL]
Oxacillin		0.5 S	[ug/mL]
Oxacillin-susceptible staphylococci are susceptible to penicillinase-stable penicillins, beta-lactamase inhibitor combinations, cephalosporins and carbapenems.			
Penicillin G		>8 R	[ug/mL]
Rifampin		<=1 S	[ug/mL]
Tetracycline		<=2 S	[ug/mL]
Trimeth/Sulfamethoxazole		>2/38 R	[ug/mL]
Vancomycin		1 S	[ug/mL]

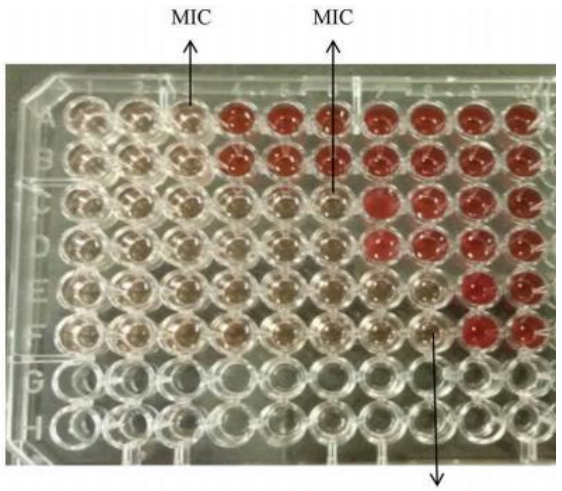
DEFINITIVE THERAPY: FACTORS FOR CONSIDERATION

BUG	DRUG	PATIENT
Site of infection	Spectrum of activity	Allergies
MIC (Susceptibility)	PK/PD	Comorbidities
Breakpoint/Interpretation	Adverse reactions	Immune status
Resistance mechanisms	Drug Interactions	Pregnancy status
	Cost	Renal/hepatic function
	Outcomes data	Weight (obesity)
	Outpatient feasibility	

MIC

- Minimum Inhibitory Concentration (MIC) = minimum antimicrobial concentration that inhibits visual bacterial growth *in vitro*

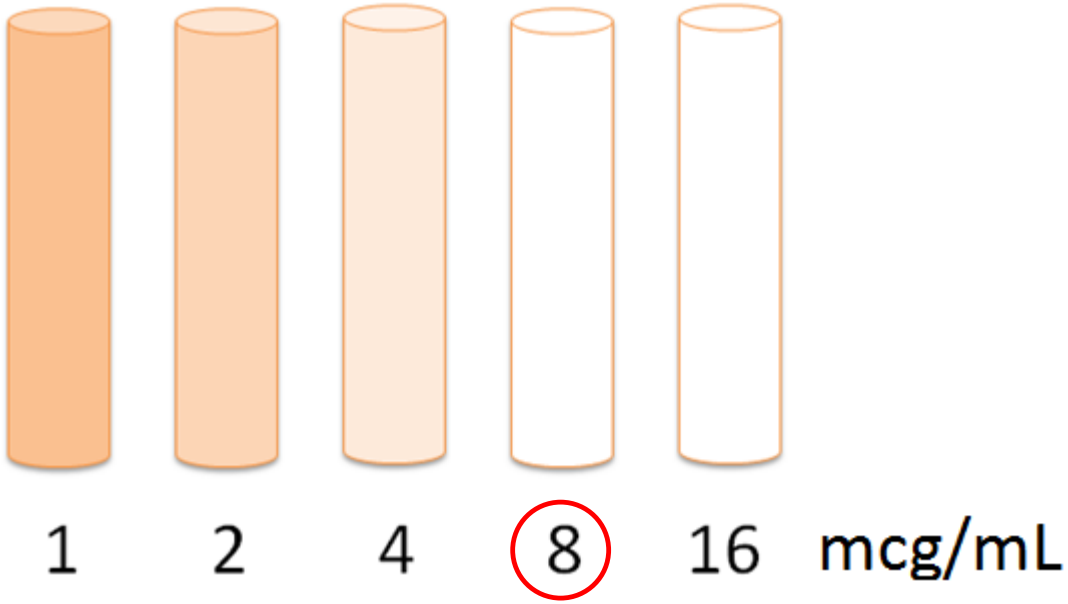


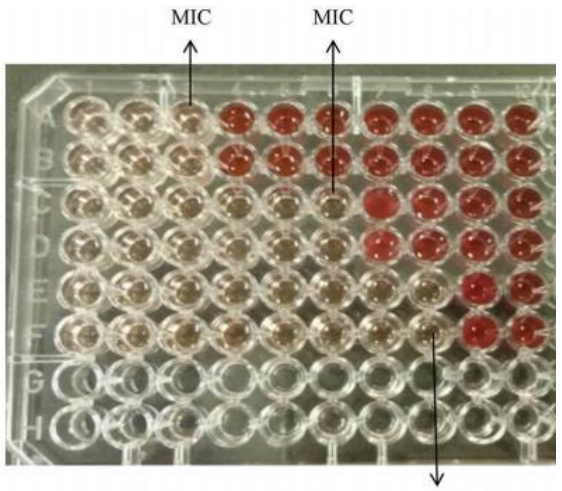


John CN et al. Front Microbiol. 2019;10:1021
Shutterstock.com. Accessed December 2019.

MIC

- Minimum Inhibitory Concentration (MIC) = minimum antimicrobial concentration that inhibits visual bacterial growth *in vitro*





John CN et al. Front Microbiol. 2019;10:1021
Shutterstock.com. Accessed December 2019.

BREAKPOINT AND INTERPRETATIVE CRITERIA

- Standard reference value correlating *in vitro* antimicrobial MIC to clinical efficacy

Susceptible	Intermediate	Resistant	Susceptible Dose-Dependent
• Inhibited by usually achievable concentrations of drug with the recommended dosage, resulting in likely clinical efficacy	• Near usually achievable serum concentrations, response rates may be lower • May be efficacious in higher doses or sites where drug physiologically concentrates	• Unlikely to inhibit at usually achievable concentrations	• Dependent on the dosing regimen (need higher drug exposure than the dose used to establish the susceptible breakpoint)

Kuper KM, et al. Pharmacotherapy. 2009;29(11):1326-1343.
CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 29th ed. CLSI supplement M100. 2019

DETERMINATION OF BREAKPOINTS

- Based on:
  - Wild-type distribution of MICs for the organism
  - Pharmacokinetics/pharmacodynamics of the drug
  - Clinical outcomes data for treatment of infections when the antibacterial is used
- Determined by:
  - Clinical Laboratory and Standards Institute (CLSI)
  - European Committee on Antimicrobial Susceptibility Testing (EUCAST)
  - FDA

Kuper KM, et al. Pharmacotherapy. 2009;29(11):1326-1343.
CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 29th ed. CLSI supplement M100. 2019

INTERPRETING SUSCEPTIBILITIES

- Cannot just "pick lowest MIC"
- Each bug/drug combination has different breakpoints

Drug	Patient MIC	Interpretation
Clindamycin	≤ 0.25	S
Erythromycin	> 8	R
Oxacillin	0.5	S
Penicillin	> 8	R
Rifampin	≤ 1	S
Tetracycline	≤ 2	S
TMP/SMX	> 2/38	R
Vancomycin	0.25	S

≤ means lab will not report any lower MICs

INTERPRETING SUSCEPTIBILITIES

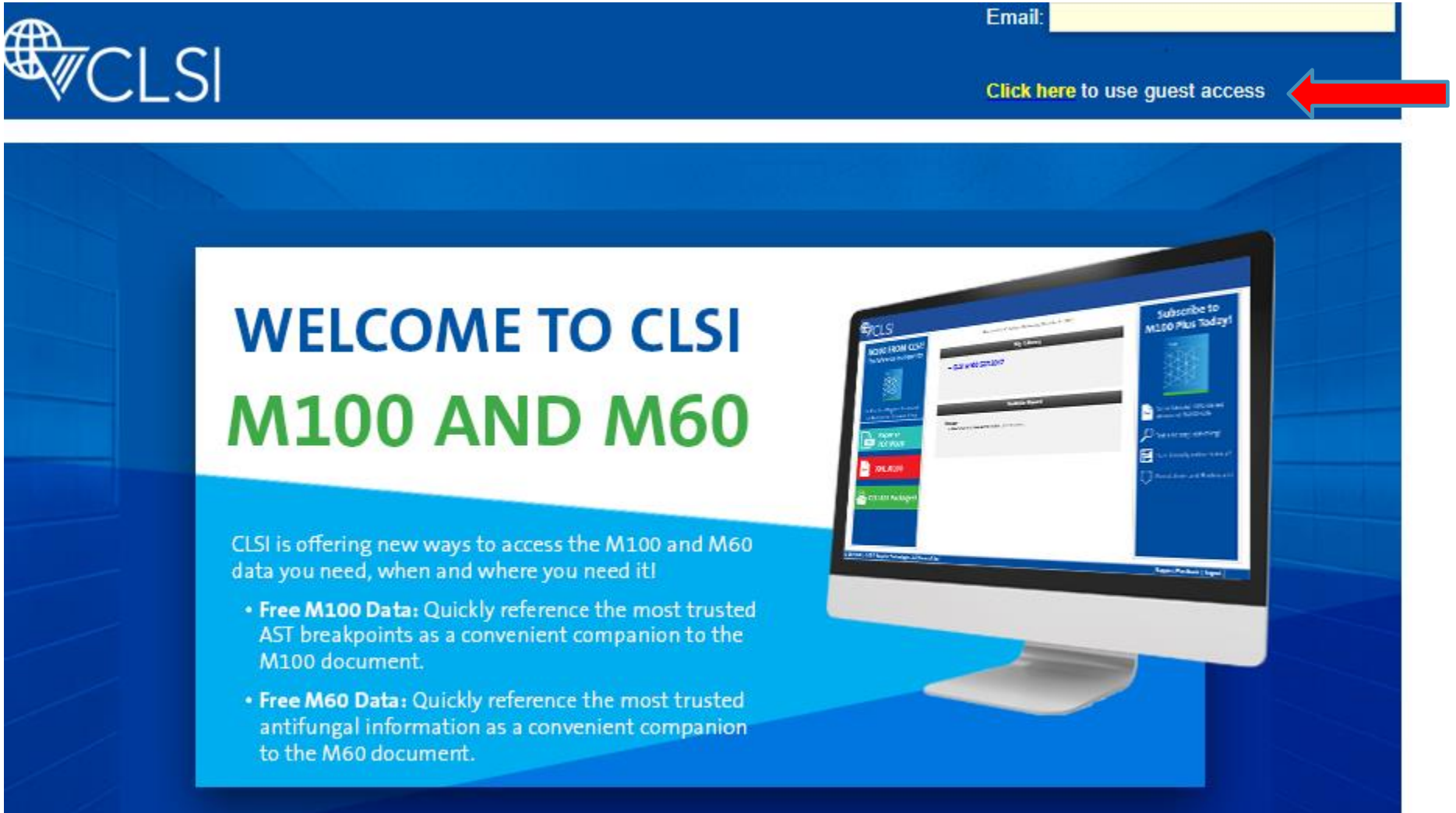
- Cannot just "pick lowest MIC"
- Each bug/drug combination has different breakpoints

Drug	Patient MIC	Breakpoint S ≤	Interpretation
Clindamycin	≤ 0.25	0.5	S
Erythromycin	> 8	0.5	R
Oxacillin	0.5	2	S
Penicillin	> 8	0.12	R
Rifampin	≤ 1	1	S
Tetracycline	≤ 2	4	S
TMP/SMX	> 2/38	2/38	R
Vancomycin	0.25	2	S

