Pharmacokinetic Pearls for Pharmacists New and Old

Alex Heringer, PharmD; Jeremy Theis, PharmD
April 16th, 2026

Disclosures

The planners and speakers have indicated that there are no relevant financial relationships with any ineligible companies to disclose.

Learning Objectives

At the end of this session, learners should be able to:

- Recognize how drug properties and Monte Carlo simulations can apply to pharmacokinetics.
- Identify benefits and use cases for vancomycin monitoring and dosing with area under the curve calculations.
- Utilize appropriate dosing strategies and calculations to correctly formulate therapeutic regimens for aminoglycosides.
- Discuss medications with unique pharmacokinetic profiles.

Outline

1. Introduction to pharmacokinetics
2. Monte Carlo simulations and applications
3. Vancomycin properties and dosing
4. Vancomycin trough and AUC monitoring
5. Aminoglycoside properties and dosing
6. Example Aminoglycoside dosing walkthrough
7. Tacrolimus pharmacokinetic pearls
8. Phenytoin pharmacokinetic pearls
9. Triazole antifungal pharmacokinetic pearls
10. Effects of hypoalbuminemia on drug concentrations

Abbreviation Key

- AAH = Advocate-Aurora Healthcare
- ADME = Absorption, Distribution, Metabolism, Excretion
- AG = Aminoglycoside
- AKI = Acute Kidney Injury
- AUC = Area Under Curve
- BID = Twice Daily
- BMI = Body Mass Index
- BSI = Blood Stream Infection
- CNS = Central Nervous System
- CRO = Ceftriaxone
- CrCl = Creatinine Clearance
- Cys C = Cystatin-C
- DDI = Drug-Drug Interaction
- EHR = Electronic Health Record
- ER = Extended Release
- FKBP = FK506 Binding Protein
- HF = Heart Failure
- IAI = Intra-abdominal Infection
- ICU = Intensive Care Unit
- IDSA = Infectious Disease Society of America
- IR = Immediate Release
- IV = Intravenous
- MIC = Minimum Inhibitory Concentration
- PCR = Polymerase Chain Reaction
- PD = Pharmacodynamics
- PK = Pharmacokinetics
- PO = By Mouth
- MAC = Mycobacterium Avium Complex
- MRSA = Methicillin Resistant Staphylococcus Aureus
- NTM = Non-tuberculosis Mycobacteria
- Scr = Serum Creatinine
- TDM = Therapeutic Drug Monitoring
- TID = Three Times Daily
- VAP = Ventilator Associated Pneumonia

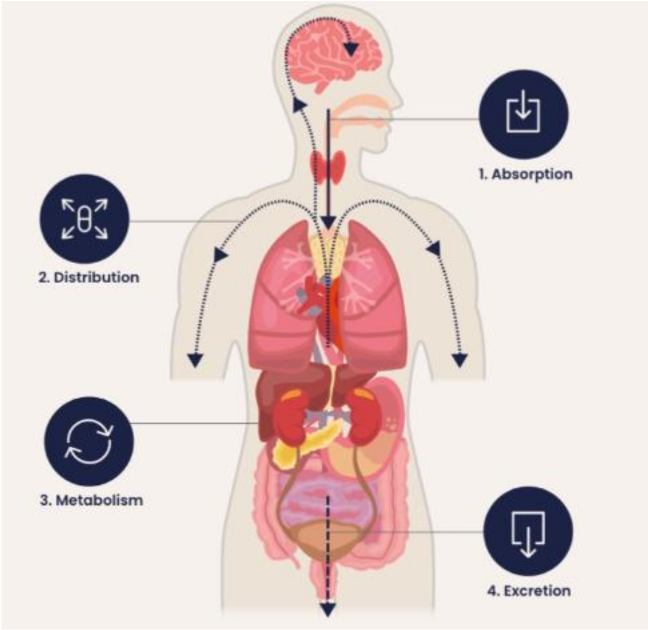
ADVOCATEHEALTH

Pharmacokinetics and Monte Carlo Simulations

ADVOCATE HEALTH

Pharmacokinetics - Intro

- Often described with the phrase: “What your body does to the drug”
- Includes absorption, distribution, metabolism, and excretion
- A cornerstone of pharmacy practice



Pharmaceutical Press. “What Is Pharmacokinetics?” Pharmaceutical Press, May 2024, www.pharmaceuticalpress.com/resources/article/what-is-pharmacokinetics/.

