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Antibiotic Pharmacokinetics and Pharmacodynamics for Laboratory Professionals

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Objectives

- **Describe the pharmacokinetics and pharmacodynamics of commonly used antibiotics**
- Summarize contemporary application of antibiotic pharmacokinetics and pharmacodynamics
- Discuss situations in which clinicians may ask for additional antibiotic susceptibility testing

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The Importance of PK/PD

- "Newer" concept in antibiotic therapy
- Preserve/increase efficacy of existent antibiotics
- Involves use of pharmacology, clinical outcomes and microbiology to optimize antimicrobial use
  - Improve outcomes
  - Minimize toxicity and resistance

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Pharmacokinetics ("ADME")

- **Absorption**
  - The process by which a drug proceeds from the site of administration to the site of measurement; most often the blood.
- **Distribution**
  - The process of reversible transfer of drug to the and from the site of measurement
- **Metabolism**
  - The process of a conversion of one chemical species to another chemical species
- **Elimination**
  - The irreversible loss of drug from the site of measurement. By metabolism or excretion.

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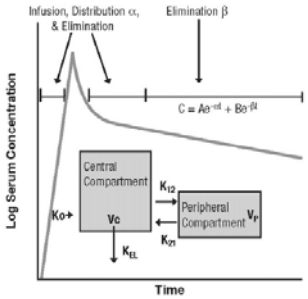
Adopted from Rowland M, Tozer TN. Clinical Pharmacokinetics: Concepts and Applications. Third Edition. 1995.

Antimicrobial PK/PD

Pharmacokinetics (PK):

the action of the body on the administered agent, absorption, distribution, metabolism & excretion, that define drug exposure.



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Pharmacodynamics (PD):

the biochemical & physiologic response of a drug and its mechanism of action.

- The relationship between drug potency, drug concentration and effect.
- Antimicrobials are unique in that the target is the pathogen – not the host.
- Relationship between PK and drug effect on pathogen based on potency / activity of the drug vs the organism.
- ***In vitro***: microbial death, growth inhibition, emergence of resistance .
- ***In vivo***: clinical response.

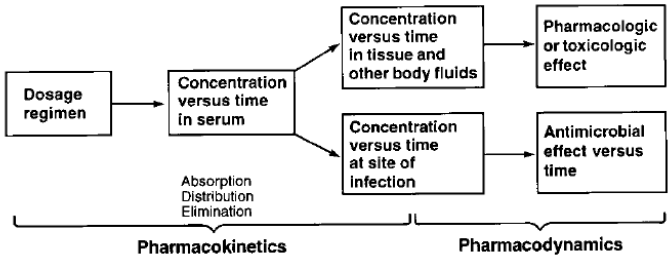
Rybak MJ. *Clin Infect Dis.* 2006;42 Suppl 1:S35-9.

Drusano G. *Nature Rev Microb* 2004;2:289-300.

Antimicrobial PK/PD

Pharmacokinetics (PK) & Pharmacodynamics (PD) of Antimicrobial Therapy

- PK: Quantified exposure
- PD: Antimicrobial effect. Host toxicity. Resistance.
  - The relationship between drug potency, drug concentration and effect.



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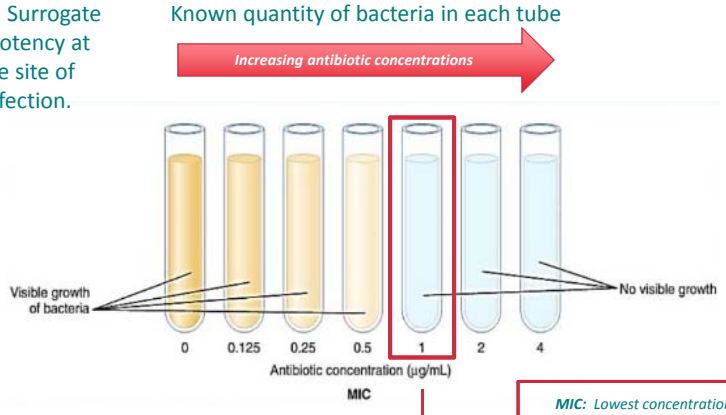
Craig WA. *Clin Infect Dis* 1998;26:1-10.