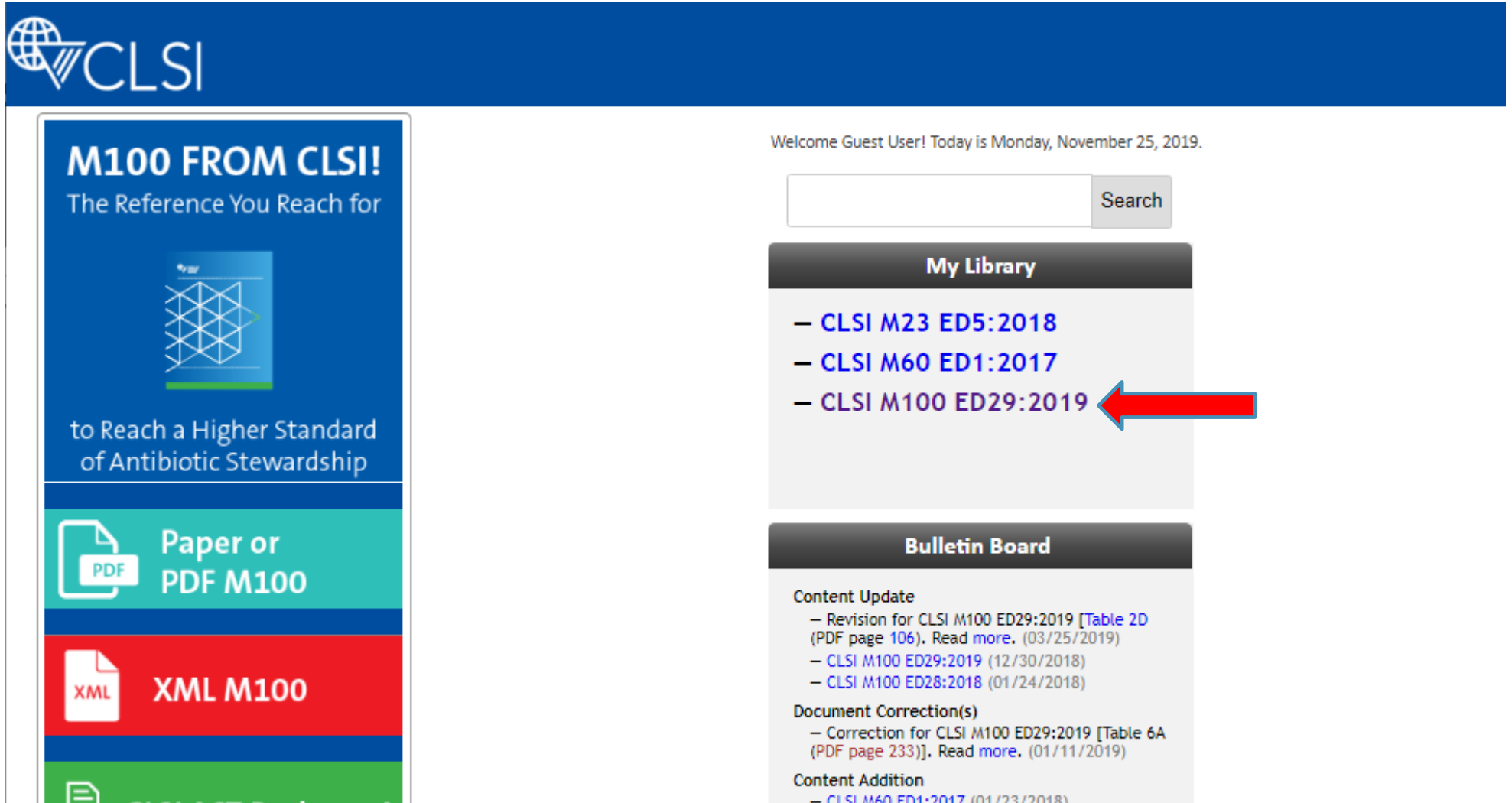
≤ means lab will not report any lower MICs

CLSI BREAKPOINTS (M100)

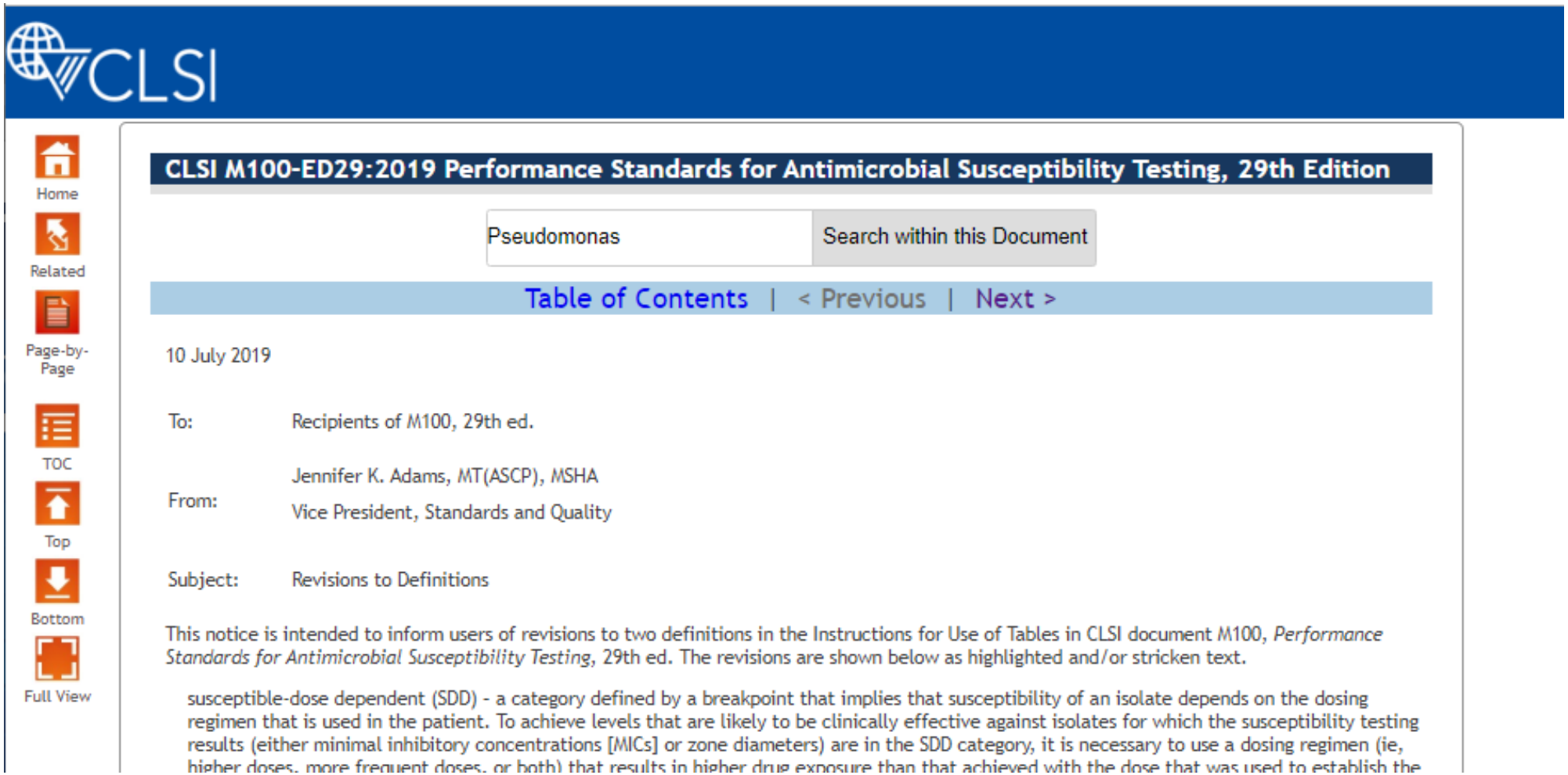
CLSI BREAKPOINTS (M100)



CLSI BREAKPOINTS (M100)



CLSI BREAKPOINTS (M100)



CLSI BREAKPOINTS (M100)

CLSI

Home

Top

Bottom

Full View

Search Results

Search Tokens: Pseudomonas, **Scope:** CLSI M100 ED29:2019

- CLSI M100-ED29:2019 Performance Standards for Antimicrobial Susceptibility Testing, 29th Edition
  - Overview of Changes
  - Table 2B-1. Zone Diameter and MIC Breakpoints for *Pseudomonas aeruginosa*
  - Introduction to Tables 3B and 3C. Tests for Carbapenemases in *Enterobacteriaceae* and *Pseudomonas aeruginosa*
  - Table 3B. CarbaNP Test for Suspected Carbapenemase Production in *Enterobacteriaceae* and *Pseudomonas aeruginosa*[1-7]
  - Table 3B-1. Modifications of Table 3B When Using MIC Breakpoints for Carbapenems Described in M100-S20 (January 2010)[1-5]
  - Table 3C. Modified Carbapenem Inactivation Methods for Suspected Carbapenemase Production in *Enterobacteriaceae* and *Pseudomonas aeruginosa*[1-4]
  - Table 1A. Suggested Groupings of Antimicrobial Agents Approved by the US Food and Drug Administration for Clinical Use That Should Be Considered for Testing and Reporting on Nonfastidious Organisms by Microbiology Laboratories in the United States
  - Table 2B-3. Zone Diameter and MIC Breakpoints for *Burkholderia cepacia* complex
  - Table 2B-5. MIC Breakpoints for Other Non-*Enterobacteriaceae* (Refer to General Comment 1)
  - Table 2A. Zone Diameter and MIC Breakpoints for *Enterobacteriaceae*
  - Table 2B-2. Zone Diameter and MIC Breakpoints for *Acinetobacter* spp.

CLSI BREAKPOINTS (M100)

Test/Report Group	Antimicrobial Agent	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm			Interpretive Categories and MIC Breakpoints, µg/mL			Comments
			S	I	R	S	I	R	
PENICILLINS									
O	Piperacillin	100 µg	≥ 21	15-20	≤ 14	≤ 16	32-64	≥ 128	**(5)** Breakpoints for piperacillin (alone or with tazobactam) are based on a piperacillin dosage regimen of at least 3 g **administered** every 6 h.
B-LACTAM COMBINATION AGENTS									
A	Piperacillin-tazobactam	100/10 µg	≥ 21	15-20	≤ 14	≤ 16/4	32/4-64/4	≥ 128/4	**(6)** Breakpoints for piperacillin (alone or with tazobactam) are based on a piperacillin dosage regimen of at least 3 g **administered** every 6 h.
B	Ceftazidime-avibactam	30/20 µg	≥ 21	-	≤ 20	≤ 8/4	-	≥ 16/4	**(7)** Breakpoints are based on a dosage regimen of 2.5 g (2 g ceftazidime + 0.5 g avibactam) **administered** every 8 h over 2 h.
B	Ceftolozane-tazobactam	30/10 µg	≥ 21	17-20	≤ 16	≤ 4/4	8/4	≥ 16/4	**(8)** Breakpoints are based on a dosage regimen of 1.5 g **administered** every 8 h.

CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 29th ed. CLSI supplement M100. 2019

WHICH OF THE FOLLOWING IS TRUE REGARDING CULTURE AND SUSCEPTIBILITY TESTING RESULTS?

A. Breakpoint values for bacterial pathogens are standardized nationally and internationally
B. Generally, the antibiotic with the lowest minimum inhibitory concentration is most effective
C. A culture result interpretation of "susceptible" to an antibiotic indicates that the antibiotic will work at all infection sites
D. Susceptibility breakpoint values may change with new literature on antimicrobial pharmacokinetic/pharmacodynamics or new clinical outcomes data

DEFINITIVE THERAPY: FACTORS FOR CONSIDERATION

BUG	DRUG	PATIENT
Site of infection	Spectrum of activity	Allergies
MIC (Susceptibility)	PK/PD	Comorbidities
Breakpoint/Interpretation	Adverse reactions	Immune status
Resistance mechanisms	Drug Interactions	Pregnancy status
	Cost	Renal/hepatic function
	Outcomes data	Weight (obesity)
	Outpatient feasibility	

RESISTANCE MECHANISMS

- In vitro susceptibility does not necessarily predict development of resistance/clinical failure
- Examples:
  - Rifampin monotherapy—rapid emergence of resistance due to high spontaneous chromosomal mutations
  - AmpC beta-lactamases—inducible cephalosporinases
  - Extended spectrum beta-lactamases (ESBL)—may be reported "resistant" to one 3rd generation cephalosporin and "susceptible" to another

O'Neill AJ et al. J Antimicrob Chemother. 2001;47(5):647-650
Forrest GN, Tamura K. Clin Microbiol Rev. 2010 Jan;23(1):14-34

DEFINITIVE THERAPY: FACTORS FOR CONSIDERATION

BUG	DRUG	PATIENT
Site of infection	Spectrum of activity	Allergies
MIC (Susceptibility)	PK/PD	Comorbidities
Breakpoint/Interpretation	Adverse reactions	Immune status
Resistance mechanisms	Drug Interactions	Pregnancy status
	Cost	Renal/hepatic function
	Outcomes data	Weight (obesity)
	Outpatient feasibility	

