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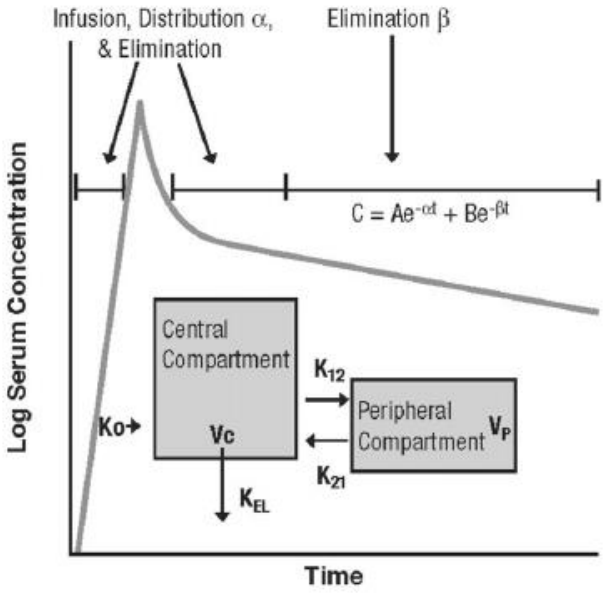
Adopted from Rowland M, Tozer TN. Clinical Pharmacokinetics: Concepts and Applications. Third Edition. 1995.

# Antimicrobial PK/PD

## *Pharmacokinetics (PK):*

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




## *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.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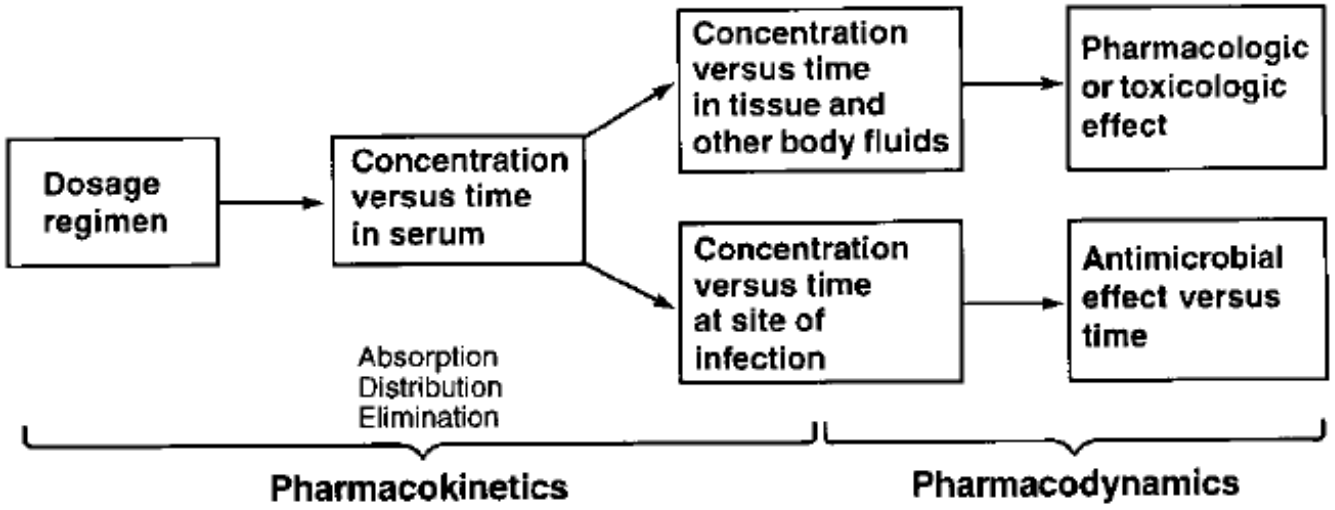
# Antimicrobial PK/PD