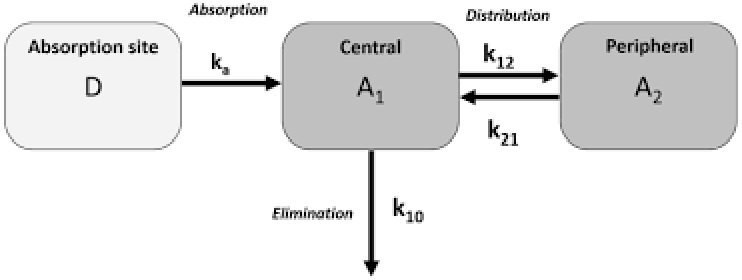
Absorption

- Affected by dosage form and route
- Enteral vs parenteral administration
  - Can be significantly impacted by conditions such as short bowel
- Effect of food – varies depending on the drug
  - Food content, pH impact, gastric emptying
- Bioavailability – extent of absorption
- Passive diffusion vs carrier-mediated membrane transport

Alagga AA, Gupta V, Pellegrini MV. Drug Absorption. PubMed. Published February 27, 2024. https://www.ncbi.nlm.nih.gov/books/NBK557405/
Porter RS. The Merck Manual of Diagnosis and Therapy. 20th ed. Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc; 2018.

Distribution

- Distribution of drug through the body
- Drug distribution is impacted by many factors
  - Lipophilicity, pH, protein binding, dose, delivery system, etc.
- Volume of distribution (Vd): proportion that relates the amount of drug in the body compared to the plasma concentration
  - $V_d = \frac{Dose}{Concentration}$
- Compartment Models
  - One compartment
  - Two compartment



Talevi, Alan, and Carolina L. Bellera. "Two-Compartment Pharmacokinetic Model." *The ADME Encyclopedia*, 2022, pp. 1167–1174, https://doi.org/10.1007/978-3-030-84860-6_59.

ADVOCATE HEALTH

Onetto AJ, Sharif S. Drug distribution. PubMed. Published June 26, 2023. https://www.ncbi.nlm.nih.gov/books/NBK567736/

Metabolism

- Alteration of chemicals so they can be excreted out of the body
- Made up of Phase 1 and Phase 2 reactions
  - Phase 1 – Modification: oxidation, reduction, hydrolysis
  - Phase 2 – Conjugation: methylation, glucuronidation, acetylation
- First pass metabolism
- Prodrugs
  - Clopidogrel, codeine, valacyclovir, levodopa, prednisone, etc.

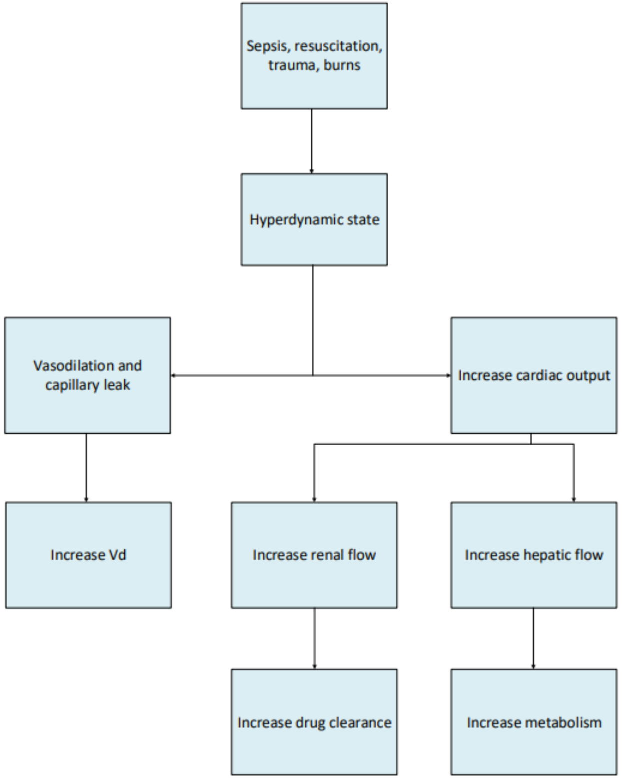
Susa ST, Preuss CV, Hussain A. Drug Metabolism. Nih.gov. Published August 17, 2023. https://www.ncbi.nlm.nih.gov/books/NBK442023/

Excretion

- Primarily made up of renal and biliary excretion
- Renal – water soluble excretion
  - Compounds are filtered through the glomerulus and polar molecules cannot diffuse back into circulation
  - Drugs bound to plasma proteins are not filtered
    - Higher protein binding can contribute to reduced dosing frequencies (ex: CRO)
  - Estimated through surrogate markers like Scr and Cys C
- Biliary – Bile excretion
  - Higher molecular weight and more lipophilic drugs
  - Requires active transport against concentration gradient
- Elimination rate constant: Ke

Le, J. (2024). *Drug Excretion*. In The Merck Manual of diagnosis and therapy (Section 22: Administration and kinetics of drugs). Merck Sharp & Dohme. https://www.merckmanuals.com/home/drugs/administration-and-kinetics-of-drugs/drug-elimination