OUTCOMES DATA: WORSE OUTCOMES WITH VANCOMYCIN VS BETA-LACTAM FOR MSSA

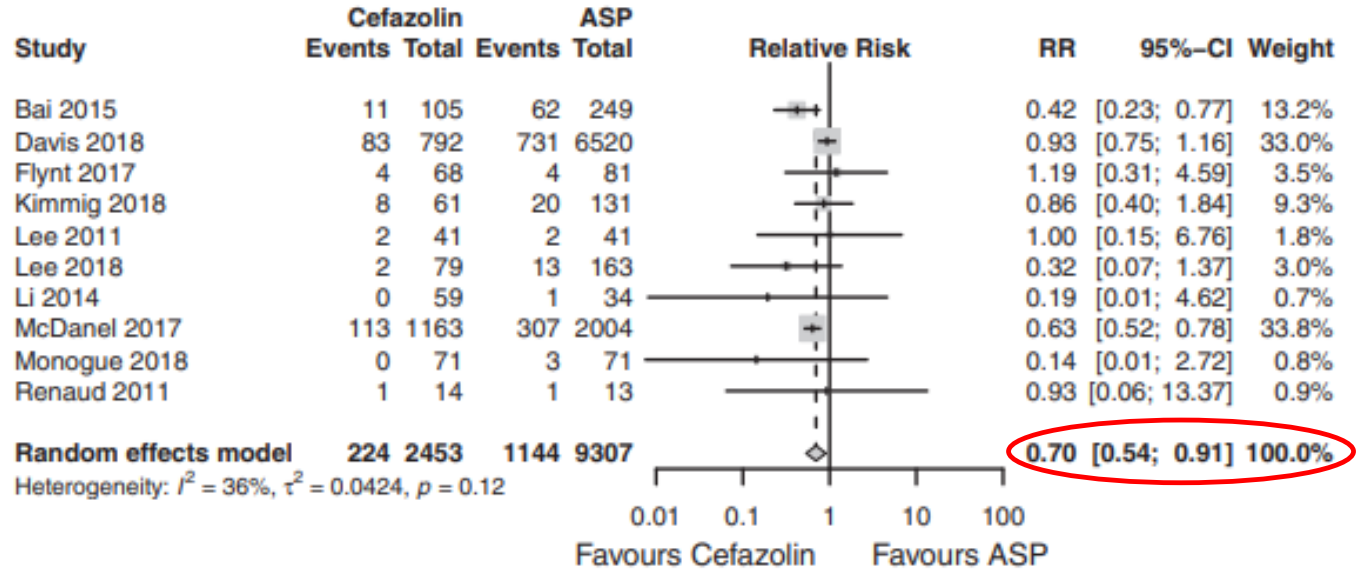
Authors	Design	Results (Vancomycin vs Beta-lactam)
Chang FY et al.	Multicenter, prospective observational study N=505 patients with S. aureus bacteremia	Significantly higher bacteriologic failure (persistent bacteremia or relapse)
Stryjewski ME et al.	Prospective observational study N=123 hemodialysis-dependent patients with MSSA bacteremia	Significantly higher treatment failure (death or recurrence) for those continuing on vancomycin vs switch to 1st generation cephalosporin (OR 3.5)
Schweizer ML et al.	Retrospective cohort study N=267 patients with MSSA bacteremia	Significantly higher 30-day in-hospital mortality for those continuing on vancomycin vs switched to nafcillin or cefazolin
Kim SH et al.	Retrospective cohort study N=294 patients with MSSA bacteremia	Significantly higher mortality (37% vs 18%, p=0.02) vs beta-lactam
McDanel JS et al.	Retrospective cohort study N=5633 patients with MSSA bacteremia	Significantly higher mortality (35% higher) vs beta-lactam; 43% higher vs nafcillin/oxacillin/cefazolin

Chang FY et al. Medicine. 2003;82(5):333-339.
Kim SH et al. Antimicrob Agents Chemother. 2008 Jan;52(1);192-197.
McDanel JS et al. Clin Infect Dis. 2015;61(3):361-367
Schweizer ML et al. BMC infect Dis. 2011;11(279). doi:10.1186/1471-2334-11-279
Stryjewski ME et al. Clin Infect Dis. 2007;44:190–6

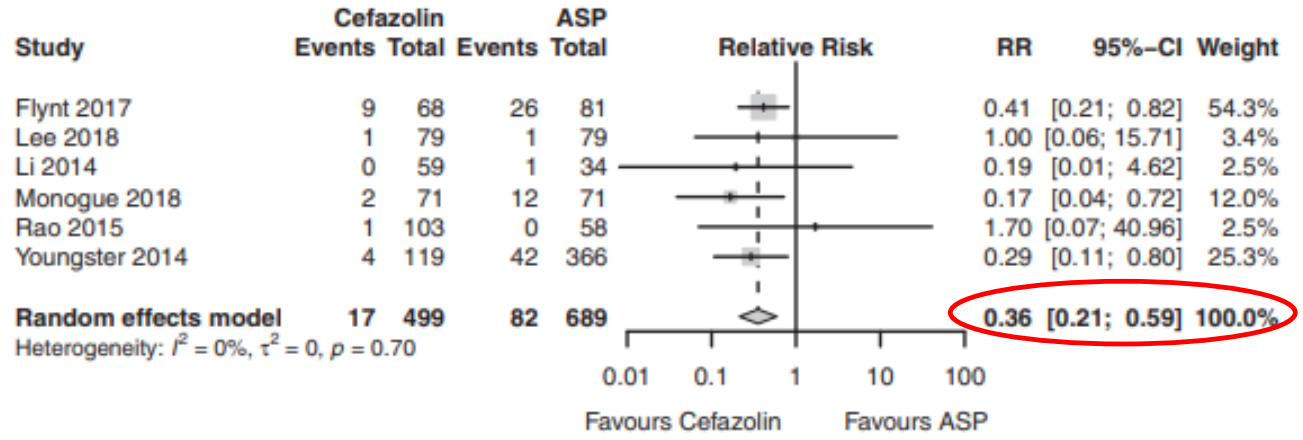
OUTCOMES DATA: CEFAZOLIN VS PENICILLINS

- Theoretical concern for inoculum effect with cefazolin
- Recent meta-analysis of 14 retrospective cohort studies of MSSA bacteremia
  - Cefazolin at least as effective as antistaphylococcal penicillins (oxacillin, nafcillin), possibly lower rates of nephrotoxicity

30−day all−cause mortality



Nephrotoxicity



Weis S et al. Clin Microbiol Infect. 2019;25:818-827

PK CONSIDERATIONS: CENTRAL NERVOUS SYSTEM PENETRATION

Therapeutic Levels in CSF With or Without Inflammation		
Chloramphenicol	Metronidazole	Linezolid
Rifampin	SMX/TMP	
Therapeutic Levels in CSF With Inflammation of Meninges		
Penicillin	Ampicillin	Oxacillin
Piperacillin	Aztreonam	Cefuroxime
Ceftriaxone	Ceftazidime	Cefepime
Imipenem	Meropenem	Fluroquinolones
Vancomycin		
Nontherapeutic Levels in CSF With or Without Inflammation		
Aminoglycosides	Beta-lactamase inhibitors	1st and 2nd gen cephs (except cefuroxime)
Clindamycin	Daptomycin	Ertapenem

Lutsar I et al. Clin Infect Dis. 1998;27:1117-1129

Nau R et al. Clin Microbiol Rev. 2010 Oct;23(4):858-883

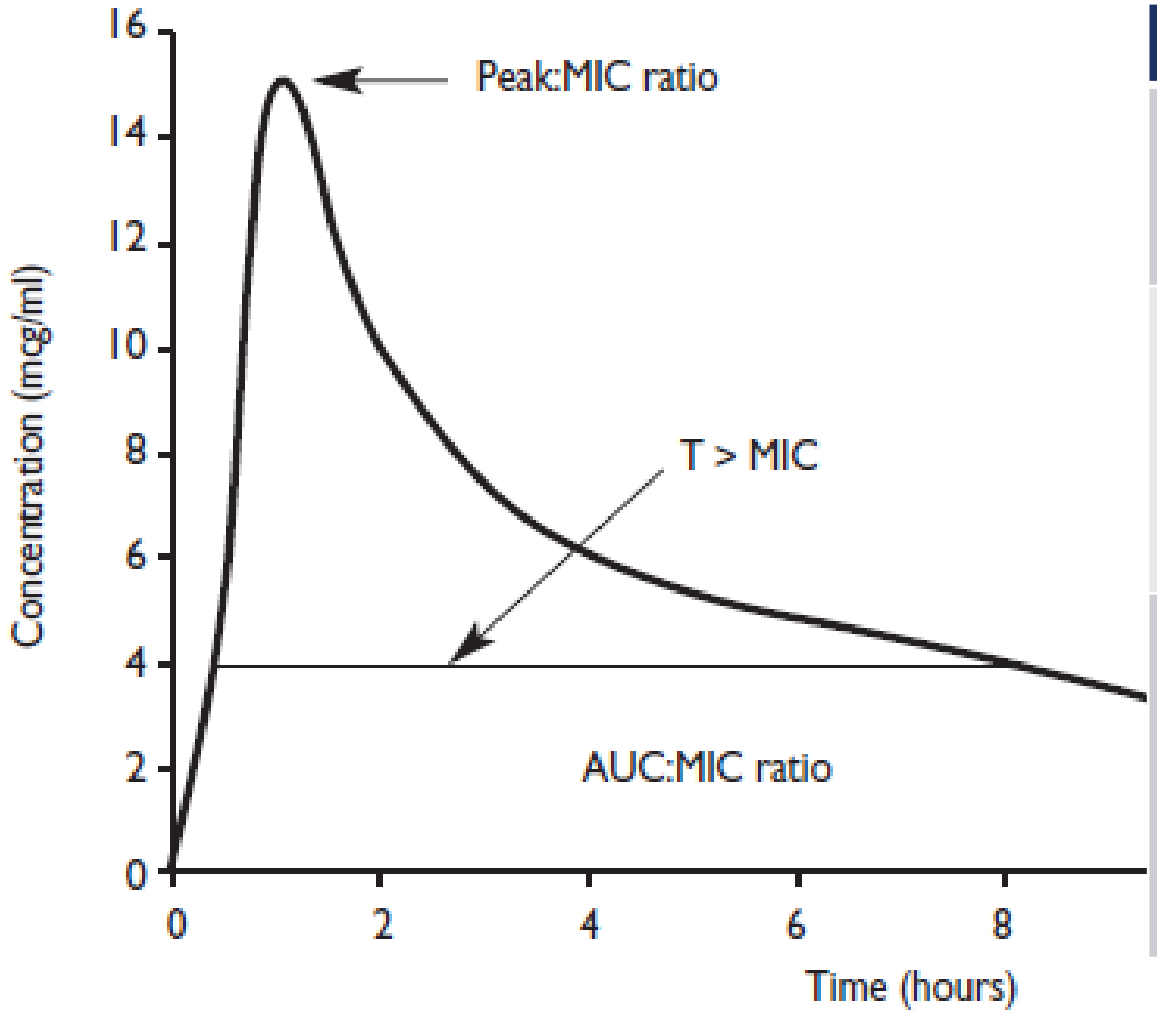
CASE 2

- AJ is a 60 year old male with a history of meningioma and hydrocephalus requiring ventriculoperitoneal (VP) shunt placement 2 months ago, who was transferred from an OSH with nausea, emesis, increased lethargy, and low grade fever.
- A shunt tap revealed 150 nucleated cells and low glucose in CSF. Vancomycin and cefepime are initiated.
- 48 hours later, both blood and CSF cultures reveal *Staphylococcus aureus*.
- Which of the following therapies would you recommend?

A. Cefazolin
B. Oxacillin
C. Rifampin
D. Vancomycin

Organism H	Methicillin-Susceptible Staphylococcus aureus		
Organism H			[ug/mL]
Methicillin-Susceptible Staphylococcus aureus			
Method H	Minimum Inhibitory Concentration		
Clindamycin		<=0.25 S	[ug/mL]
This organism does not demonstrate inducible clindamycin resistance in vitro.			
Erythromycin		>8 R	[ug/mL]
Oxacillin		0.5 S	[ug/mL]
Oxacillin-susceptible staphylococci are susceptible to penicillinase-stable penicillins, beta-lactamase inhibitor combinations, cephalosporins and carbapenems.			
Penicillin G		>8 R	[ug/mL]
Rifampin		<=1 S	[ug/mL]
Tetracycline		<=2 S	[ug/mL]
Trimeth/Sulfamethoxazole		>2/38 R	[ug/mL]
Vancomycin		1 S	[ug/mL]