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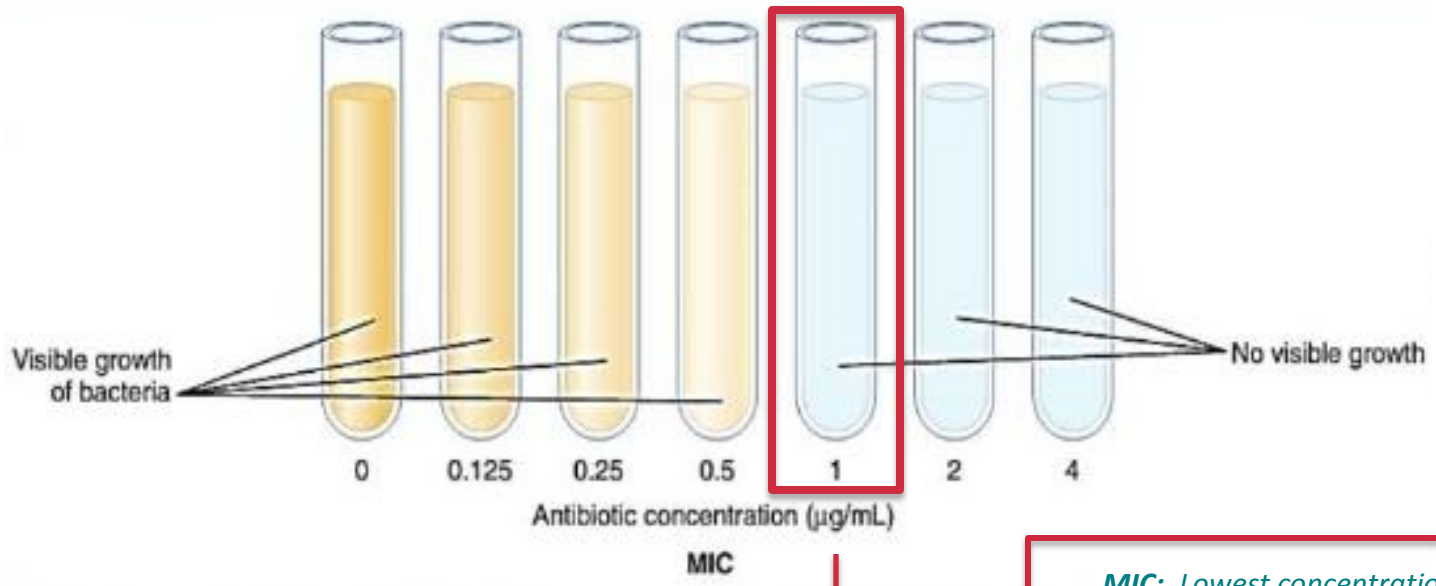
Craig WA. *Clin Infect Dis* 1998;26:1-10.

# Minimum Inhibitory Concentration (MIC)

MIC: Surrogate of potency at the site of infection.

Known quantity of bacteria in each tube

***Increasing antibiotic concentrations***




***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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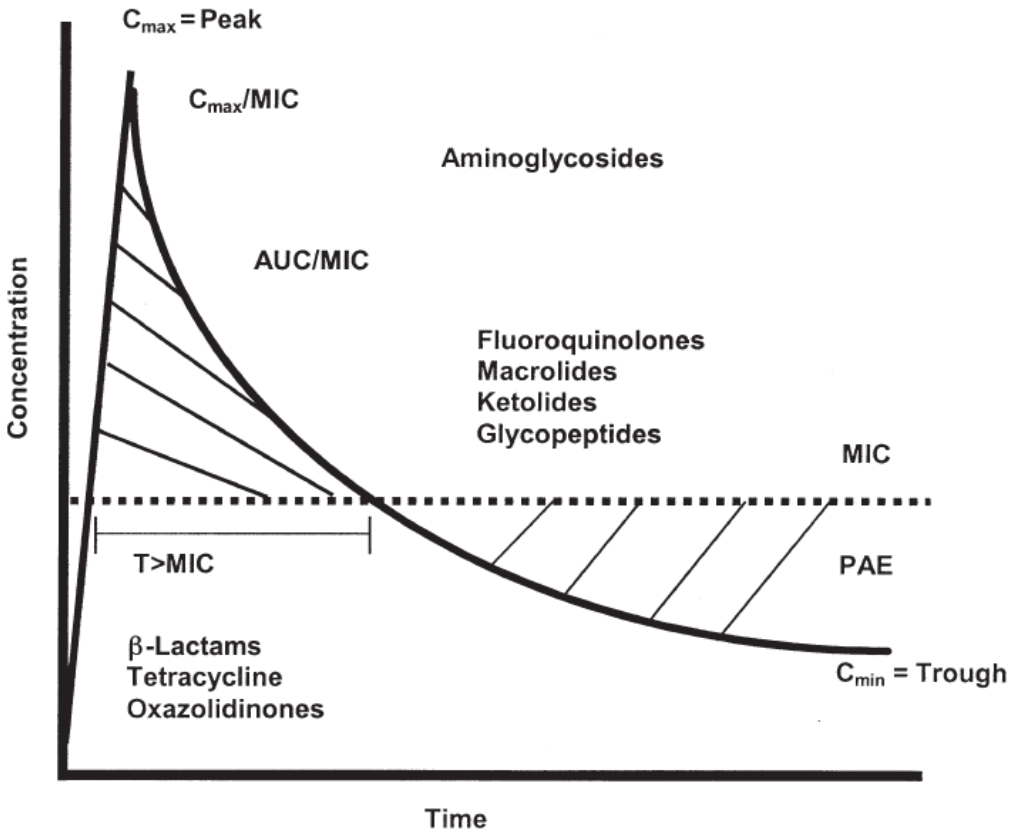
# Pharmacodynamic Parameters Relating to Efficacy