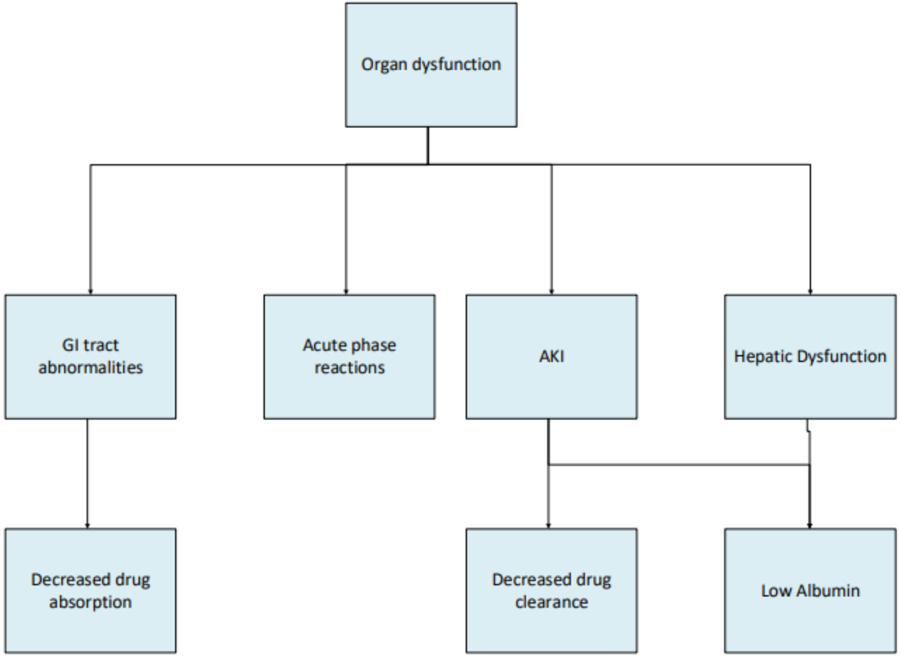
PK in Critical Illness



Adapted from: Morales Castro D, Dresser L, Granton J, Fan E. Pharmacokinetic alterations associated with critical Illness. *Clinical Pharmacokinetics*. 2023;62(2):209-220. doi:https://doi.org/10.1007/s40262-023-01213-x

ADVOCATE HEALTH

PK in Critical Illness



Adapted from: Morales Castro D, Dresser L, Granton J, Fan E. Pharmacokinetic alterations associated with critical Illness. *Clinical Pharmacokinetics*. 2023;62(2):209-220. doi:https://doi.org/10.1007/s40262-023-01213-x

The Monte Carlo Method

- Simulation technique to evaluate the impact of uncertainty in the probability of an outcome
  - Method developed for the Manhattan Project during World War II
  - Utilized in a variety of settings, including finances, economics, and chemistry
- Typically involves a combination of generating random inputs and aggregating the results to approximate what the most likely result is

Tsvetelina Velikova, Niya Mileva, Naseva EK. Method “Monte Carlo” in Healthcare. *World Journal of Methodology*. 2024;14(3):93930. doi:https://doi.org/10.5662/wjm.v14.i3.93930
Toropova MA. Drug Metabolism as an Object of Computational Analysis by the Monte Carlo Method. *Current Drug Metabolism*. 2018;18(12):1123-1131. doi:https://doi.org/10.2174/1389200218666171010124733

Monte Carlo Applications to Pharmacy

- Applications in PK/PD target attainment and susceptibility breakpoint evaluations
- Particularly useful during drug development
  - Used in combination with pharmacokinetic models to predict drug behavior across patient populations (ex: predict how a drug will be metabolized)
  - Can reduce need for initial clinical trials by simulating dose-response relationships