Minimum Inhibitory Concentration (MIC)

MIC: Surrogate of potency at the site of infection.

Known quantity of bacteria in each tube



MIC: *Lowest concentration of an antimicrobial that results in inhibtion of visible growth of a microorganism*

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Automated Susceptibility Testing – Clinical Caveats

- ± one doubling dilution
  - Multiple isolates, different MICs
- Specific issues:
  - *P. aeruginosa* and Vitek II
  - Pip/tazo issues on Vitek II
  - *S. aureus* vancomycin MIC
- Lack of testing for newer agents

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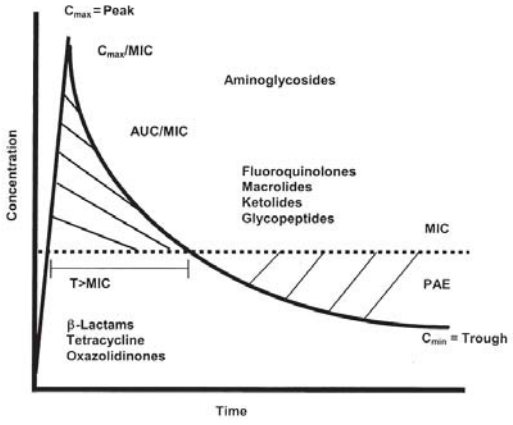
Pharmacodynamic Parameters Relating to Efficacy

Time Dependent Antibiotics:
Beta-lactams, Linezolid, Tetracycline, TMP/SMX
Time > MIC

Concentration Dependent Antibiotics:
Peak/MIC:
Aminoglycosides
AUC/MIC:
Fluoroquinolones, vancomycin, azithromycin



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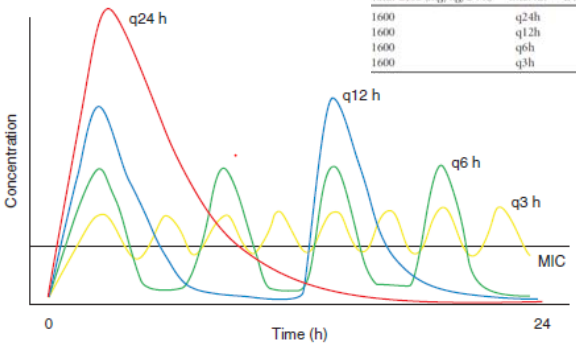
Craig WA *Clin Infect Dis* 1998;26:1-12. Rybak M. Am J Med 2006;119:S37-44.
Pai, MP et al. Pharmacokinetics & pharmacodynamics of anti-infective agents. Mandells 2015.

Modification of Dose & Frequency: Effect on Concentration Time Profiles

Fractionating a total daily dose into once-, twice-,four-times-, and eight-times-daily fractions (same total daily dose)

- AUC will remain ~ unchanged. Cmax progressively declines.
- Time > MIC progressively increases .

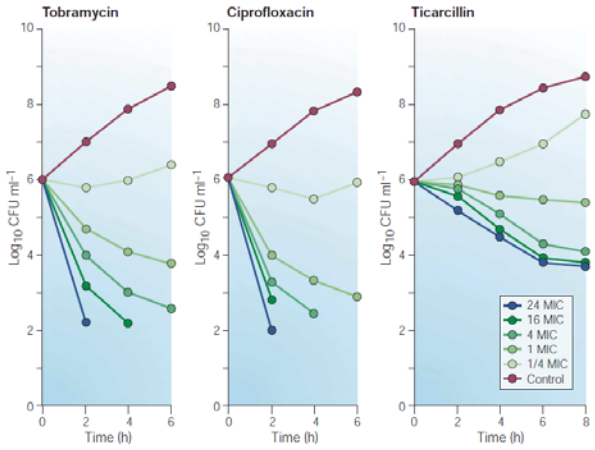
Total dose (mg/kg/24 h)	Interval	Dose (mg/kg) administered	AUC/MIC	C_{max}/MIC	% T > MIC
1600	q24h	1600 × 1	No change	↑↑↑	-
1600	q12h	800 × 2	No change	↑↑	↑
1600	q6h	400 × 4	No change	↑	↑↑
1600	q3h	200 × 8	No change	-	↑↑↑