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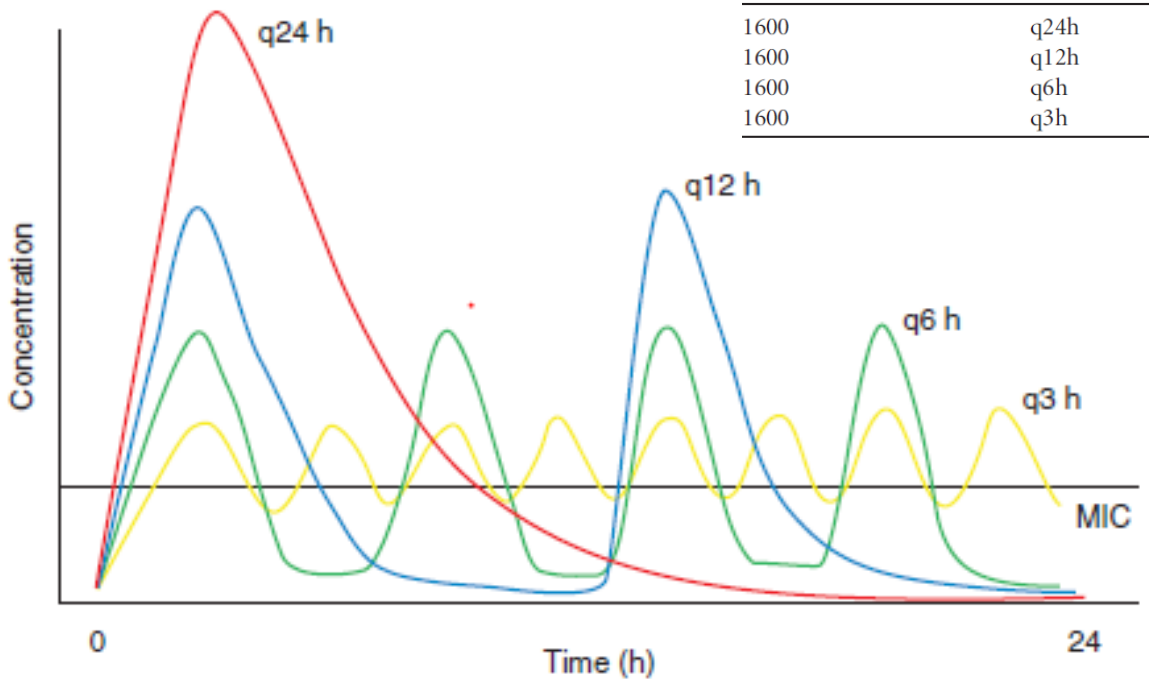
Craig WA *Clin Infect Dis* 1998;26:1-12. Rybak M. Am J Med 2006;119:S37-44.
Pai, MP et al. Pharmacokinetics & pharmacodynamics of anti-infective agents. Mandells 2015.