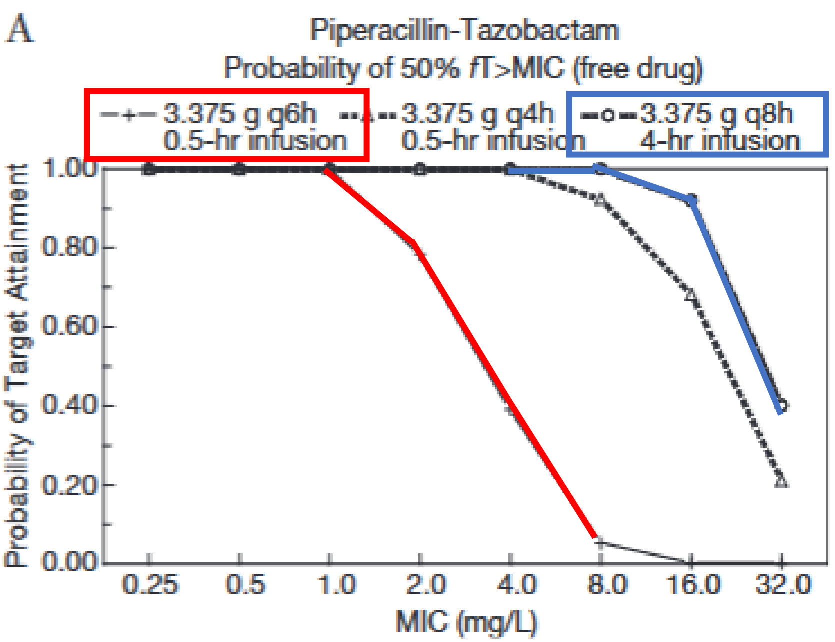
Tsvetelina Velikova, Niya Mileva, Naseva EK. Method “Monte Carlo” in Healthcare. *World Journal of Methodology*. 2024;14(3):93930. doi:https://doi.org/10.5662/wjm.v14.i3.93930
Toropova MA. Drug Metabolism as an Object of Computational Analysis by the Monte Carlo Method. *Current Drug Metabolism*. 2018;18(12):1123-1131. doi:https://doi.org/10.2174/1389200218666171010124733

Extended Infusion Beta Lactams

- One application of population PK and Monte Carlo simulations to optimize pharmacodynamic parameters
- Beta lactams exhibit time-dependent bactericidal activity
- Can simulate giving volunteers an antibiotic and observing the variability in concentration-time profiles
  - Gives a spread of peak concentration and AUC values after a particular dose

Lodise TP, Lomaestro BM, Drusano GL. Application of Antimicrobial Pharmacodynamic Concepts into Clinical Practice: Focus on β-Lactam Antibiotics: Insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy*. 2006;26(9):1320-1332. doi:https://doi.org/10.1592/phco.26.9.1320

Extended Infusion Beta Lactams



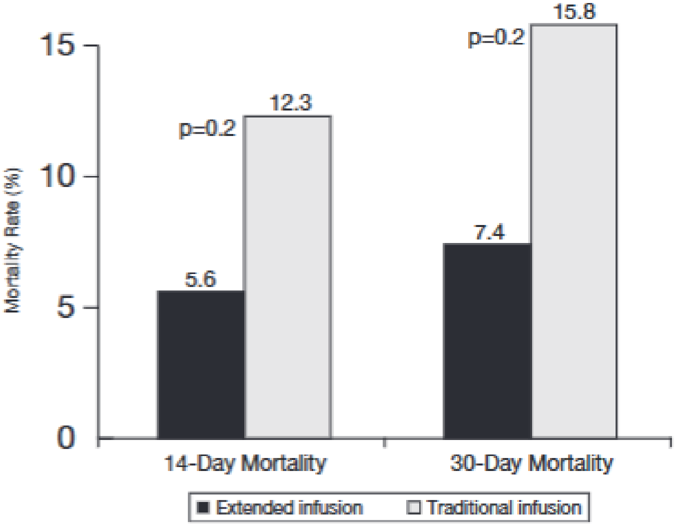


Figure 4. Comparison of 14-day and 30-day mortality after onset of *Pseudomonas aeruginosa* infection between the piperacillin-tazobactam extended-infusion (4-hr) group and the traditional-infusion (30-min) group. (From reference 35.)

Lodise TP, Lomaestro BM, Drusano GL. Application of Antimicrobial Pharmacodynamic Concepts into Clinical Practice: Focus on β-Lactam Antibiotics: Insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy*. 2006;26(9):1320-1332. doi:https://doi.org/10.1592/phco.26.9.1320

Assessment Question - PK

Which of the following is **NOT** an appropriate application of Monte Carlo simulations to pharmacy practice?

A. Model the exact response a patient will have when given a drug

B. PK/PD modeling to optimize antibiotic drug dosing regimens

C. Support clinical trials by simulating dose-response relationships

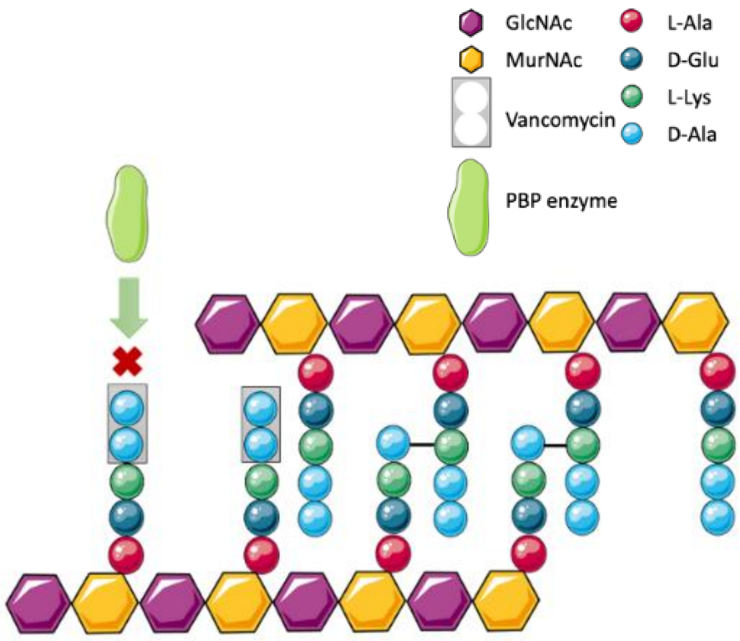
D. Simulate drug metabolism and variance across a patient population