Lepak AJ, Andes DR. *Cold Spring Harb Perspect Med* 2015;5:a019653

Concentration vs Time

Time kill curves for P. aeruginosa following exposure at ***one-quarter to 64x MIC***



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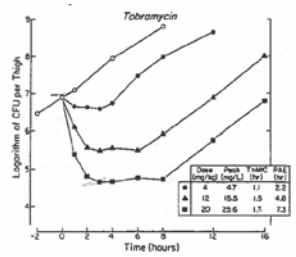
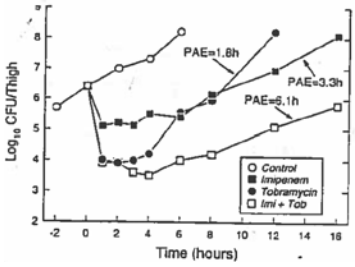
Drusano G. *Nature Reviews Microb* 2004;2:289-300.

Concentration Dependent Agents

Classic example – Aminoglycosides, but also Fluoroquinolones, Daptomycin.
Dosed-related increase in magnitude of kill & suppression of resistance
PAE: Persistent suppression of bacterial growth at concentrations below the MIC.



Growth curves of *P. aeruginosa* in neutropenic mice following single doses of tobramycin 4, 12, 20mg/kg



Growth curves of *P. aeruginosa* in neutropenic mice following imipenem 200mg/kg and tobramycin 8mg/kg, alone and in combination.

Aurora Health Care® Craig WA, et al. Postantibiotic effect: In Lorian V, ed Antibiotics in Laboratory Medicine. 1996.

PK/PD From Mice to Men

Septic shock, *P. aeruginosa* pneumonia, Severe ARDS on ECMO

Index: BAL Pseudomonas

Culture & Susceptibility
PSEUDOMONAS AERUGINOSA

Antibiotic	Sensitivity	Result
AZTREONAM	Sensitive	4
CEFEPIME	Sensitive	<=2
CEFTAZIDIME	Sensitive	<=2
CIPROFLOXACIN	Sensitive	<=0.5
GENTAMICIN	Sensitive	4
IMIPENEM	Sensitive	<=1
LEVOFLOXACIN	Sensitive	<=0.5
MEROPENEM	Sensitive	<=1
PIPERACILLIN/TAZOBAC	Sensitive	<=8
TOBRAMYCIN	Sensitive	2

Comments PSEUDOMONAS AERUGINOSA (MIC)
MANY PSEUDOMONAS AERUGINOSA

7 days later: BAL Pseudomonas
Day 5 Meropenem 2 Q8hours over 3 hours

Culture & Susceptibility
PSEUDOMONAS AERUGINOSA

Antibiotic	Sensitivity	Result
AZTREONAM	Intermediate	16
CEFEPIME	Sensitive	4
CEFTAZIDIME	Sensitive	4
CIPROFLOXACIN	Sensitive	<=0.5
GENTAMICIN	Sensitive	4
IMIPENEM	Resistant	>8
LEVOFLOXACIN	Sensitive	<=0.5
MEROPENEM	Resistant	8
PIPERACILLIN/TAZOBAC	Sensitive	<=8
TOBRAMYCIN	Sensitive	2

Comments PSEUDOMONAS AERUGINOSA (MIC)
MODERATE PSEUDOMONAS AERUGINOSA

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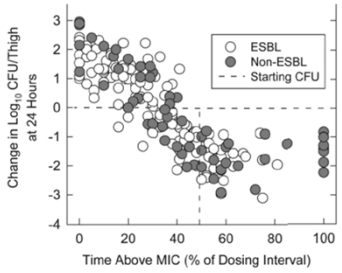
Time Dependent Agents