# 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 .

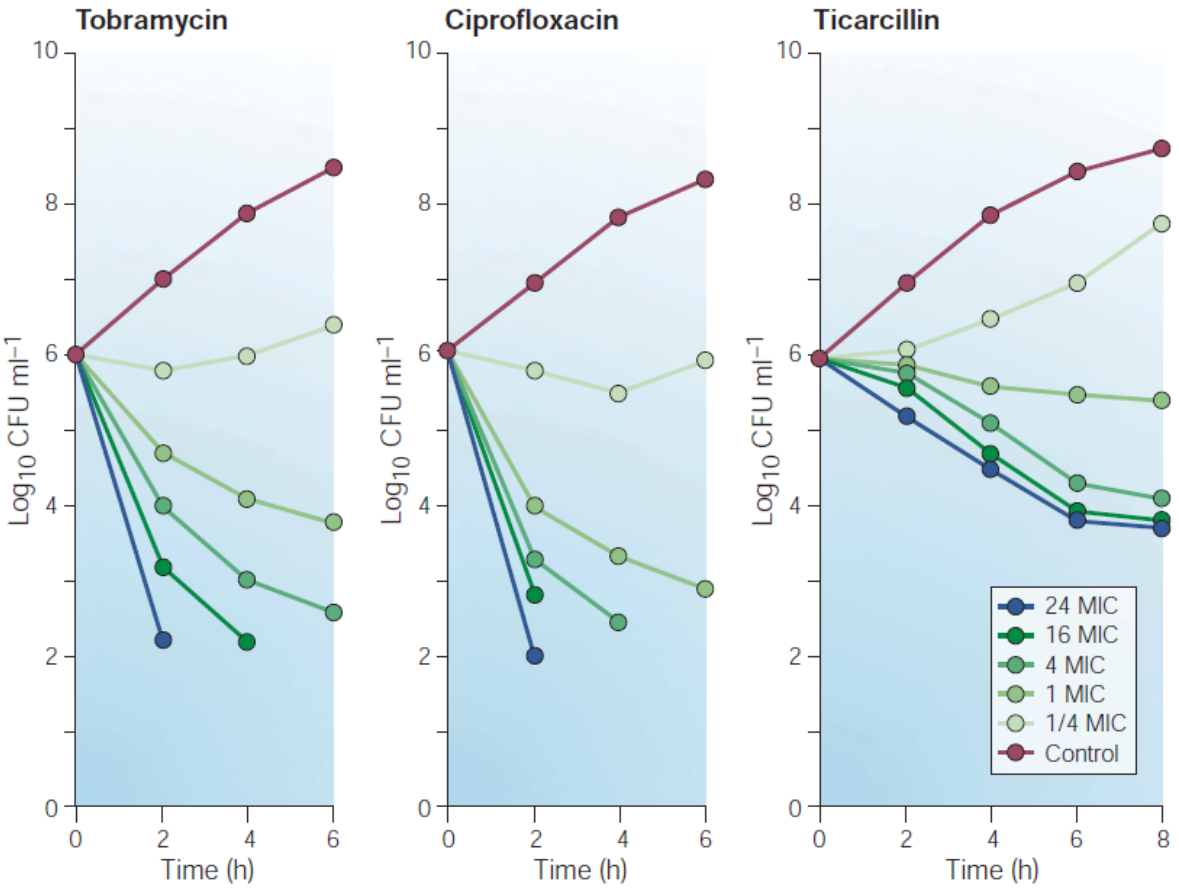
| Total dose (mg/kg/24 h) | Interval | Dose (mg/kg) administered | AUC/MIC | $C_{max}$/MIC | % $T >$ MIC |
|---|---|---|---|---|---|
| 1600 | q24h | 1600 × 1 | No change | ↑↑↑ | - |
| 1600 | q12h | 800 × 2 | No change | ↑↑ | ↑ |
| 1600 | q6h | 400 × 4 | No change | ↑ | ↑↑ |
| 1600 | q3h | 200 × 8 | No 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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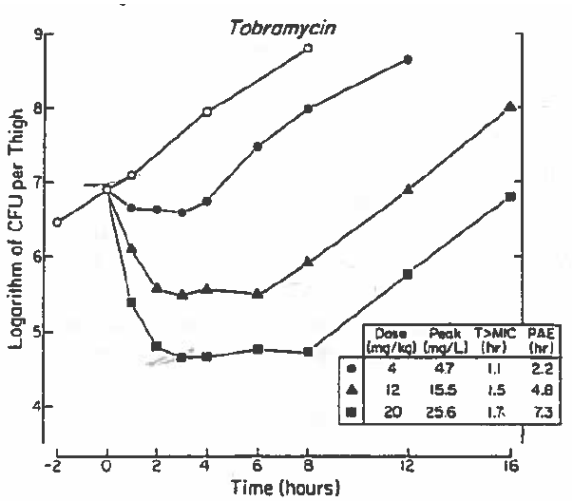
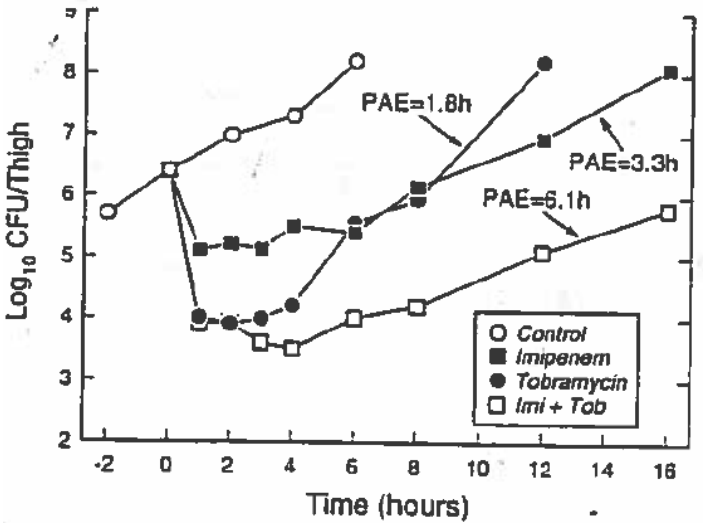
Drusano G. *Nature Reviews Microb* 2004;2:289-300.

# 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.

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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 |
| Method: | MIC | |
| CEFEPIME | Sensitive | <=2 |
| Method: | MIC | |
| CEFTAZIDIME | Sensitive | <=2 |
| Method: | MIC | |
| CIPROFLOXACIN | Sensitive | <=0.5 |
| Method: | MIC | |
| GENTAMICIN | Sensitive | 4 |
| Method: | MIC | |
| IMIPENEM | Sensitive | <=1 |
| Method: | MIC | |
| LEVOFLOXACIN | Sensitive | <=0.5 |
| MEROPENEM | Sensitive | <=1 |
| PIPERACILLIN/TAZOBAC | Sensitive | <=8 |
| Method: | MIC | |
| TOBRAMYCIN | Sensitive | 2 |
| Method: | MIC | |

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 |
| Method: | MIC | |
| CEFEPIME | Sensitive | 4 |
| Method: | MIC | |
| CEFTAZIDIME | Sensitive | 4 |
| Method: | MIC | |
| CIPROFLOXACIN | Sensitive | <=0.5 |
| Method: | MIC | |
| GENTAMICIN | Sensitive | 4 |
| Method: | MIC | |
| IMIPENEM | Resistant | >8 |
| Method: | MIC | |
| LEVOFLOXACIN | Sensitive | <=0.5 |
| MEROPENEM | Resistant | 8 |
| PIPERACILLIN/TAZOBAC | Sensitive | <=8 |
| Method: | MIC | |
| TOBRAMYCIN | Sensitive | 2 |
| Method: | MIC | |