Vancomycin

ADVOCATE HEALTH

Vancomycin Mechanism of Action

- Class: Tricyclic glycopeptide
- Mechanism: Cell wall synthesis inhibitor
  - Inhibits polymerization of peptidoglycan structures in the bacterial cell wall
- PK/PD monitoring parameter: 24-hour AUC / MIC
- Bactericidal against all Gram-positive organisms
  - Exception: Bacteriostatic against enterococci



Loll, Patrick. “PDB101: Global Health: Antimicrobial Resistance: Undefined: Vancomycin.” RCSB: PDB-101, 2016, pdb101.rcsb.org/global-health/antimicrobial-resistance/drugs/antibiotics/

Patel, Shivali, et al. “Vancomycin.” National Library of Medicine, StatPearls Publishing, 29 Oct. 2024, www.ncbi.nlm.nih.gov/books/NBK459263/.
Tharp, Rick. “PK/PD Approach to Antibiotic Therapy Review.” Www.rxkinetics.com, www.rxkinetics.com/antibiotic_pk_pd.html.

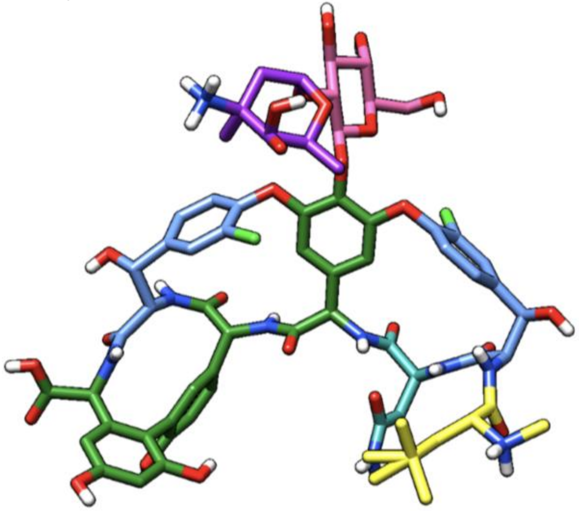
Vancomycin Pharmacokinetics

- Absorption:
  - Large, complex structure limits vancomycin's oral bioavailability

- Distribution:
  - Wide distribution to body tissues and fluids
  - ~50% protein bound
  - Poor CNS penetration

- Metabolism:
  - Does not undergo major metabolism
  - Elimination is greatly prolonged with renal dysfunction

- Elimination:
  - 1st order elimination
  - IV form is primarily eliminated via glomerular filtration
  - Oral form is not systemically absorbed

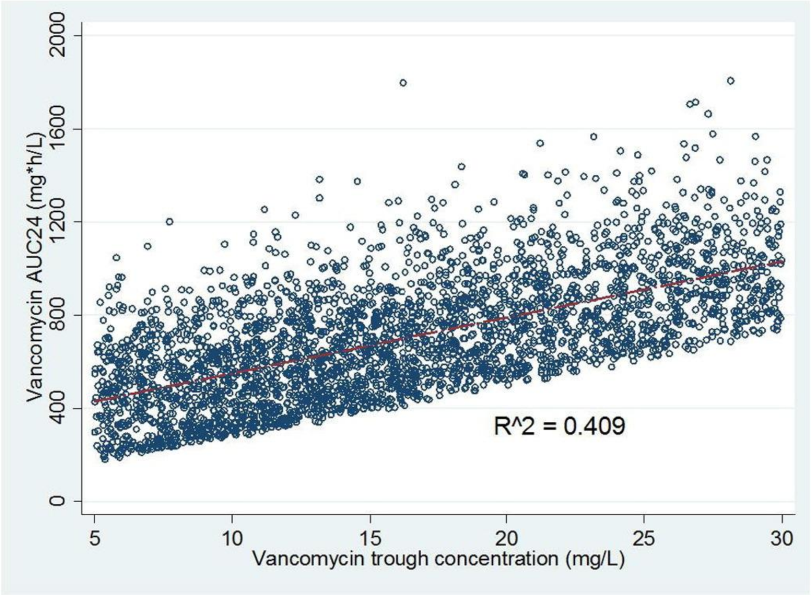


Loll, Patrick. "PDB101: Global Health: Antimicrobial Resistance: Undefined: Vancomycin." RCSB: PDB-101, 2016, pdb101.rcsb.org/global-health/antimicrobial-resistance/drugs/antibiotics/