Beta-Lactams: Time above MIC Matters
Plateau of bactericidal effect at concentrations >4x MIC
AHC Extended Infusion Protocols: Meropenem, Pip/Tazobactam, Cefepime

Drug Class	Fraction of Dosing Interval Required for Free Drug Concentrations to Exceed the MIC	
	Bacteriostatic Effects	Near-Maximal Bactericidal Effects
Penicillins	30%	50%
Cephalosporins	35-40%	60-70%
Carbapenems	20%	40%
Cefepime may be unique in the time above the MIC to achieve maximal cidal effect (Craig 2002) due to more rapid penetration across the gram-negative cell wall & affinity for PBP2 (same as carbapenems). *Most cefepime studies define optimal target concentrations as those that exceed the MIC for 50-60% of the dosing interval.*		



Impact of Time above the MIC for Enterobacteriaceae
Percent of dosing interval in which free-drug concentrations exceed the MIC (T > MIC) required for 3rd/4th gen cephalosporins vs. *E.coli, Klebsiella, Enterobacter & Serratia* spp producing varying β-lactamases in a murine thigh infection model .

Lodise TP, et al. *Pharmacotherapy* 2006;26:1320-32.
Dudley MN, et al. *Clin Infect Dis* 2013;56:1301-9.

Cefepime: Risk of Failure Leading to Modified Breakpoints

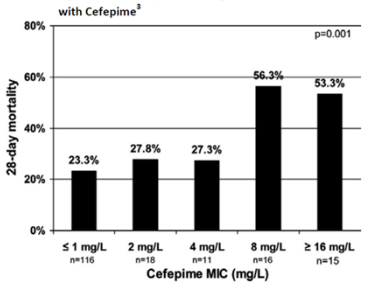
Antimicrobial Agents and Chemotherapy, Dec. 2007, p. 4300–4305 Vol. 51, No. 12
0066-4804/07/$08.00+0 doi:10.1128/AAC.01487-06

Failure of Current Cefepime Breakpoints To Predict Clinical Outcomes of Bacteremia Caused by Gram-Negative Organisms[▽]

Sunil V. Bhat,[1] Anton Y. Peleg,[2] Thomas P. Lodise, Jr.,[3] Kathleen A. Shutt,[1] Blair Capitano,[1] Brian A. Potoski,[1] and David L. Paterson[1,4]*

CLSI 2014: Clinical Failures with cefepime MICs of 4-8mcg/mL, especially when lower (FDA approved) doses were used.

Figure 2. Mortality: Gram-Negative Bacteremia Treated with Cefepime[3]



Cefepime	Old CLSI Breakpoints (2004)			New CLSI Breakpoints (2014)			
	Susc	Intermed	Resistant	Susc	SDD		Resistant
	≤8	16	≥32	≤2	4	8	≥16
Based on Dose of:	1g q8h or 2g q12h			1g q12h	1g q8h Or 2g q12h	2g q8h	N/A
Total Daily Dose	3-4g			2g	3-4g	6g	N/A
SDD: Susceptible-Dose Dependent as per CLSI reference doses. Cefepime 1g q8h and 2g q12h (both infused over 30min) achieve similar (fT>MIC).							

Pharmacodynamics & Antimicrobial Resistance

Dose optimization as a barrier to resistance.