Comments PSEUDOMONAS AERUGINOSA (MIC)
MODERATE PSEUDOMONAS AERUGINOSA

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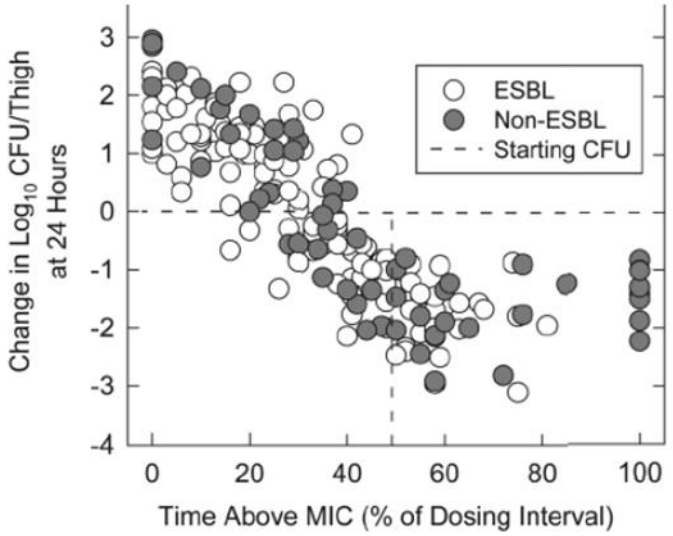
# Time Dependent Agents

## 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

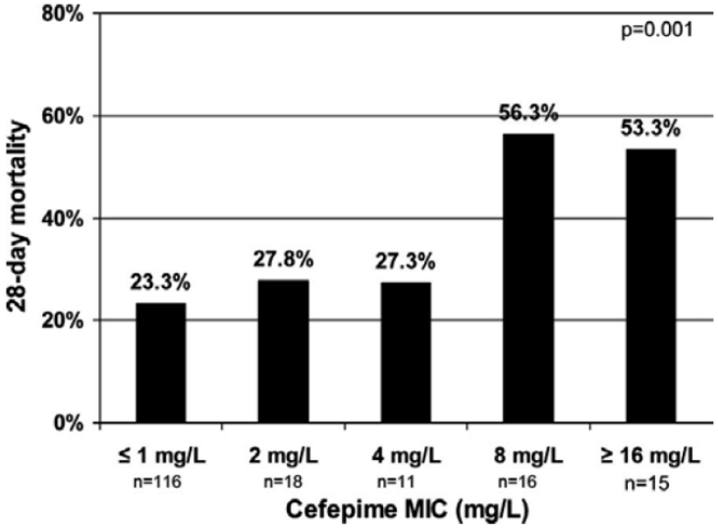
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2007, p. 4390–4395 Vol. 51, No. 12
0066-4804/07/$08.00+0 doi:10.1128/AAC.01487-06