ANTIBIOTIC PHARMACODYNAMIC TARGETS

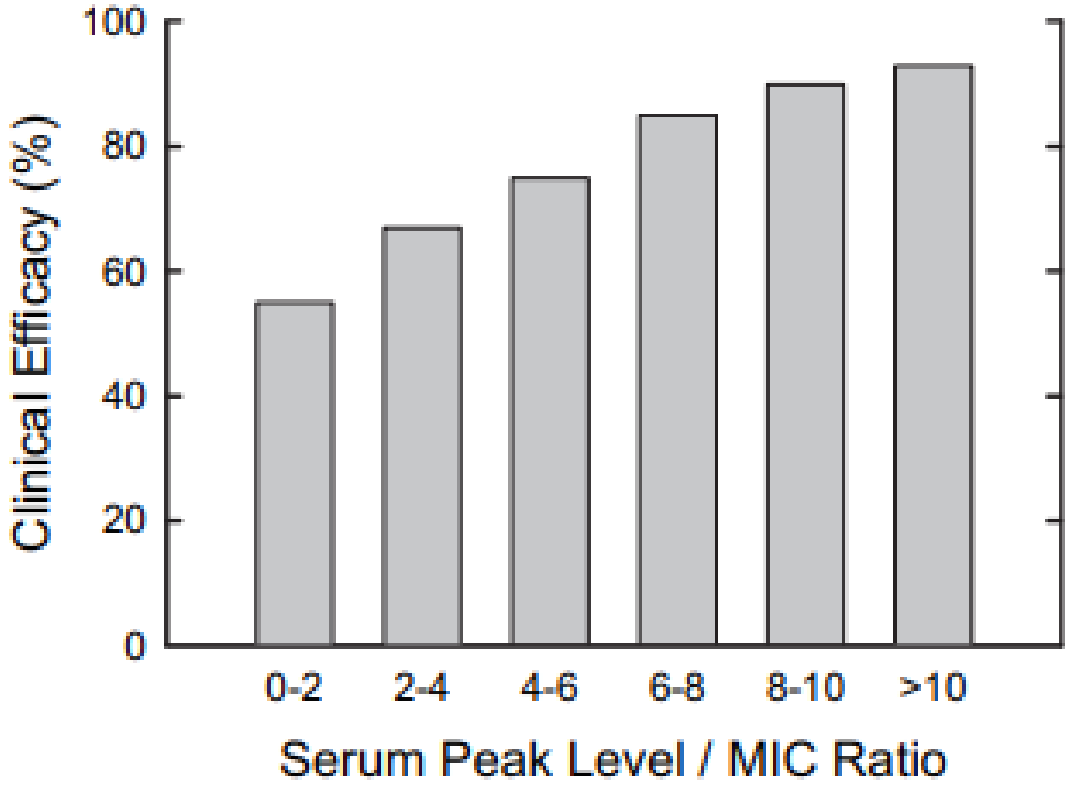


Drug Examples	PD Target Examples
Aminoglycosides Fluoroquinolones Metronidazole	Peak (Cmax): MIC 8 -12
β-lactams Macrolides Clindamycin	β-lactam free drug T>MIC PCN: >50% of dosing interval Cephalosporin/Aztreonam: >60% Carbapen: >40% Up to 100% T > 4 x MIC
Glycopeptides Daptomycin Linezolid Tetracyclines Aminoglycosides Fluoroquinolones	Vancomycin free AUC_{24}: MIC ≥400

Roberts JA, Lipman J. Clin Pharmacokinet. 2006;45(8):755-73.
Burgess DS, Frei CR. J Antimicrob Chemother. 2005;56(5):893-8.

OPTIMIZING PHARMACODYNAMICS: AMINOGLYCOSIDES

- Analysis of data from 4 randomized controlled trials including 236 patients on conventional dose gentamicin, tobramycin, or amikacin for gram-negative sepsis
- Clinical response associated with Cmax: MIC



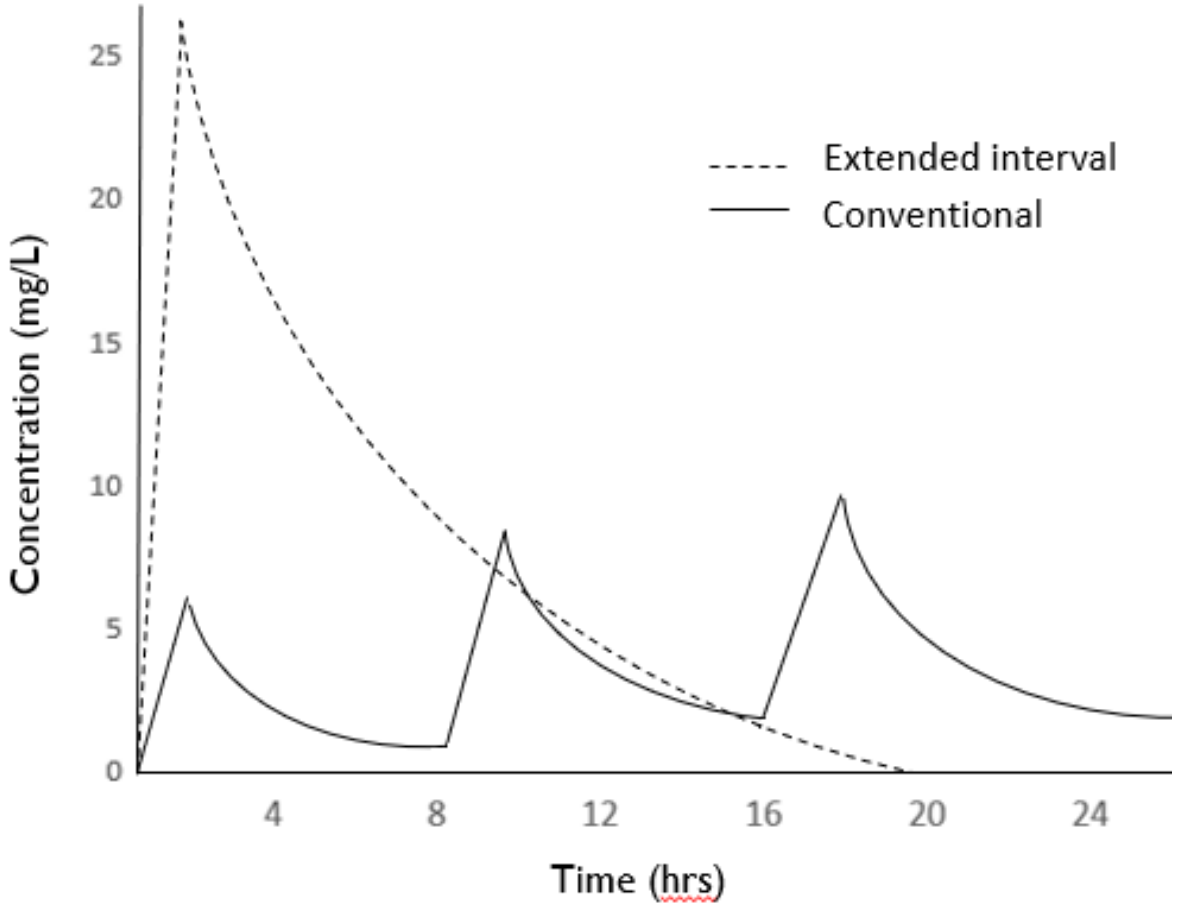
Craig WA. Crit Care Clin. 2011;27: 107–121
Moore RD et al. J Infect Dis. 1987;155(1): 93-99

OPTIMIZING PHARMACODYNAMICS: AMINOGLYCOSIDES

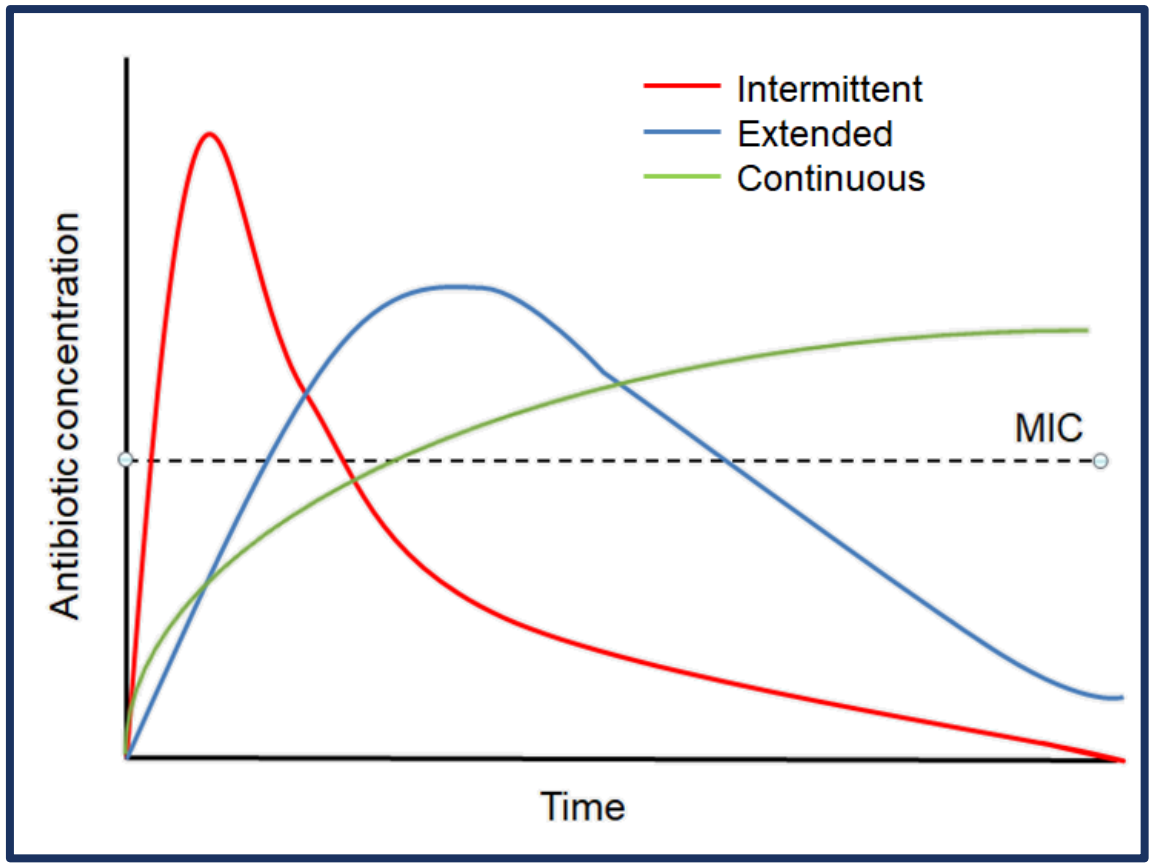
Dosing Method*	Gentamicin Tobramycin	Amikacin
Conventional	1 – 2 mg/kg q8h	7.5 mg/kg q12h
Extended interval	5 – 7 mg/kg q24h	15 – 20 mg/kg q24h

*Assuming normal renal function

Pharmacodynamic Goal Peak: MIC 8 -12



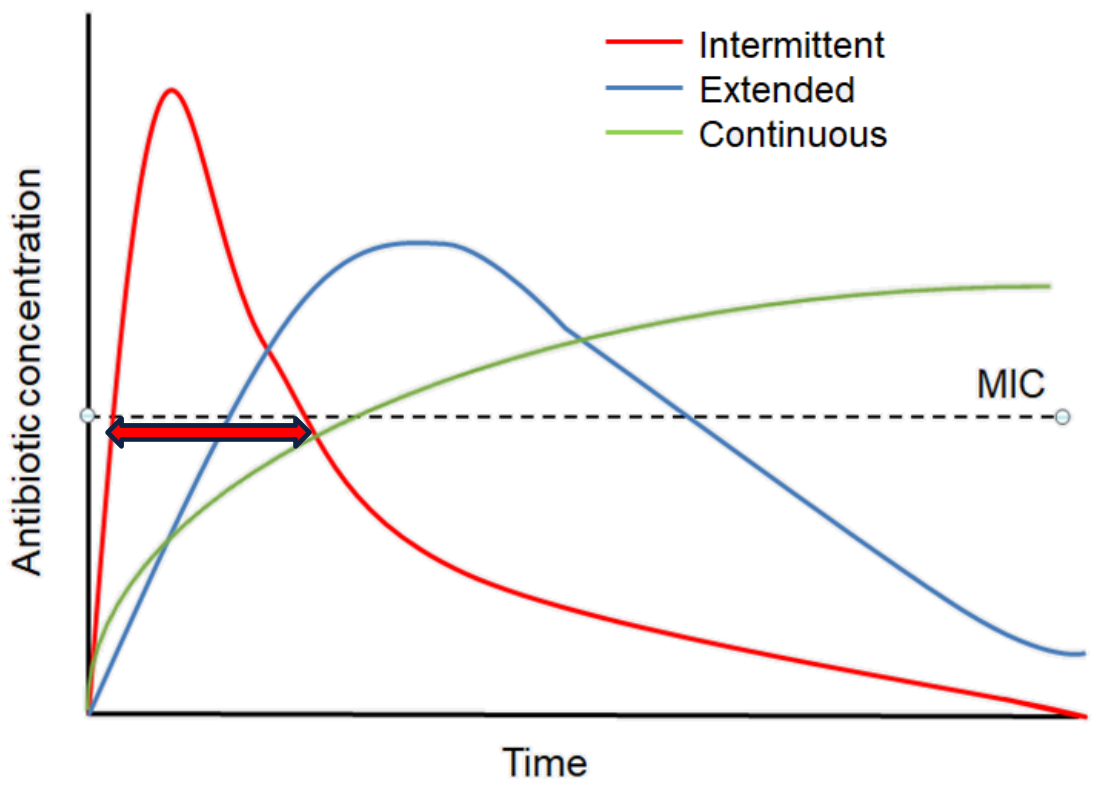
OPTIMIZING PHARMACODYNAMICS: BETA-LACTAMS