- Exposed sensitive isolates to vancomycin to target an AUC /MIC 31-510.
- AUC/MIC <250: selection for resistant mutants with elevated MICs detected at 72hrs.
- Low level exposure: Similar data with quinolones vs *Pseudomonas* and Pneumococcus

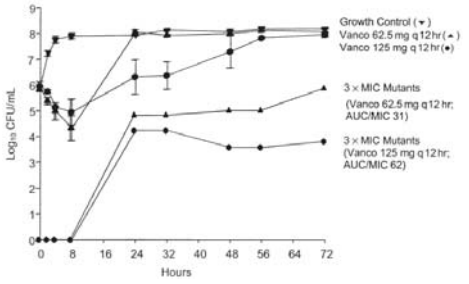


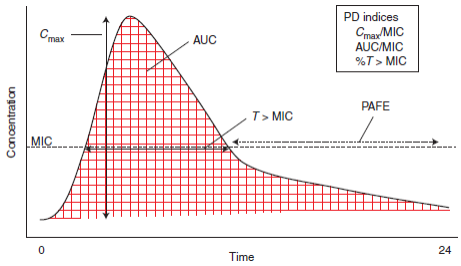
Table 2 Accessory gene regulator group II *Staphylococcus aureus* postvancomycin exposure

Dose (mg)	AUC/MIC (mg/L per hr)	Peak (mg/L)	Targeted Trough (mg/L)	MIC 0 hr	MIC 24 hr	MIC 48 hr	MIC 72 hr
62.5 q 12 hr	31	2.5	0.6	1	4–6	6	6–8
125 q 12 hr	62	5	1.2	1	4	6	6
250 q 12 hr	123	10	2.5	1	2	2	4
500 q 12 hr	264	20	5.0	1	2	2	3
750 q 12 hr	382	30	7.5	1	→	→	→
1,000 q 12 hr	510	40	10.0	1	→	→	→

AUC = area under the concentration–time curve; MIC = minimum inhibitory concentration.

Rybak, M. *Am J Med* 2006;119:S37-44.

Antifungal PK/PD



PK/PD relationship of antifungal dose over time relative to organism MIC.

- Cmax/MIC
- AUC/MIC
- T>MIC

Drug class	Concentration dependent	Prolonged PAFE	PD index predictive of efficacy
Polyene	Yes	Yes	C_{max}/MIC
Flucytosine	No	No	$T >$ MIC
Azoles	No	Yes	AUC/MIC
Echinocandins	Yes	Yes	C_{max}/MIC or AUC/MIC

Lepak AJ, Andes DR. Cold Spring Harb Perspect Med 2015;5:a019653

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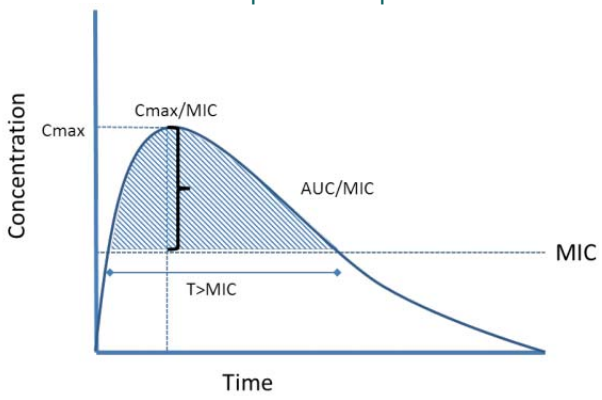
Antimicrobial Optimization: PK/PD Summary

PK/PD essential to leverage efficacy, minimize toxicity and optimize response



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AHQR. July 2013.

Objectives

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β-Lactams: Extended or Continuous Infusion

- Increase time above MIC
  - ICU patients
- Potential for lower total daily doses
  - Cost containment
  - Minimize toxicity
- IV access poses problems
- Common antibiotics include:
  - Pip/tazo, cefepime, ceftazidime, ceftaz/avibactam, aztreonam, oxacillin, nafcillin, vancomycin*, ?ceftolozane/tazo

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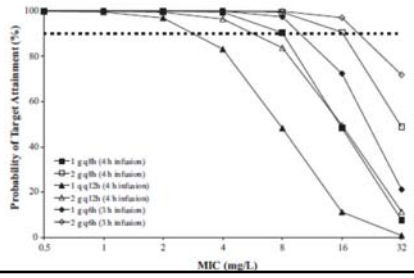
Cefepime Target Attainment