## 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

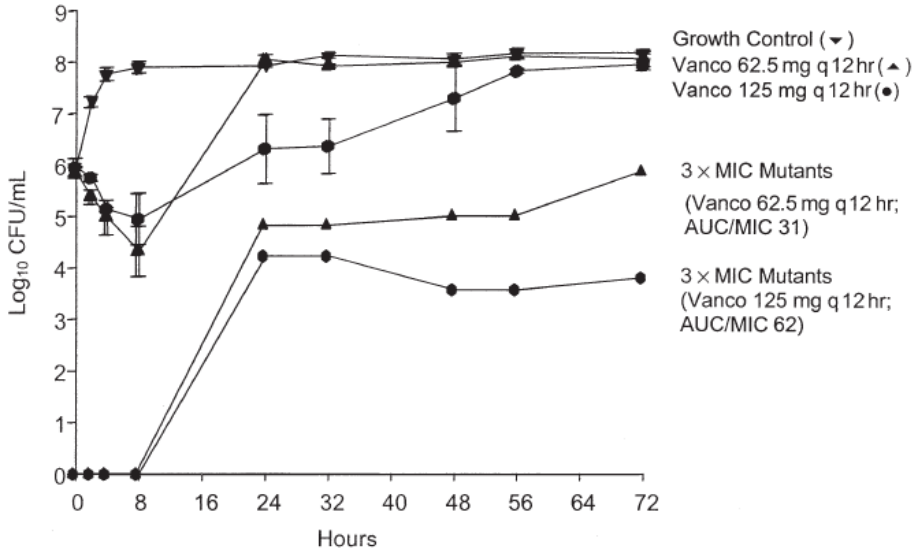


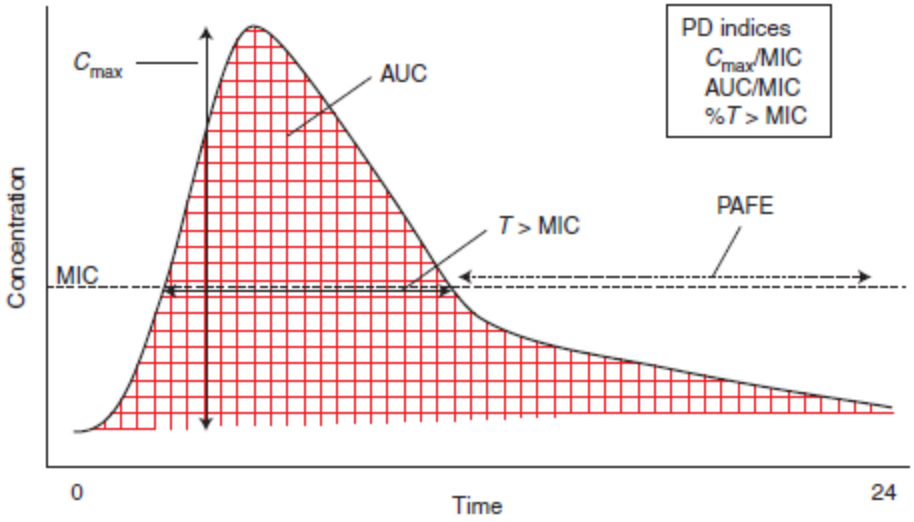

**Table 2** Accessory gene regulator group II *Staphylococcus aureus* postvancomycin exposure

| 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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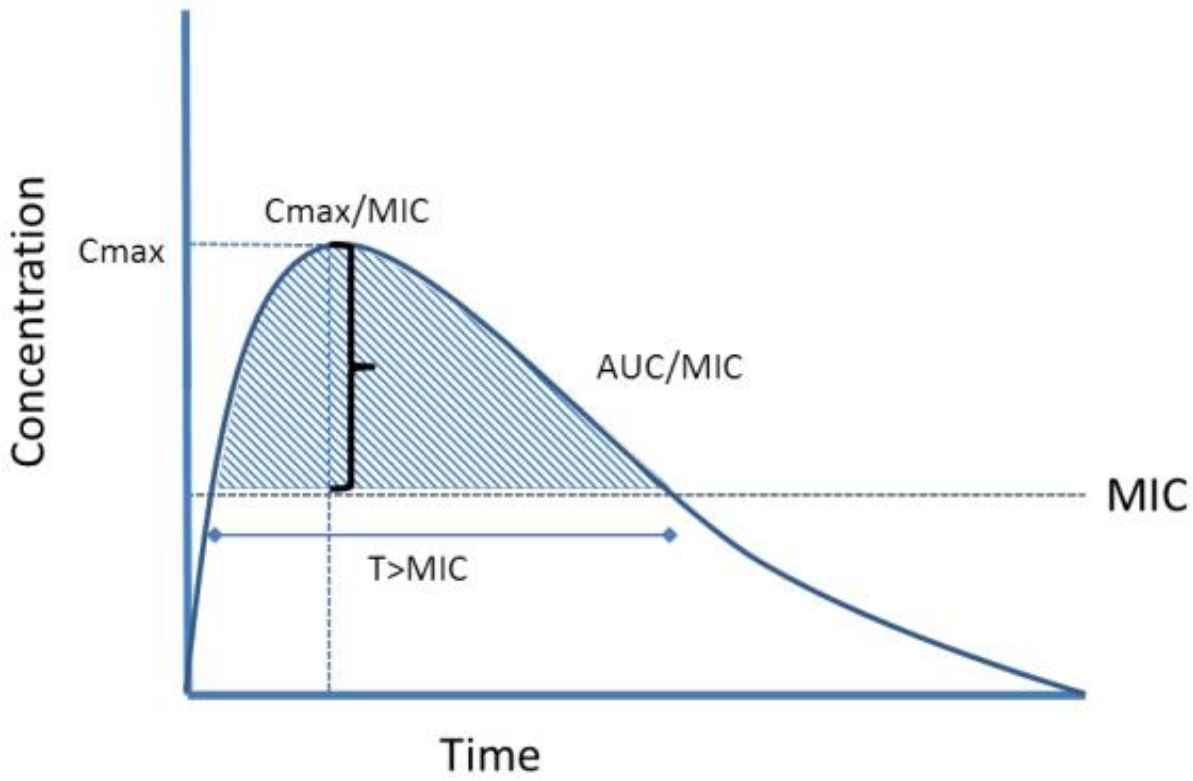
# Antimicrobial Optimization: PK/PD Summary

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

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AHQR. July 2013.