Patel, Shivali, et al. "Vancomycin." National Library of Medicine, StatPearls Publishing, 29 Oct. 2024, www.ncbi.nlm.nih.gov/books/NBK459263/.
Idasiak-Piechocka I, Lewandowski D, Świgut W, Kalinowski J, Mikosza K, Suchowiejski P, Szałek E, Karbownik A and Miedziaszczyk M (2025) Effect of hypoalbuminemia on drug pharmacokinetics. Front. Pharmacol. 16:1546465. doi: 10.3389/fphar.2025.1546465

Vancomycin Trough Dosing

- Standard at AAH
- Trough goals:
  - 10-15 most indications
  - 15-20 for CNS infections
- Pros:
  - Resource and time efficient
  - Current EHR builds in place
  - Staff familiarity with monitoring processes
- Cons:
  - Unknown 24-hour AUC/MIC level
  - Higher risk of AKI



Pai, Manjunath P., et al. "Innovative Approaches to Optimizing the Delivery of Vancomycin in Individual Patients." Advanced Drug Delivery Reviews, vol. 77, Nov. 2014, pp. 50–57, https://doi.org/10.1016/j.addr.2014.05.016. Accessed 16 Apr. 2019.

Rybak, Michael J, et al. "Therapeutic Monitoring of Vancomycin for Serious Methicillin-Resistant Staphylococcus Aureus Infections: A Revised Consensus Guideline and Review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists." American Journal of Health-System Pharmacy, vol. 77, no. 11, 19 Mar. 2020, https://doi.org/10.1093/ajhp/zxaa036.

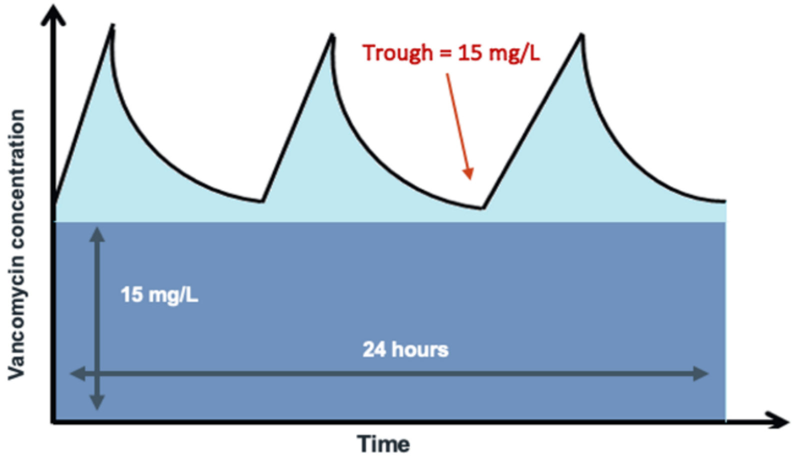
Abdelmessih, Emily, et al. "Vancomycin Area under the Curve versus Trough Only Guided Dosing and the Risk of Acute Kidney Injury: Systematic Review and Meta-Analysis." Pharmacotherapy, vol. 42, no. 9, 5 Aug. 2022, pp. 741–753, https://doi.org/10.1002/phar.2722.

Vancomycin AUC Dosing

- Goal AUC_{24} = 400-600 mg *h/L (assuming MIC of 1 mg/L)
- Obtain peak (60 min after infusion of 4th or 5th dose)
- Obtain trough (30 minutes prior to 4th of 5th maintenance dose)

- Pros:
    - Better predictor of AKI
    - Confirmed 24-hour AUC / MIC values
    - Recommended by IDSA for serious MRSA infections

- Cons:
    - Complex
    - Requires additional time or programs to do calculations
    - Costs associated with additional lab draws