- Extended and continuous infusions increase T> MIC
- Clinical outcomes data comparing prolonged infusions to intermittent are conflicting
  - Low sample sizes
  - Heterogeneous patient populations
  - Low-MIC pathogens

Vardakas KZ et al. Lancet Infect Dis. 2018;18(1):108-120

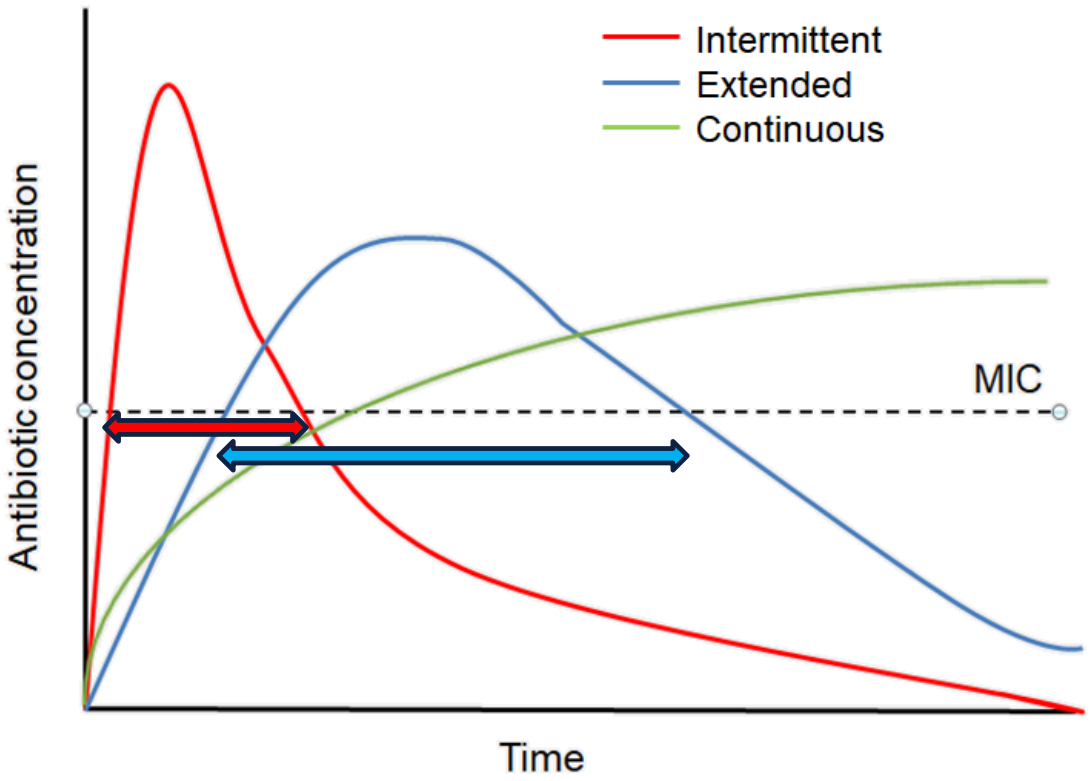
OPTIMIZING PHARMACODYNAMICS: BETA-LACTAMS



- Extended and continuous infusions increase T> MIC
- Clinical outcomes data comparing prolonged infusions to intermittent are conflicting
  - Low sample sizes
  - Heterogeneous patient populations
  - Low-MIC pathogens

Vardakas KZ et al. Lancet Infect Dis. 2018;18(1):108-120

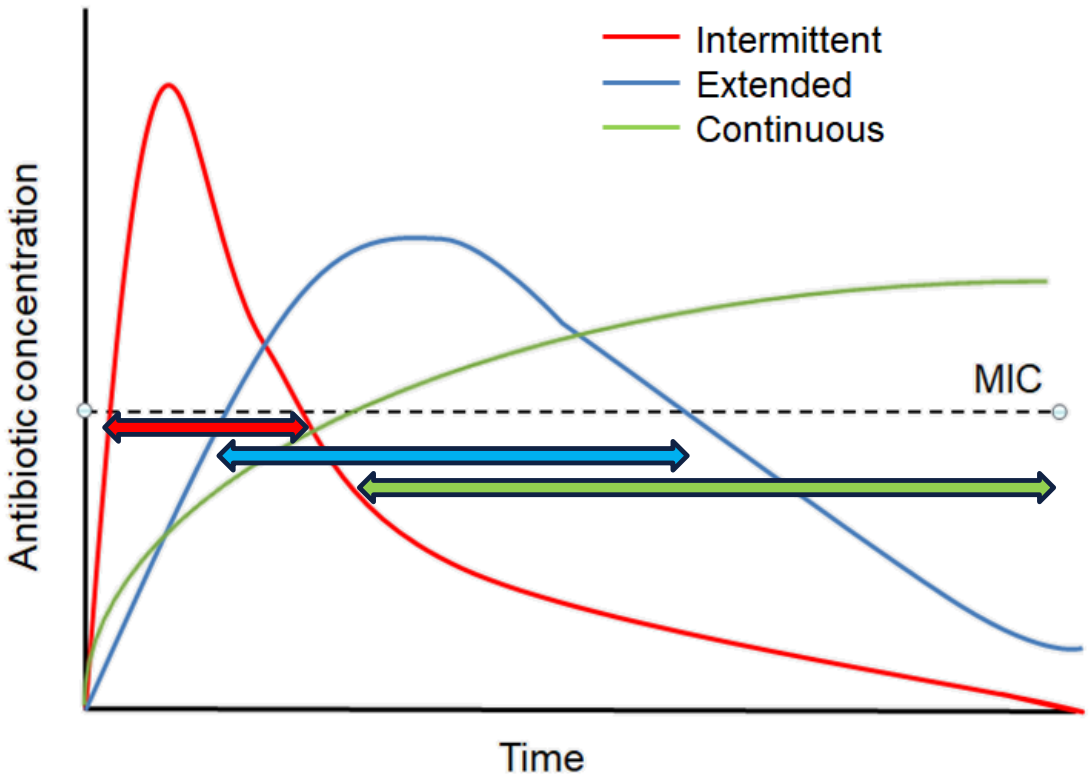
OPTIMIZING PHARMACODYNAMICS: BETA-LACTAMS



- Extended and continuous infusions increase T> MIC
- Clinical outcomes data comparing prolonged infusions to intermittent are conflicting
  - Low sample sizes
  - Heterogeneous patient populations
  - Low-MIC pathogens

Vardakas KZ et al. Lancet Infect Dis. 2018;18(1):108-120

OPTIMIZING PHARMACODYNAMICS: BETA-LACTAMS



- Extended and continuous infusions increase T> MIC
- Clinical outcomes data comparing prolonged infusions to intermittent are conflicting
  - Low sample sizes
  - Heterogeneous patient populations
  - Low-MIC pathogens

Vardakas KZ et al. Lancet Infect Dis. 2018;18(1):108-120

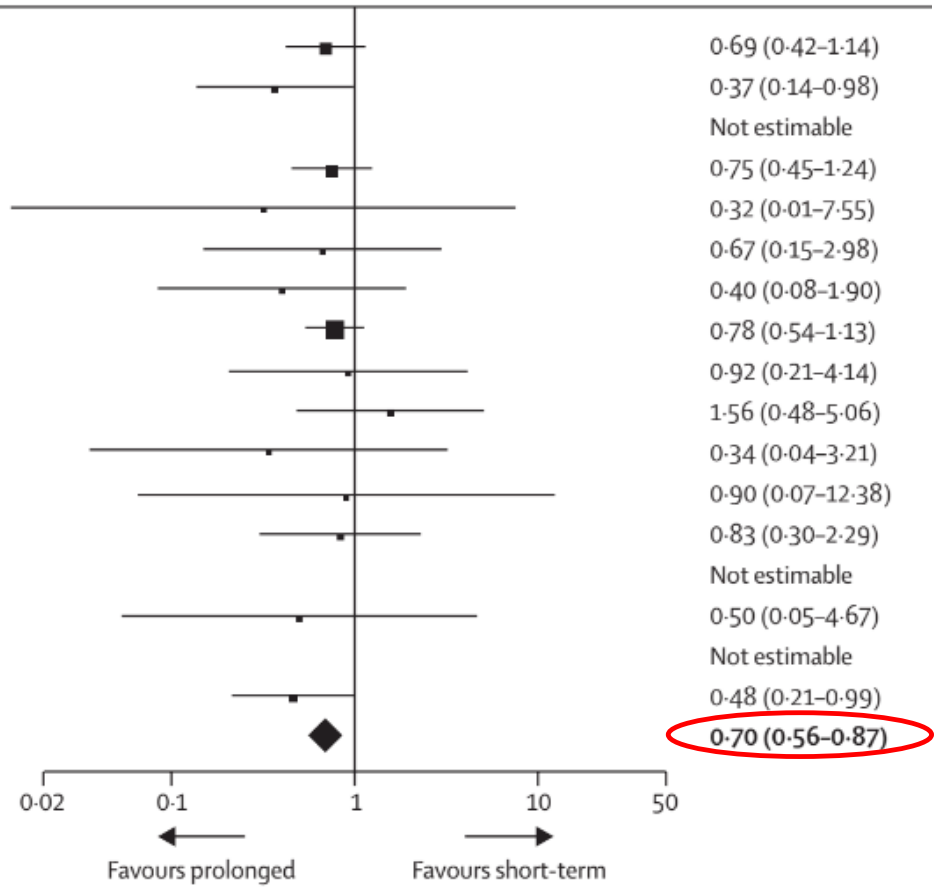
LOWER MORTALITY WITH PROLONGED INFUSION

- 2018 meta-analysis of 22 RCT (1876 patients)
- Prolonged (continuous or ≥3 h) infusion of anti-pseudomonal beta-lactams vs. short-term administration (≤60 min) in sepsis

	Prolonged		Short-term		Weight	Risk ratio (95% CI)
	Events	Total	Events	Total		
Abdul-Aziz (2016)[15]	18	70	26	70	18·5%	0·69 (0·42–1·14)
Angus (2000)[23]	3	10	9	11	4·8%	0·37 (0·14–0·98)
Bao (2016)[24]	0	25	0	25	..	Not estimable
Chytra (2012)[16]	21	120	28	120	18·1%	0·75 (0·45–1·24)
Cotrina-luque (2016)[26]	0	40	1	38	0·5%	0·32 (0·01–7·55)
Cousson (2005)[27]	2	8	3	8	2·1%	0·67 (0·15–2·98)
Dulhunty (2013)[17]	2	30	5	30	1·9%	0·40 (0·08–1·90)
Dulhunty (2015)[14]	39	212	52	220	33·9%	0·78 (0·54–1·13)
Georges (2005)[28]	3	26	3	24	2·1%	0·92 (0·21–4·14)
Lagast (1983)[30]	5	20	4	25	3·4%	1·56 (0·48–5·06)
Lau (2006)[31]	1	130	3	132	0·9%	0·34 (0·04–3·21)
Lips (2014)[32]	1	10	1	9	0·7%	0·90 (0·07–12·38)
Rafati (2006)[35]	5	20	6	20	4·5%	0·83 (0·30–2·29)
Roberts (2010)[36]	0	8	0	8	..	Not estimable
Sakka (2007)[37]	1	10	2	10	0·9%	0·50 (0·05–4·67)
Wang (2009)[38]	0	15	0	15	..	Not estimable
Wang (2014)[39]	7	38	16	40	7·8%	0·48 (0·21–0·99)
Total (95% CI)		**792**		**805**	**100·0%**	**0·70 (0·56–0·87)**
Total events	**108**		**159**			

Heterogeneity: τ^2=0·00; χ^2=6·47, df=13 (p=0·93); I^2=0%

Test for overall effect: Z=3·25 (p=0·001)



Vardakas KZ et al. Lancet Infect Dis. 2018;18(1):108-120

PHARMACODYNAMIC BREAKPOINTS

Drug	Dose (normal renal function)	"PD Breakpoint" MIC (mg/L)	CLSI Breakpoint MIC (mg/L)*
Cefepime	1 g q8h	2	S ≤ 2 S-DD 4-8
	2 g q12h	2	
	2 g q8h	8	
Meropenem	500 mg q6h	2	S ≤ 1
	1 g q8h	2	
	1 g over 3 hrs q8h	4	
	2 g q8h	4	
	2 g over 3 hrs q8h	16	
Piperacillin/ Tazobactam	4.5 g q8h	4	S ≤ 16
	4.5 g q6h	8	
	4.5 g over 4 hrs q8h	16	

*Enterobacterales

Adapted from Deryke CA, et al. Diagn Microbiol Infect Dis 2007; 58(3): 337-44
Lodise TP, et al. Pharmacotherapy. 2006; 26: 1320-32
Tam VH, et al. Antimicrob Agents Chemother 2003;47:1853–61

CASE 3

- 65 y/o IVDU with multiple positive blood cultures with Pseudomonas aeruginosa
- Dosing weight = 70 kg
- CrCl = 90 mL/min
- Allergies: NKDA
- Team would like to use dual therapy with beta-lactam and aminoglycoside until endocarditis is ruled out. Which aminoglycoside would you choose?