# Objectives

- 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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# 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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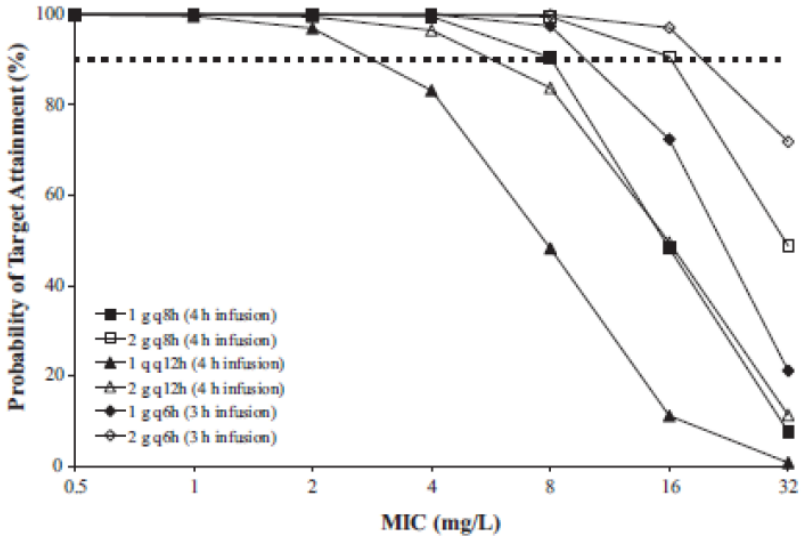
# Cefepime Target Attainment

## 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**

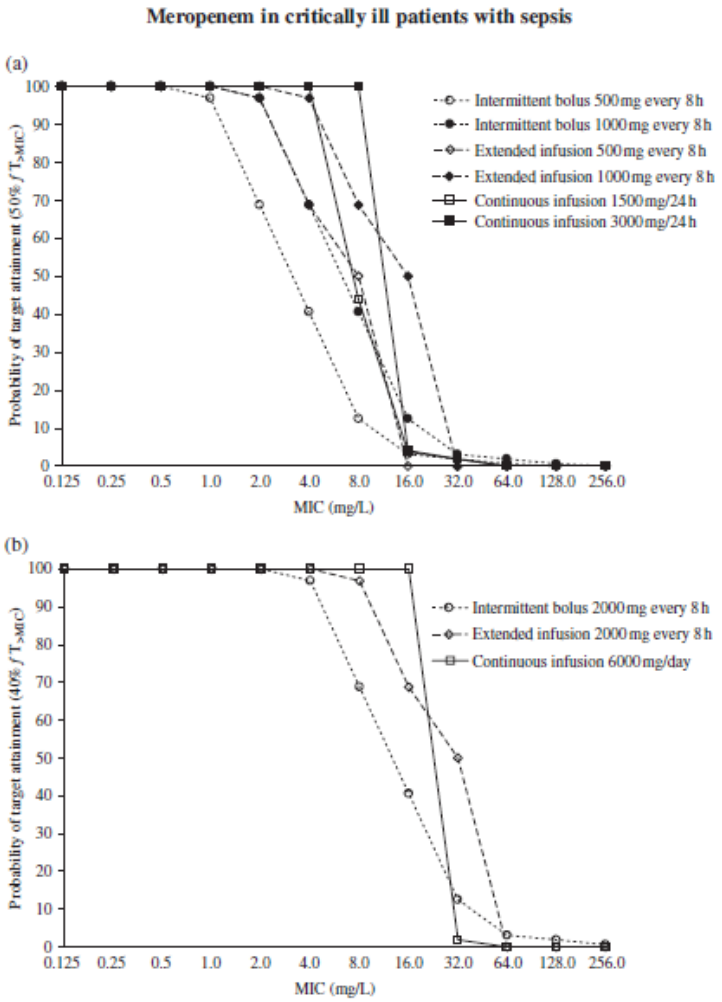
Dotted line represents the intended target for 6 doses listed, each infused over 4hours.

**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]


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.


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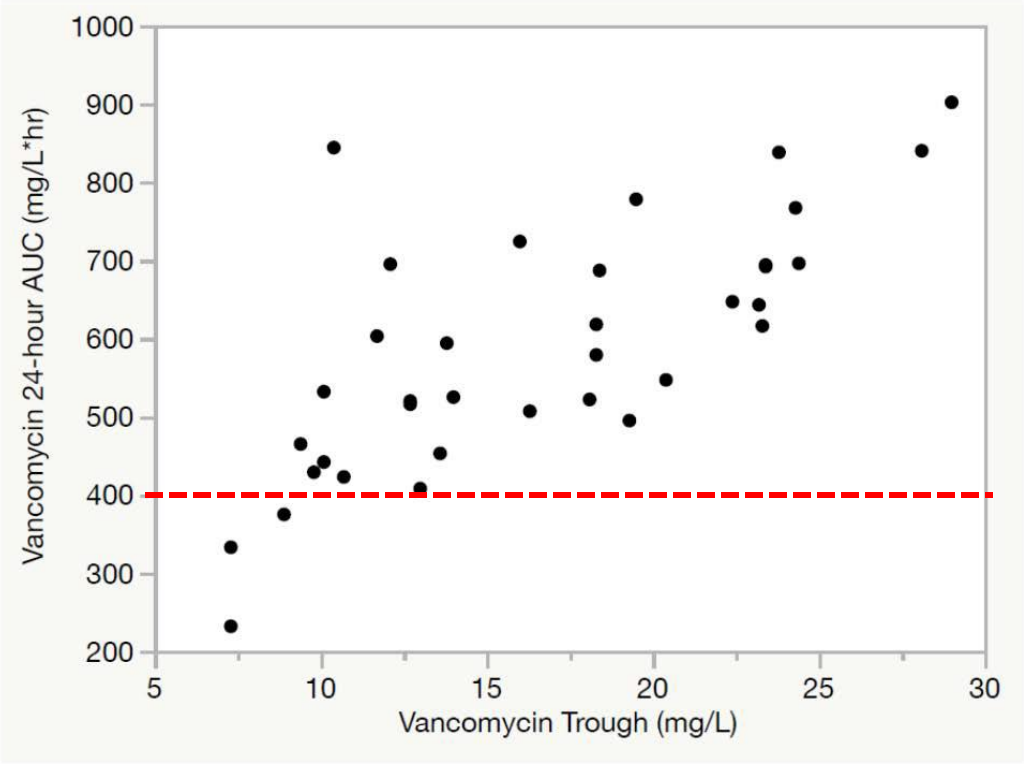
# AUC vs. Trough (n=34) [Unpublished Aurora Data]