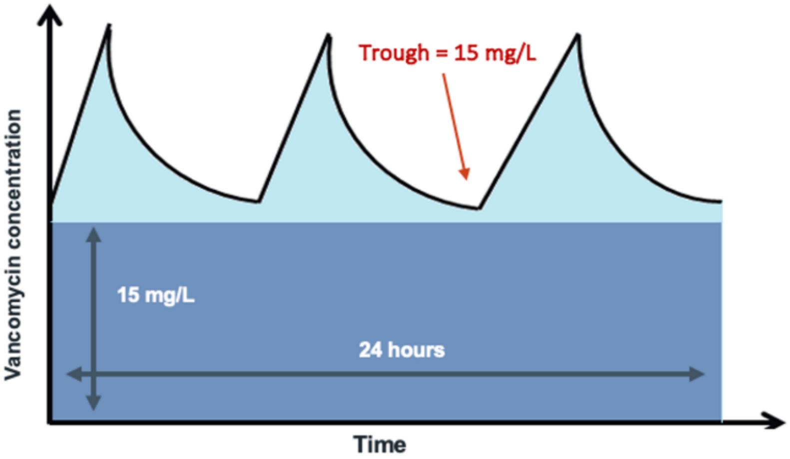


Lee, Sara. "Curve Your Enthusiasm: AUC-Guided Vancomycin Dosing and Monitoring." IDStewardship, 22 Nov. 2021, www.idstewardship.com/curve-enthusiasm-auc-guided-vancomycin-dosing-monitoring/.

Rybak, Michael J, et al. "Therapeutic Monitoring of Vancomycin for Serious Methicillin-Resistant Staphylococcus Aureus Infections: A Revised Consensus Guideline and Review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists." American Journal of Health-System Pharmacy, vol. 77, no. 11, 19 Mar. 2020, https://doi.org/10.1093/ajhp/zxaa036.

Vancomycin AUC Dosing

- Used for patient with an elevated risk of nephrotoxicity:
  - Serious MRSA infections
  - Receiving more than 4 grams of vancomycin per day
  - Vancomycin therapy lasting longer than 2 weeks
  - Morbidly obese patients (BMI ≥ 40 kg/m^2 or > 140 kg)



Lee, Sara. "Curve Your Enthusiasm: AUC-Guided Vancomycin Dosing and Monitoring." IDStewardship, 22 Nov. 2021, www.idstewardship.com/curve-enthusiasm-auc-guided-vancomycin-dosing-monitoring/.

Rybak, Michael J, et al. "Therapeutic Monitoring of Vancomycin for Serious Methicillin-Resistant Staphylococcus Aureus Infections: A Revised Consensus Guideline and Review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists." American Journal of Health-System Pharmacy, vol. 77, no. 11, 19 Mar. 2020, , https://doi.org/10.1093/ajhp/zxaa036.

Vancomycin AUC Models

- Modeling: Population-based PK models used to predict future serum concentrations
- Bayesian-derived AUC monitoring:
  - Advantage: Potentially less biased (lower mean prediction error) compared to Sawchuk-Zaske and does not require steady-state conditions
- Sawchuk-Zaske method:
  - Advantage: calculations are easy to perform, and more practical to implement without modeling programs

Garrelts JC, Godley PJ, Horton MW, Karboski JA. Accuracy of Bayesian, Sawchuk-Zaske, and nomogram dosing methods for vancomycin. Clinical Pharmacy. 1987 Oct;6(10):795-799. PMID: 3505841.
Miller CL, Winans SA, Veillette JJ, Forland SC. Use of Individual Pharmacokinetics to Improve Time to Therapeutic Vancomycin Trough in Pediatric Oncology Patients. J Pediatr Pharmacol Ther. 2018;23(2):92-99. doi:10.5863/1551-6776-23.2.92

Vancomycin AUC Dosing

Definitions:
T = dosing interval (hr)
t' = infusion duration (hr)
t''= time since completion of infusion when C1 drawn (hr)
C1 = first level drawn off dose: higher level (mcg/mL)
C2 = second level drawn off dose: lower level (mcg/mL)
Δt = the time difference between C1 and C2 (hr)

Value	Equation
Elimination rate constant	$Ke = \frac{\ln C1 - \ln C2}{\Delta t}$
Half-life	T $1/2 = \frac{0.693}{Ke}$
True peak	$C\ max = \frac{C1}{e^{-Ke\ (T-t'')}}$
True trough	$C \min = C \max \times [e^{-Ke(T-t')}]$
Area under the curve	$AUC\ 24\ \text{hour} = \frac{[t' \times (C \max + C \min)]}{2} + \frac{(C \max - C \min)}{Ke}$

ADVOCATEHEALTH

“Enterprise Adult Vancomycin Dosing & Monitoring Guidelines” Advocate Healthcare Internal Documentation. January 2025

Vancomycin AUC Monitoring

- Internal guidance on subsequent monitoring and dosing:

Table 15. AUC Decision Guidance

AUC_{24hour} (mg*h/L)	Dose Adjustment	Level Guidance
< 400	If increased exposure desired, increase total daily dose proportionally to achieve AUC_{24hour} of 400 – 600 mg*h/L	Repeat level with 4th or 5th dose of new regimen
400 – 600	Maintain current dose [1]	Repeat level 5 – 7 days [2]
> 600	If reduced exposure desired, reduce total daily dose proportionally to achieve AUC_{24hour} of 400 – 600 mg*h/L	Repeat level with 4th or 5th dose of new regimen

[1] If concern for toxicity and/or suboptimal clinical response, consider alternative antibiotic therapy.
[2] If patient is stable, estimate a trough that approximates the AUC goal then subsequently draw a trough level.