Drug	MIC	Interpretation
Aztreonam	4	Susceptible
Ceftazidime	8	Susceptible
Cefepime	8	Susceptible
Meropenem	8	Resistant
Piperacillin-tazobactam	16	Susceptible
Amikacin	4	Susceptible
Gentamicin	4	Susceptible
Levofloxacin	1	Susceptible

BEDSIDE PK/PD APPLICATION: CONVENTIONAL AMINOGLYCOSIDES

Gentamicin:

C = Dose/Vd

C = (2 mg/kg*70 kg)/
(0.3 L/kg*70 kg)

C = 6.7 mg/L

Amikacin:

C = Dose/Vd

C = (7.5 mg/kg*70 kg)/
(0.3 L/kg*70 kg)

C = 25 mg/L

Scheetz MH, et al. Am J Health-Syst Pharm 2006;63:1346-60

BEDSIDE PK/PD APPLICATION: CONVENTIONAL AMINOGLYCOSIDES

Gentamicin:

C = Dose/Vd

C = (2 mg/kg*70 kg)/
(0.3 L/kg*70 kg)

C = 6.7 mg/L

Cmax:MIC = 6.7/4 = 1.7
Not at goal

Amikacin:

C = Dose/Vd

C = (7.5 mg/kg*70 kg)/
(0.3 L/kg*70 kg)

C = 25 mg/L

Cmax:MIC = 25/4 = 6.25
Not at goal

Scheetz MH, et al. Am J Health-Syst Pharm 2006;63:1346-60

BEDSIDE PK/PD APPLICATION: EXTENDED INTERVAL AMINOGLYCOSIDES

Gentamicin:

C = Dose/Vd

C = (7 mg/kg*70 kg)/
(0.3 L/kg*70 kg)

C = 23.3 mg/L

Amikacin:

C = Dose/Vd

C = (15 mg/kg*70 kg)/
(0.3 L/kg*70 kg)

C = 50 mg/L

Scheetz MH, et al. Am J Health-Syst Pharm 2006;63:1346-60

BEDSIDE PK/PD APPLICATION: EXTENDED INTERVAL AMINOGLYCOSIDES

Gentamicin:

C = Dose/Vd

C = (7 mg/kg*70 kg)/
(0.3 L/kg*70 kg)

C = 23.3 mg/L

Cmax:MIC = 23.3/4 = 5.8
Still not at goal!

Amikacin:

C = Dose/Vd

C = (15 mg/kg*70 kg)/
(0.3 L/kg*70 kg)

C = 50 mg/L

Cmax:MIC = 50/4 = 12.5
At goal!

Scheetz MH, et al. Am J Health-Syst Pharm 2006;63:1346-60

CASE 3

- 65 y/o IVDU with *Pseudomonas aeruginosa* bacteremia from presumed pulmonary source
- Dosing weight = 70 kg
- CrCl = 90 mL/min
- Allergies: NKDA
- Team would like to know which cephalosporin they should use

Drug	MIC	Interpretation
Aztreonam	4	Susceptible
Ceftazidime	8	Susceptible
Cefepime	8	Susceptible
Meropenem	8	Resistant
Piperacillin-tazobactam	16	Susceptible
Amikacin	4	Susceptible
Gentamicin	4	Susceptible
Levofloxacin	1	Susceptible

BEDSIDE PK/PD APPLICATION: BETA-LACTAMS

- Ceftazidime vs Cefepime?
- MIC = 4 for both, Breakpoint ≤ 8 for both
- Adequate T > MIC?
- Population-based PK parameters found in Sanford Guide
- Pulmonary penetration per literature ~20-30% Ceftazidime vs 100% Cefepime

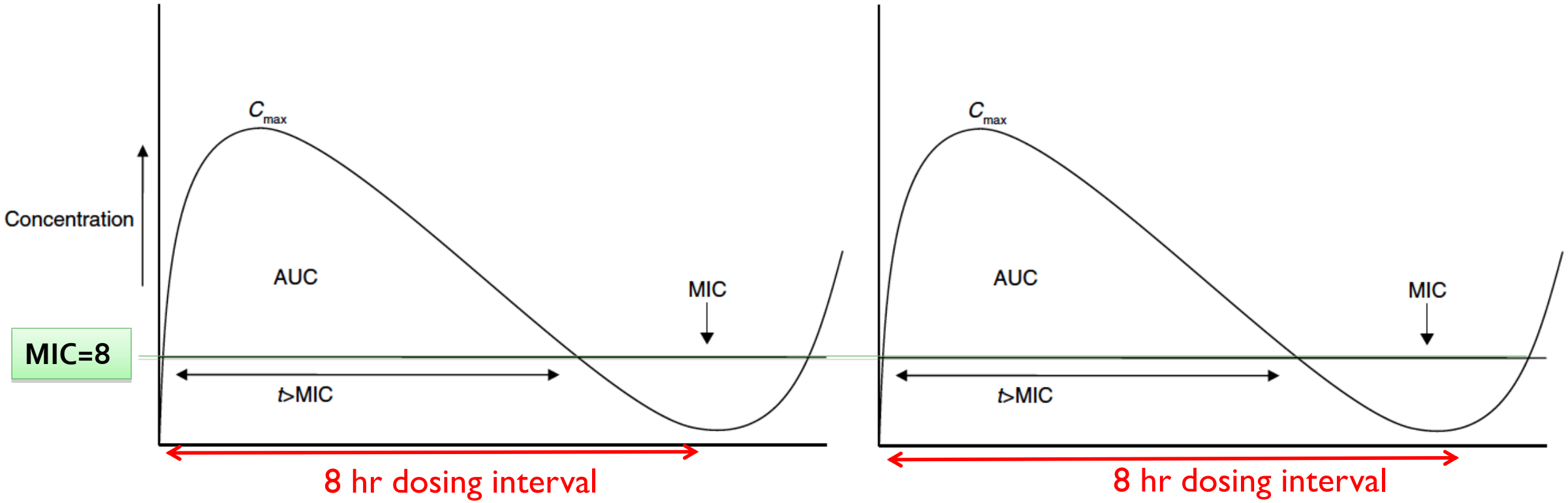
Drug	Dose	Peak serum level (mcg/mL)	Protein binding (%)	Average serum half-life (hrs)
Ceftazidime	1 g	69	<10	2
Cefepime	2 g	164	20	2

Turnridge JD. Clin Infect Dis. 1998;27:10-22
The Sanford Guide to Antimicrobial Therapy 2019. 49th ed. Antimicrobial Therapy, Inc, Sperryville, VA; 2019

APPLICATION EXAMPLE: DRUG SELECTION

Ceftazidime 2 g iv q8h:

Cefepime 2 g iv q8h:



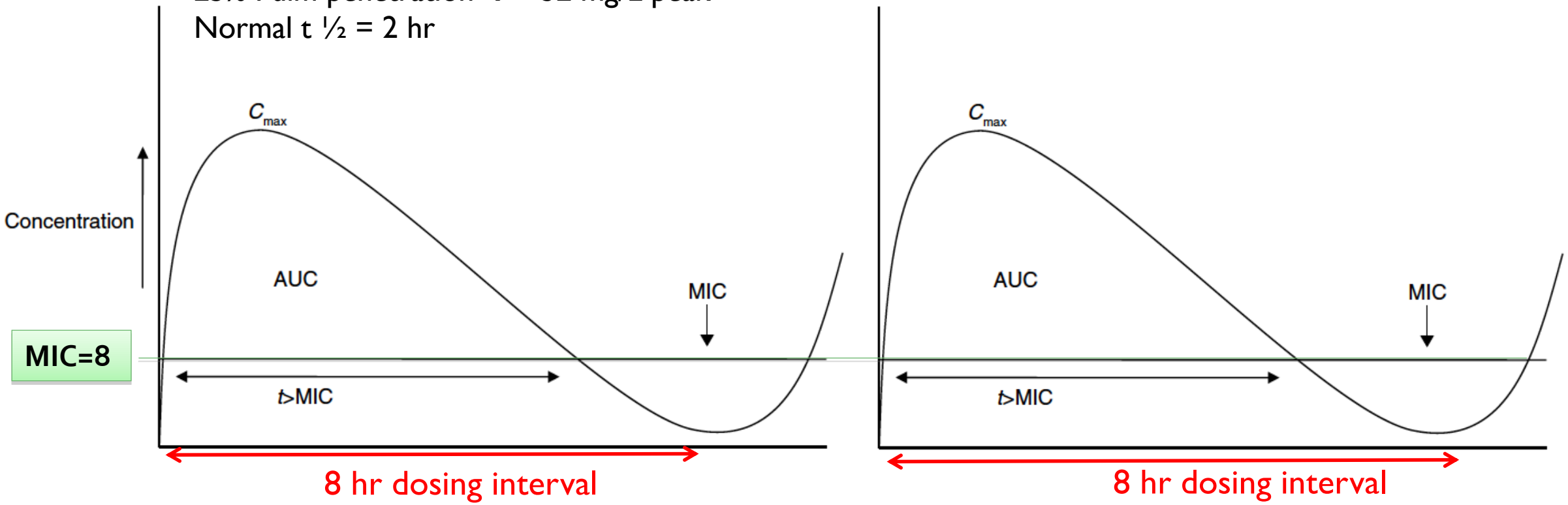
Scheetz MH, et al. Am J Health-Syst Pharm 2006;63:1346-60

APPLICATION EXAMPLE: DRUG SELECTION

Ceftazidime 2 g iv q8h:

1 g → 69 mg/L; 2 g → 138 mg/L (serum peak)
10% Pb → 124 mg/L (free serum peak)
25% Pulm penetration → ~32 mg/L peak
Normal t ½ = 2 hr

Cefepime 2 g iv q8h:



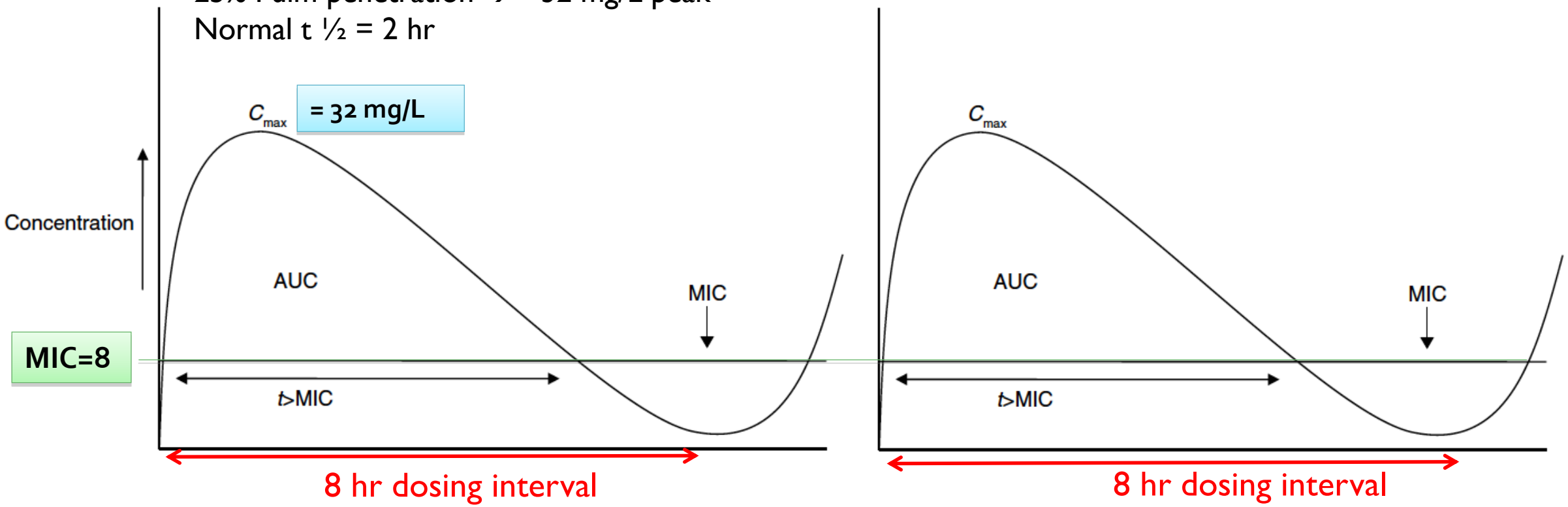
Scheetz MH, et al. Am J Health-Syst Pharm 2006;63:1346-60

APPLICATION EXAMPLE: DRUG SELECTION

Ceftazidime 2 g iv q8h:

1 g → 69 mg/L; 2 g → 138 mg/L (serum peak)
10% Pb → 124 mg/L (free serum peak)
25% Pulm penetration → ~32 mg/L peak
Normal t ½ = 2 hr

Cefepime 2 g iv q8h:



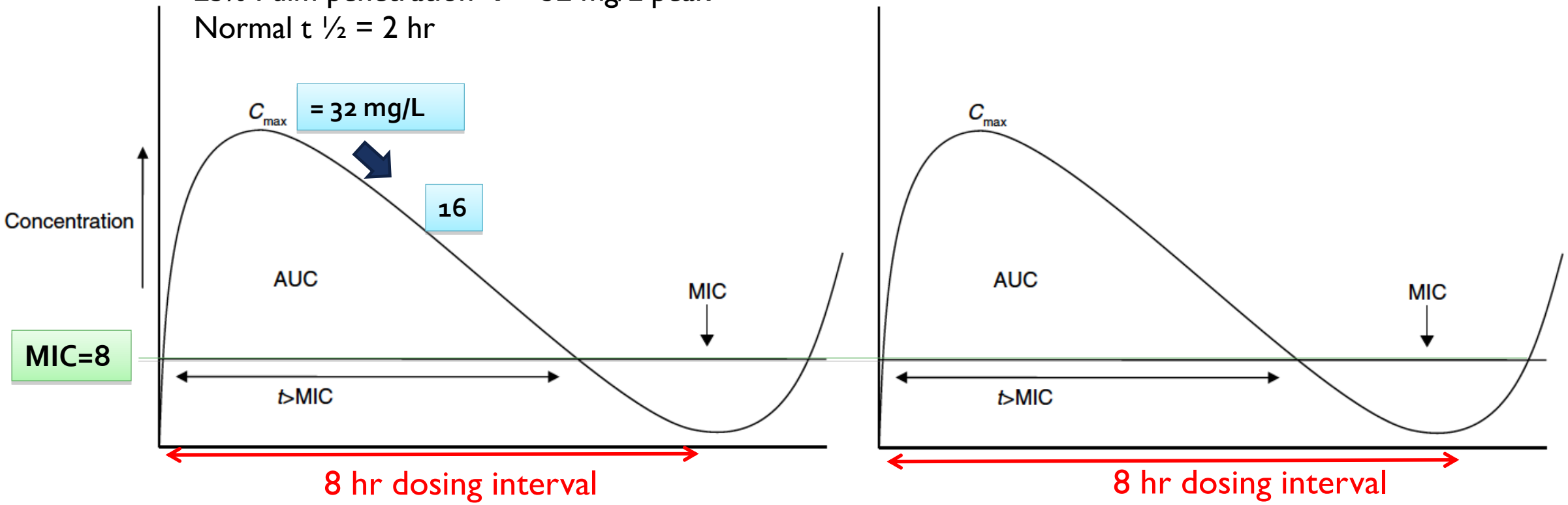
Scheetz MH, et al. Am J Health-Syst Pharm 2006;63:1346-60

APPLICATION EXAMPLE: DRUG SELECTION

Ceftazidime 2 g iv q8h:

1 g → 69 mg/L; 2 g → 138 mg/L (serum peak)
10% Pb → 124 mg/L (free serum peak)
25% Pulm penetration → ~32 mg/L peak
Normal t ½ = 2 hr

Cefepime 2 g iv q8h:



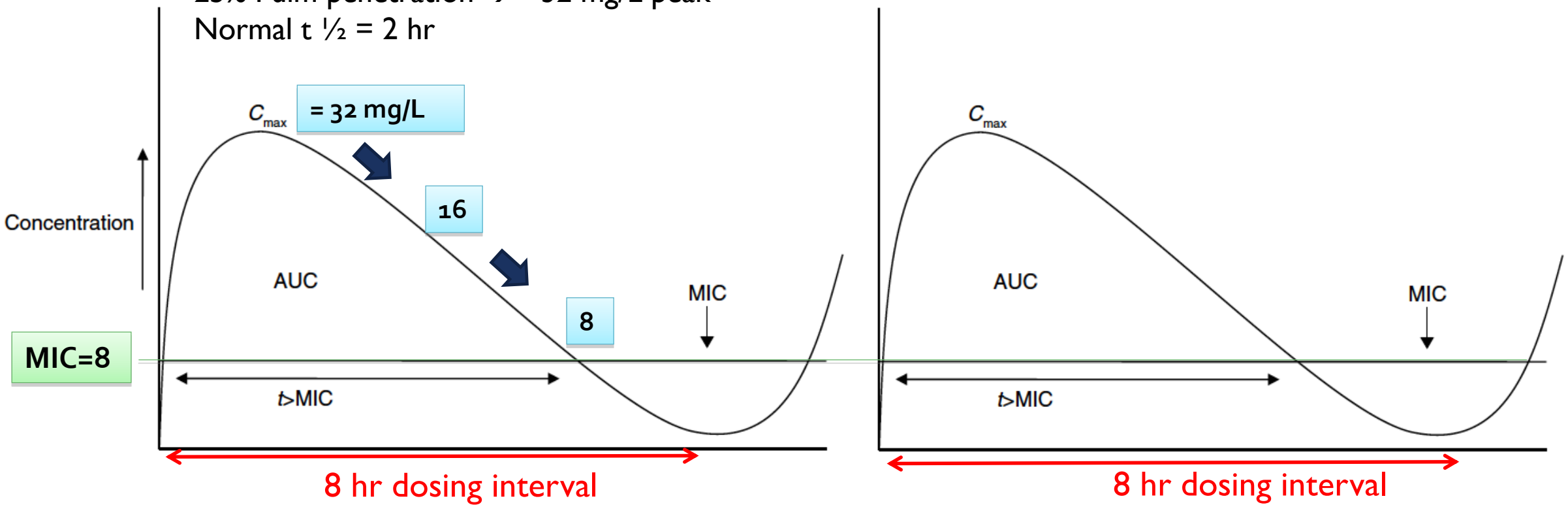
Scheetz MH, et al. Am J Health-Syst Pharm 2006;63:1346-60

APPLICATION EXAMPLE: DRUG SELECTION

Ceftazidime 2 g iv q8h:

1 g → 69 mg/L; 2 g → 138 mg/L (serum peak)
10% Pb → 124 mg/L (free serum peak)
25% Pulm penetration → ~32 mg/L peak
Normal t ½ = 2 hr

Cefepime 2 g iv q8h:

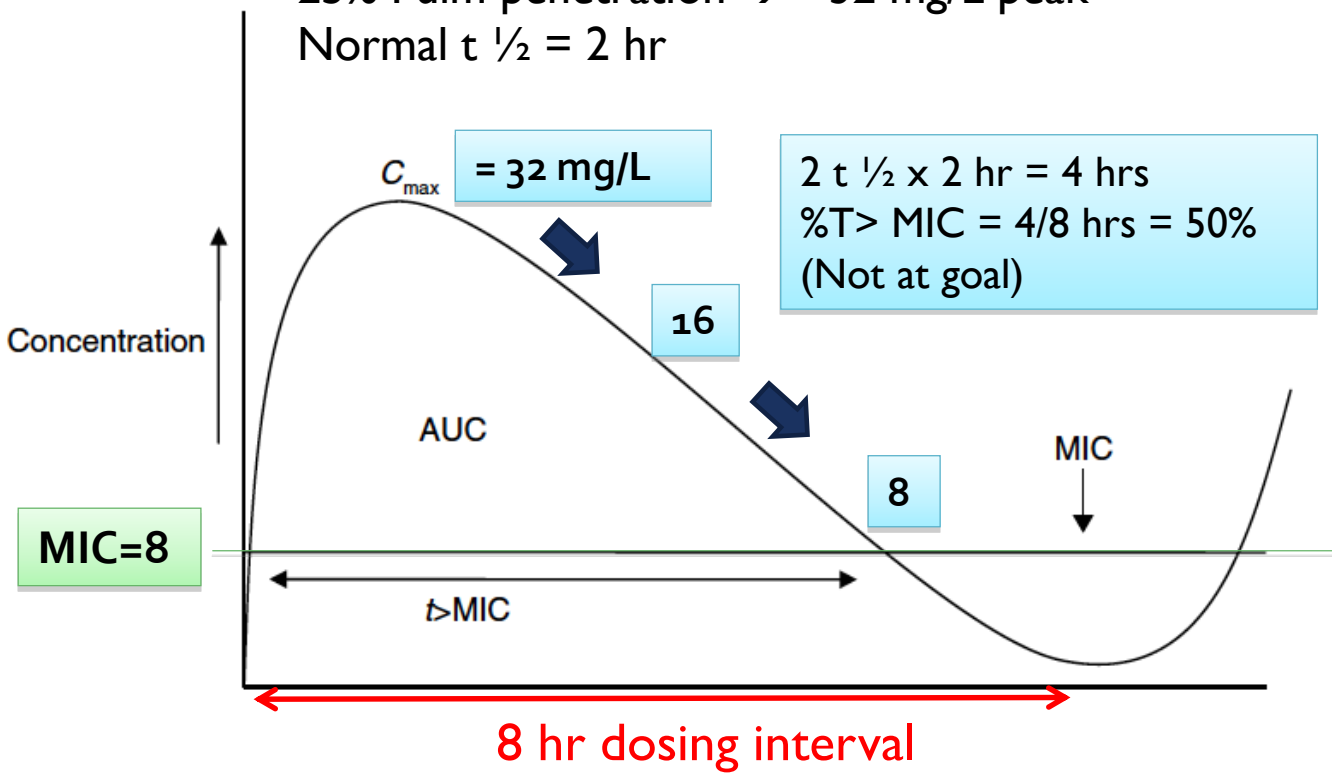


Scheetz MH, et al. Am J Health-Syst Pharm 2006;63:1346-60

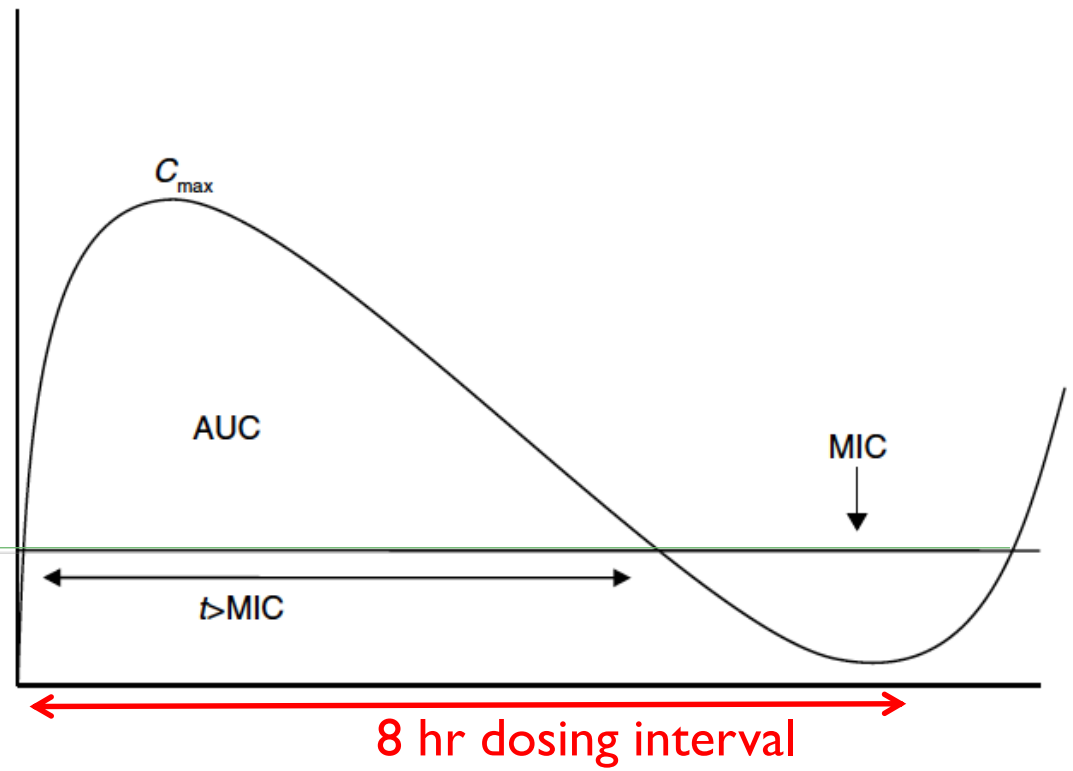
APPLICATION EXAMPLE: DRUG SELECTION

Ceftazidime 2 g iv q8h:

1 g → 69 mg/L; 2 g → 138 mg/L (serum peak)
10% Pb → 124 mg/L (free serum peak)
25% Pulm penetration → ~32 mg/L peak
Normal t ½ = 2 hr



Cefepime 2 g iv q8h:



Scheetz MH, et al. Am J Health-Syst Pharm 2006;63:1346-60

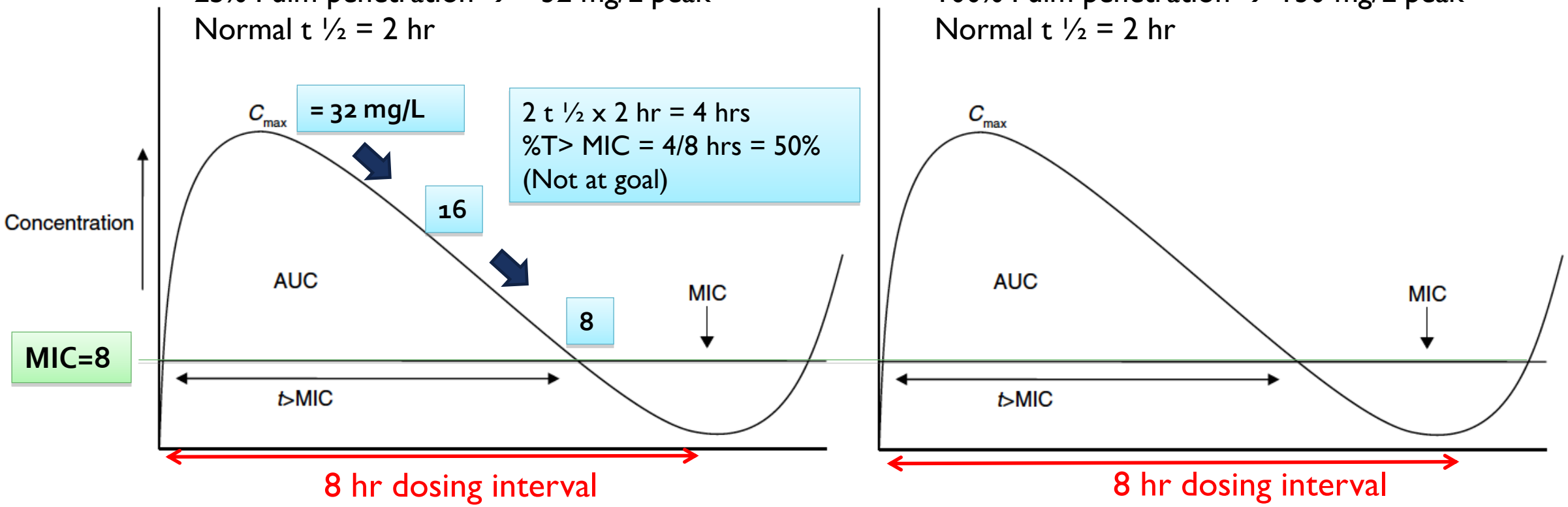
APPLICATION EXAMPLE: DRUG SELECTION

Ceftazidime 2 g iv q8h:

1 g → 69 mg/L; 2 g → 138 mg/L (serum peak)
10% Pb → 124 mg/L (free serum peak)
25% Pulm penetration → ~32 mg/L peak
Normal t ½ = 2 hr

Cefepime 2 g iv q8h:

2 g → 164 mg/L (serum peak)
20% Pb → 130 mg/L (free serum peak)
100% Pulm penetration → 130 mg/L peak
Normal t ½ = 2 hr



Scheetz MH, et al. Am J Health-Syst Pharm 2006;63:1346-60

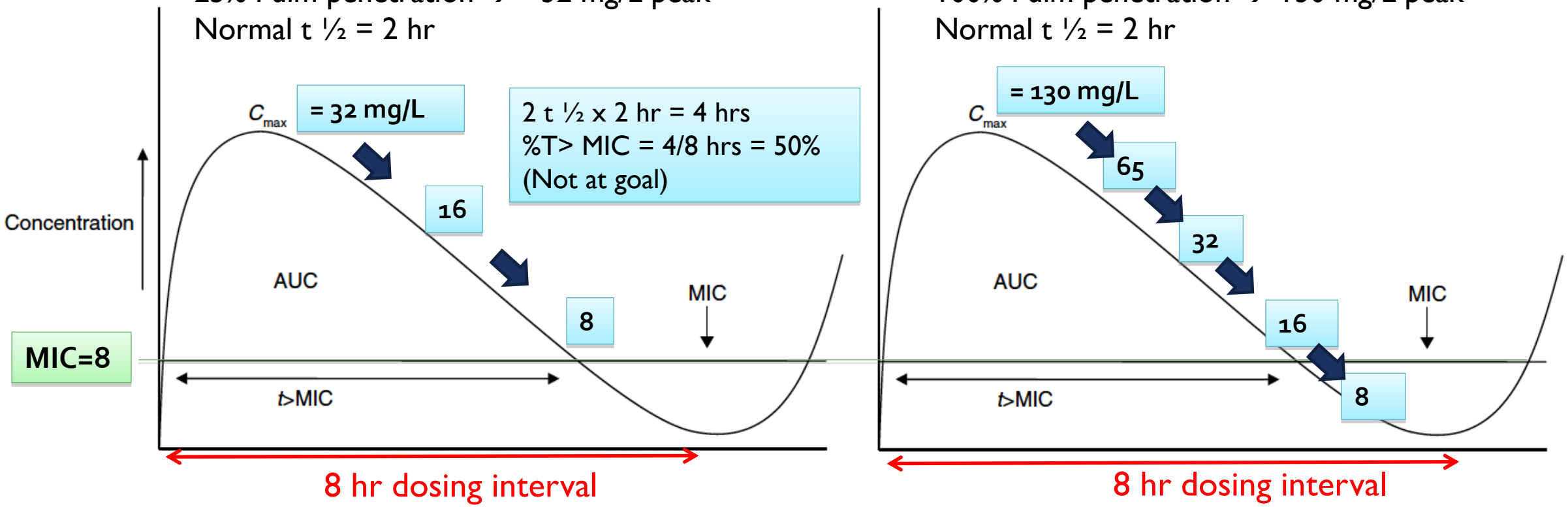
APPLICATION EXAMPLE: DRUG SELECTION

Ceftazidime 2 g iv q8h:

1 g → 69 mg/L; 2 g → 138 mg/L (serum peak)
10% Pb → 124 mg/L (free serum peak)
25% Pulm penetration → ~32 mg/L peak
Normal t ½ = 2 hr

Cefepime 2 g iv q8h:

2 g → 164 mg/L (serum peak)
20% Pb → 130 mg/L (free serum peak)
100% Pulm penetration → 130 mg/L peak
Normal t ½ = 2 hr



Scheetz MH, et al. Am J Health-Syst Pharm 2006;63:1346-60

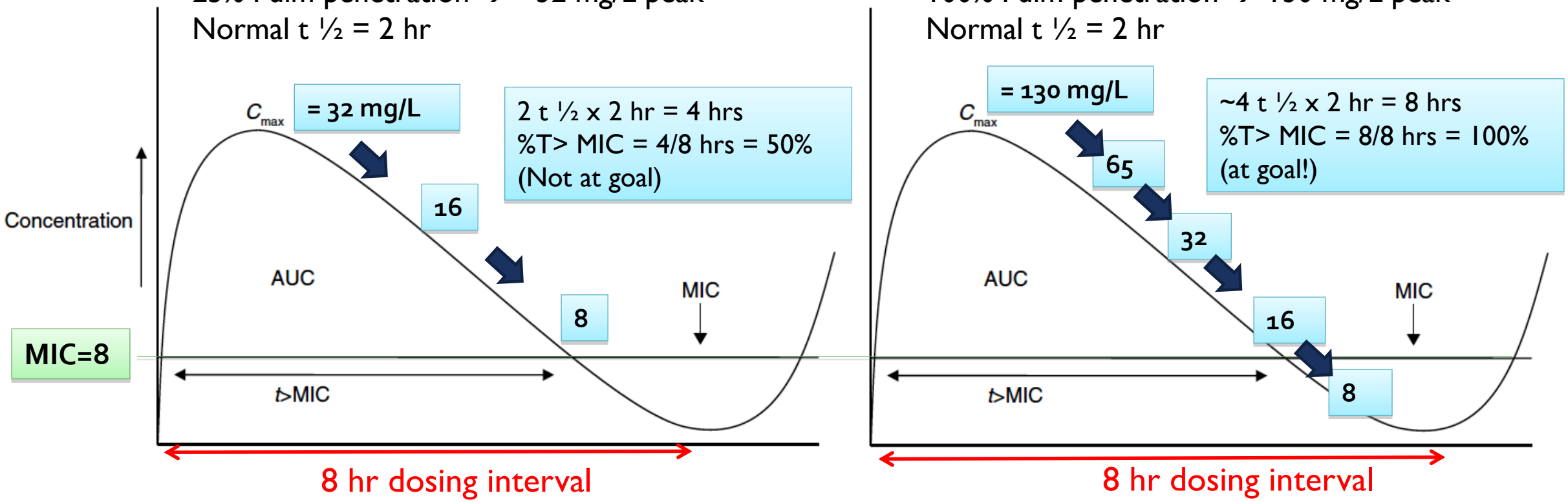
APPLICATION EXAMPLE: DRUG SELECTION

Ceftazidime 2 g iv q8h:

1 g → 69 mg/L; 2 g → 138 mg/L (serum peak)
10% Pb → 124 mg/L (free serum peak)
25% Pulm penetration → ~32 mg/L peak
Normal t ½ = 2 hr

Cefepime 2 g iv q8h:

2 g → 164 mg/L (serum peak)
20% Pb → 130 mg/L (free serum peak)
100% Pulm penetration → 130 mg/L peak
Normal t ½ = 2 hr



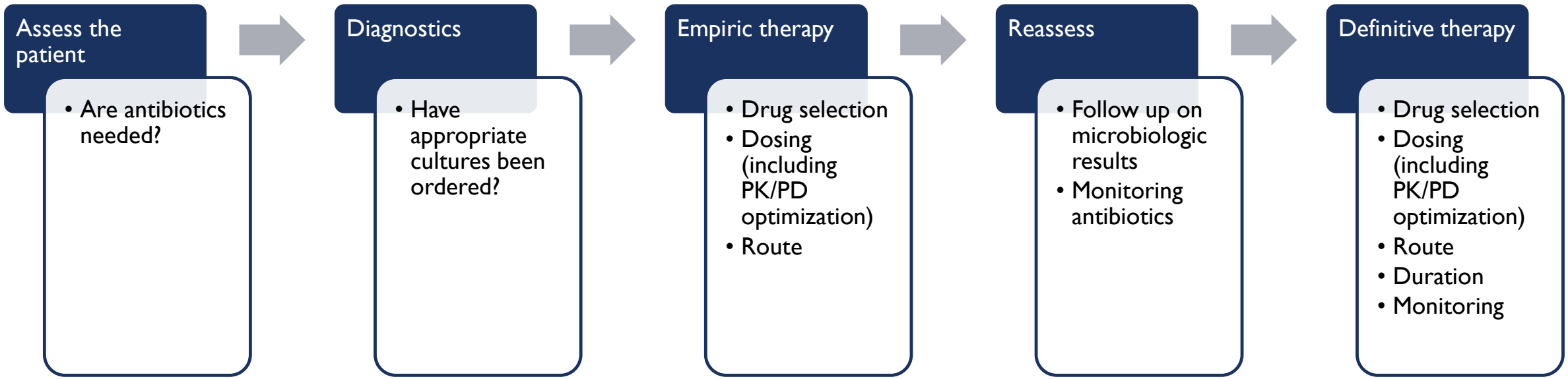
Scheetz MH, et al. Am J Health-Syst Pharm 2006;63:1346-60

ANTIMICROBIAL STEWARDSHIP

- "Coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy, and route of administration"
- Goal is to achieve best clinical outcomes while minimizing toxicity, limiting selective pressure on bacterial populations that drives emergence of antimicrobial resistance

SHEA. Infect Control Hosp Epidemiol 2012;33(4):322

PHARMACIST'S ROLE IN ANTIMICROBIAL STEWARDSHIP



WHICH OF THE FOLLOWING DEMONSTRATES AN EXAMPLE OF A PHARMACIST PERFORMING ANTIMICROBIAL STEWARDSHIP?

A. Pharmacist rounding with the intensive care unit team recommends extended infusion piperacillin-tazobactam for an organism with an elevated minimum inhibitory concentration

B. Upon profile review, pharmacist notices that a patient has been on levofloxacin for 15 days for a urinary tract infection and contacts the physician to consider discontinuation

C. Pharmacist recommending a switch from intravenous to oral trimethoprim/sulfamethoxazole

D. All of the above

SUMMARY

- Selection of appropriate antimicrobial therapy is a complex process, requiring consideration of bug, drug, and patient
  - Cannot just pick "S" or the lowest MIC

- Pharmacists play a critical role in considering all the factors and optimizing drug therapy, especially focusing on PK/PD and antimicrobial stewardship

ID ABC'S: ANTIBIOTICS, BACTERIA, AND CORE CONCEPTS

ANGELA LOO, PHARM.D., BCPS-AQ ID, BCIDP
NEWYORK-PRESBYTERIAN/WEILL CORNELL MEDICAL CENTER
JANUARY 8, 2020