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

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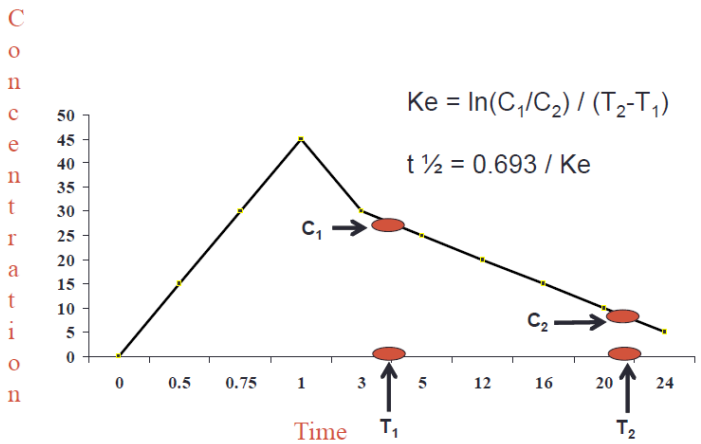
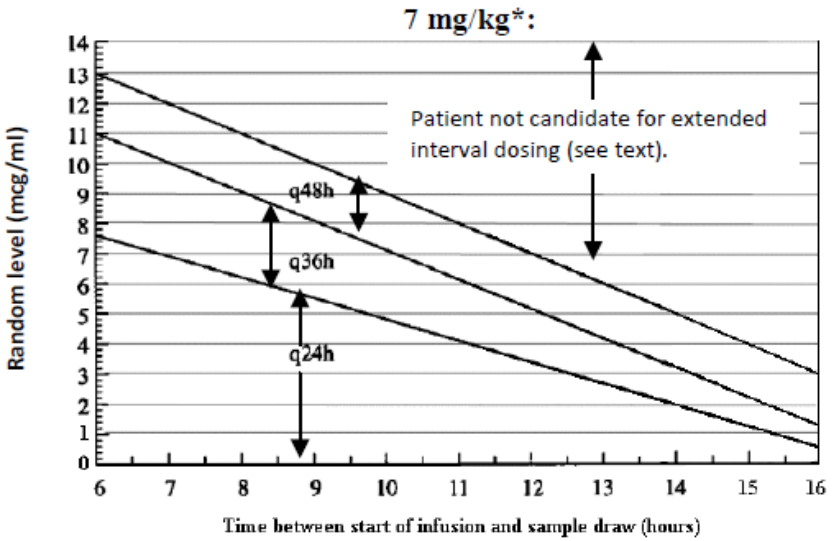
# High Dose Aminoglycosides for Gram-Negative Infections

- 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.

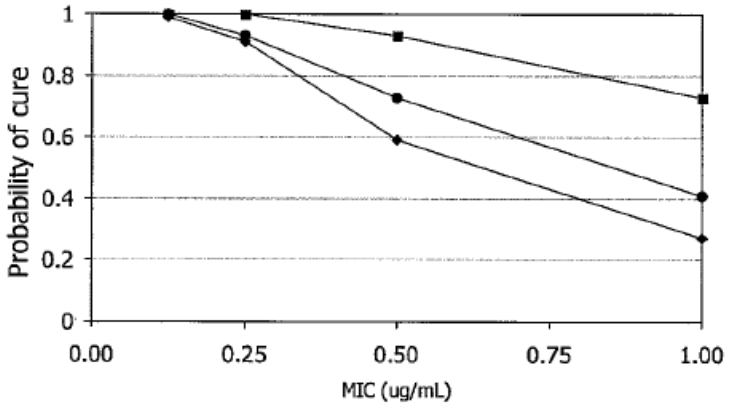


FIG. 6. Relative efficacies of ciprofloxacin dosing regimens across MIC categories using Monte Carlo simulations. ◆, recommended standard dose; ●, recommended high dose; ■, PD-targeted regimen.

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

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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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# 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

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

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# 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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