Conventional Dose Methods & Target Attainment (30min infusions)

Dose (All over 30min)	Percent Expected PTA			
	E.coli	*Klebsiella*	*Pseudomonas*	*Acinetobacter*
1g q4h	95.3	95.3	82.6	57.9
1g q8h	**93**	**93**	**45-71**	--
2g q8h	95.8	95.8	**84.9**	61.1
1g q6h	91.9	91.9	69.5	41.5
2g q12h	**78.9**	**78.9**	**53.6**	28.2
1g q12h	66.1	66.1	35.5	11.6



Probability of Target Attainment at 60% ƒT>MIC for Prolonged Infusion Regimens

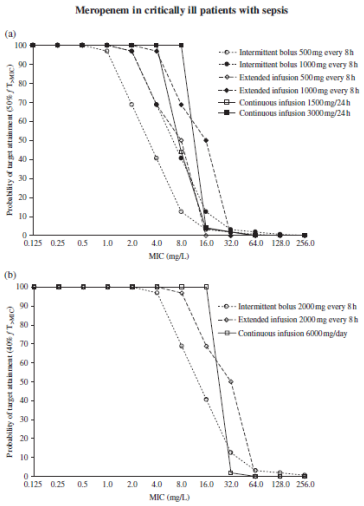
Dotted line represents the intended target for 6 doses listed, each infused over 4hours.

Goal: 90% probability of free drug concentration above the MIC for 60% of the dose interval.

Cheatham SC. *International J Antimicrobial Agents* 2011; 37:46-50.

Meropenem Target Attainment

- Extended infusion is "gold standard" in ICU patient
  - Can use if MIC ≥ 2
- Product stability at room temperature prohibits continuous infusion



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Roberts JA. *J Antimicrobial Agents* 2009; 64(1):142-50.

Vancomycin

- Glycopeptide antibiotic, 60 years + clinical use
- Concentration-independent kill, post-abx effect
  - Slowly cidal vs. *Staphylococcus* spp.
  - Static vs. *Enterococcus* spp.
- Narrow therapeutic index, potential for toxicity → therapeutic drug monitoring
- $AUC_{24\text{-hour}}$/MIC > 400mg/L*hr predicts efficacy against *S. aureus*

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Rybak MJ, et al. CID. 2006;42 Suppl 1:S35-9.

2009 Vanco Consensus Guidelines

- Maintain troughs > 10mg/L to prevent resistance
- Trough of 15-20mg/L surrogate for $AUC_{24\text{-hour}}$ of ≥ 400mg/L*hr
  - Based on practicality and *presumed* relationships to $AUC_{24\text{-hour}}$ target attainment
  - Limited human data
- Abandon when vancomycin *MIC > 1mg/L*

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Rybak MJ, et al. Pharmacotherapy. 2009;29(11):1275-9.

Troughs of 15-20mg/L?

- Troughs of 15-20mg/L may yield $AUC_{24\text{-hour}}$ > 400mg/L*hr for many patients.[1]
- *Direct relationship* between vancomycin exposure and nephrotoxicity.[2]
- Two-level AUC monitoring decreased median vanco trough level and rate of nephrotoxicity compared to historical trough-based monitoring.[3]
- Prospective observational, multicenter study found elevated AUCs did not correlate with clinical efficacy but rather with nephrotoxicity.[4]

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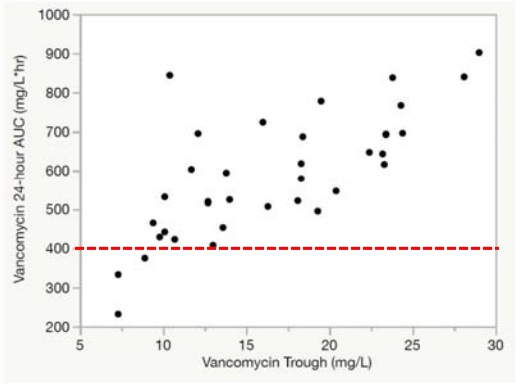
1. Neely MN et al. AAC. 2014;58(1):309-16
2. Lodise TP et al. CID. 2009;49(4):507-14.
3. Finch NA et al. AAC. 2017 Sep 18. pii: AAC.01293-17.
4. Lodise TP et al. Oral abstract. ID Week 2017 Conference, San Diego, CA.

AUC vs. Trough (n=34) [Unpublished Aurora Data]



*91.2% ICU; 85.3% of patients had bacteremia, endocarditis or pneumonia

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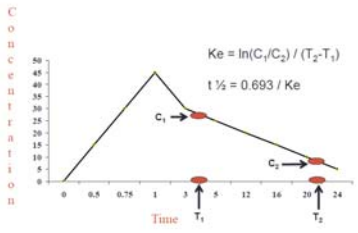
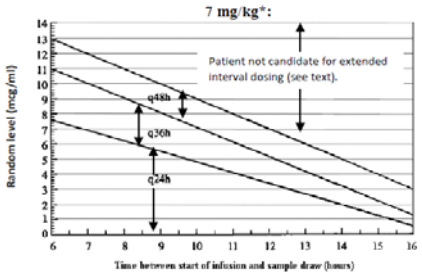
High Dose Aminoglycosides for Gram-Negative Infections

- Hartford Nomogram vs. 2-level approach
- **Hartford**: simple, fine for MICs ≤ 1mg/L
- **2-level approach**: patient-specific, better for MICs of 2mg/L





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Fluoroquinolones (FQs)

- Breakpoints matter, especially for gram-negatives
- FDA's FQ breakpoints are controversial

Version 3.0, valid from 01/31/2017

Table 1. USCAST MIC breakpoints compared to three other antimicrobial agent breakpoint organizations when testing the fluoroquinolone class compounds (modified from the Quinolone Report, 2017; V.1.2).

Organism/Antimicrobial	MIC breakpoints in µg/mL by criteria organization (Susceptible/Resistant)			
	CLSI[a]	USA-FDA	EUCAST[b]	USCAST
Enterobacteriaceae				
Ciprofloxacin	≤1 / ≥4	≤1 / ≥4[c]	≤0.25 / >0.5[b]	≤0.25 / ≥1
Levofloxacin	≤2 / ≥8	≤2 / ≥8[d]	≤0.5 / >1	≤0.5 / ≥2
Moxifloxacin	--	≤2 / ≥8[e]	≤0.25 / >0.25	≤0.25 / ≥0.5 (valid for *E. coli*,

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USCAST. http://www.uscast.org/breakpoints.html.

Ciprofloxacin and *P. aeruginosa*

- Cipro 400mg IV Q12h is standard dose
- 400 mg IV Q8h for *P. aeruginosa* improves PD target attainment and clinical cure.

Ineffective if MIC is 1mg/L, warranting consideration of a lower MIC breakpoint.

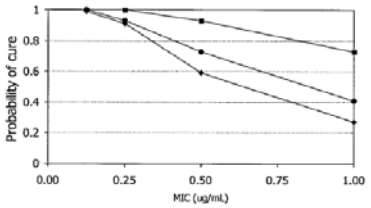

FIG. 6. Relative efficacies of ciprofloxacin dosing regimens across MIC categories using Monte Carlo simulations. ◆, recommended standard dose; ●, recommended high dose; ■, PD-targeted regimen.

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Zelenitsky S et al. *Antimicrob Agents Chemother.* 2005;49(10):4009-14.

Objectives

- Describe the pharmacokinetics and pharmacodynamics of commonly used antibiotics
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- **Discuss situations in which clinicians may ask for additional antibiotic susceptibility testing**

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Reasons Clinicians Request Additional Susceptibility Testing

- Drug interactions
- Allergies
- Outpatient “convenience”
- Synergy
- MIC at the “breakpoint”

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Antibiotic *Allergies*

- B-lactam "allergy" is common
  - Up to 20% of hospitalized patients
    - Mostly "penicillins"
  - Up to 90% able to tolerate penicillin
- Poor history + clinician hesitancy = alternative therapy
- Alternative therapy associated with worse outcomes and adverse events

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Huang KG et al. *Clin Infect Dis.* 2018 [epub ahead of print]
MacFadden DR et al. *Clin Infect Dis.* 2016;63(7):904-910.

Allergy Example

- 60 year old Female with chronic kidney disease and catheter-associated urinary tract infection.

- > 100,000 cfu/mL
P. aeruginosa
-Blood cultures (2/2) NGTD
-Allergies:
  - TMP/SMX (rash)
  - Pip/tazo (rash)
  - Levofloxacin (rash, anxiety)

*patient tolerated cefepime

Antibiotic	MIC	Interpretation
Amikacin	4	S
Aztreonam	>8	R
Cefepime	16	R
Ceftazidime	16	R
Ciprofloxacin	1	S
Gentamicin	2	S
Levofloxacin	2	S
Meropenem	8	R
Tobramycin	2	S

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Allergy Example (continued)

- MD requesting ceftolozane/tazo Etest
  - doesn't want AG due to MIC and kidney disease
  - doesn't want FQ due to MIC and allergy history
- Empirically treated with ceftolozane/tazo and RUO Etest MIC comes back as 1mg/L ("Susceptible")

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Outpatient Convenience Example

- 55 year old male with MSSA bacteremia and MSSA recovered from knee joint s/p debridement. Treated with Nafcillin 2g every 4hours in the hospital but this is not possible for him as an outpatient.
  - Insurance won't cover home health
  - Patient also wants to return to work
- MD requests the daptomycin MIC which is hidden by your lab for MSSA isolates.
  - Will allow for once daily dosing at infusion clinic

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Extenuating Circumstances Example

- 29yo male, injection drug user with MSSA bacteremia and native, right-sided (tricuspid valve) endocarditis.
- Receiving nafcillin and repeat blood cultures are negative.
- Patients attempting to leave AMA.
- ID MD calls and asks for levofloxacin MIC for the MSSA isolate.

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Extenuating Circumstances Example

- Cipro and Levo MICs for MSSA?
- Both are “susceptible”

- MD writes prescriptions for oral ciprofloxacin and rifampin
  - Effective for native, right-sided MSSA endocarditis in small U.S. cohort

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Heldman AW, et al. *Am J Med.* 1996;101(1):68-76.

Drug Interaction Example

- VRE abdominal wall abscess responding to daptomycin (MIC 4mg/L) and now the MD hopes to finish therapy with an oral antibiotic.
- The linezolid MIC is 2mg/L but the patient is on sertraline (anti-depressant), trazodone (for sleep) and amitriptyline (for fibromyalgia).

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Drug Interaction Example (continued)

- Linezolid is a reversible, nonselective inhibitor of monoamine oxidase and has the potential for interaction with adrenergic and serotonergic agents
  - Serotonin syndrome; severe side effect
- MD is asking for tedizolid MIC as this agent much less likely to interact with her other medications
- "Send out" susceptibility test

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Hidden susceptibility Example

- 90 year old female with a vancomycin-resistant E. faecium UTI. MD would like oral therapy and the isolate is linezolid non-susceptible (4mg/L) and resistant to nitrofurantoin (64mg/L). The daptomycin MIC is 2mg/L.
- MD is asking for tetracycline MIC and a fosfomycin Etest MIC.

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Hidden susceptibility Example (continued)

- Why tetracycline?
- Doxycycline can be used for VRE UTI
  - Cite data
  - Tetracycline susceptibility predicts doxycycline susceptibility (M100)
- Fosfomycin has a broad-spectrum of activity and is a good option for UTI.
  - NOT for pyelonephritis nor bacteremia

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Conclusions

- PK/PD commonly used by clinicians to optimize anti-infective therapy while minimizing toxicity and resistance development
- PK/PD literature is dynamic
- Clinicians are often confronted with situations in which additional susceptibility data can be informative

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Questions

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