- Doses are adjusted based using proportions due to vancomycin's linear kinetics

- $$\frac{\text{Prior total daily maintenance dose (mg)}}{\text{New total daily dose (mg)}} = \frac{\text{Calculated AUC}_{24\ hour}}{\text{Goal AUC}_{24\ hour}}$$

ADVOCATEHEALTH

"Enterprise Adult Vancomycin Dosing & Monitoring Guidelines" Advocate Healthcare Internal Documentation. January 2025

Trough vs AUC

	Trough	AUC
Pros	• Resource and time efficient • Current EHR builds in place • Staff familiarity with monitoring processes	• Better predictor of AKI • Confirmed 24-hour AUC / MIC values • Recommended by IDSA for serious MRSA infections
Cons	• Unknown 24-hour AUC/MIC level • Higher risk of AKI	• Complex • Requires additional time/programs to do calculations • Cost associated with additional lab draws

Lim AS, Seng JJB, Ng TTM, Chng HT, Han Z. 1097. A Comparison of Area-Under Curve (AUC)-Guided vs Trough-Guided Monitoring of Vancomycin and Its Impact on Nephrotoxicity: A Systematic Review and Meta-analysis. *Open Forum Infect Dis*. 2021;8(Suppl 1):S640-S641. Published 2021 Dec 4. doi:10.1093/ofid/ofab466.1291

ADVOCATEHEALTH

Assessment Question - Vancomycin

Which patient receiving vancomycin would be most likely to benefit from AUC monitoring instead of standard trough monitoring?

A. An ICU patient receiving vancomycin 1500 mg TID for severe MRSA IAI
B. An obese patient receiving vancomycin 1250 mg BID for MRSA PNA
C. A patient receiving vancomycin 1750 mg BID for empiric treatment of a BSI with negative MRSA nasal PCR
D. An ICU patient recently started on vancomycin 1000 mg TID for empiric coverage of a CNS infection

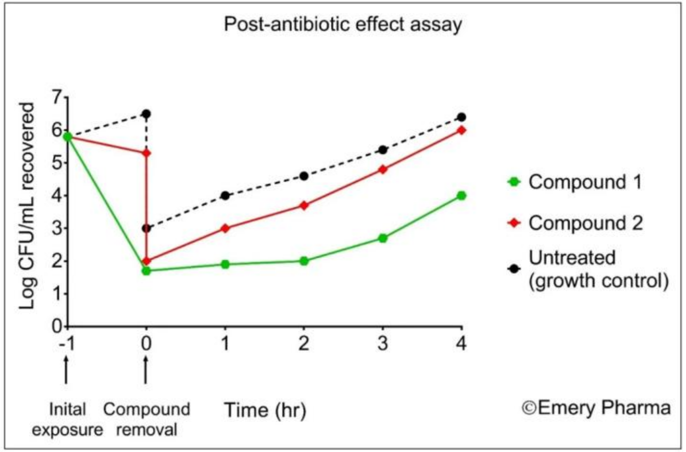
ADVOCATE HEALTH

Aminoglycosides

ADVOCATE HEALTH

Mechanism of Action

- Aminoglycosides act through inhibition of protein synthesis
    - Irreversibly bind to the 16S rRNA of the 30S ribosome
- Peak to MIC related killing
- Express a substantial post-antibiotic effect with inhibition of bacterial growth after drug clearance



Liu J. Post Antibiotic Effect: The Importance of Assessing Microbial Response After an Initial Antimicrobial Challenge - Emery Pharma. Emery Pharma. Published March 20, 2025. https://emerypharma.com/blog/post-antibiotic-effect-the-importance-of-assessing-microbial-response-after-an-initial-antimicrobial-challenge/

Moore RD, Lietman PS, Smith CR. Clinical Response to Aminoglycoside Therapy: Importance of the Ratio of Peak Concentration to Minimal Inhibitory Concentration. *Journal of Infectious Diseases*. 1987;155(1):93-99. doi:https://doi.org/10.1093/infdis/155.1.93
Block M, Blanchard DL. Aminoglycosides. Nih.gov. Published July 17, 2023. https://www.ncbi.nlm.nih.gov/books/NBK541105/?report=printable

ADVOCATE HEALTH

Adverse Effects of Aminoglycosides

- Primary toxicities of aminoglycosides include nephrotoxicity and ototoxicity which are dose and time dependent
  - Neuromuscular blockade has been reported as well
- Ototoxicity can be irreversible
- Nephrotoxicity is typically reversible

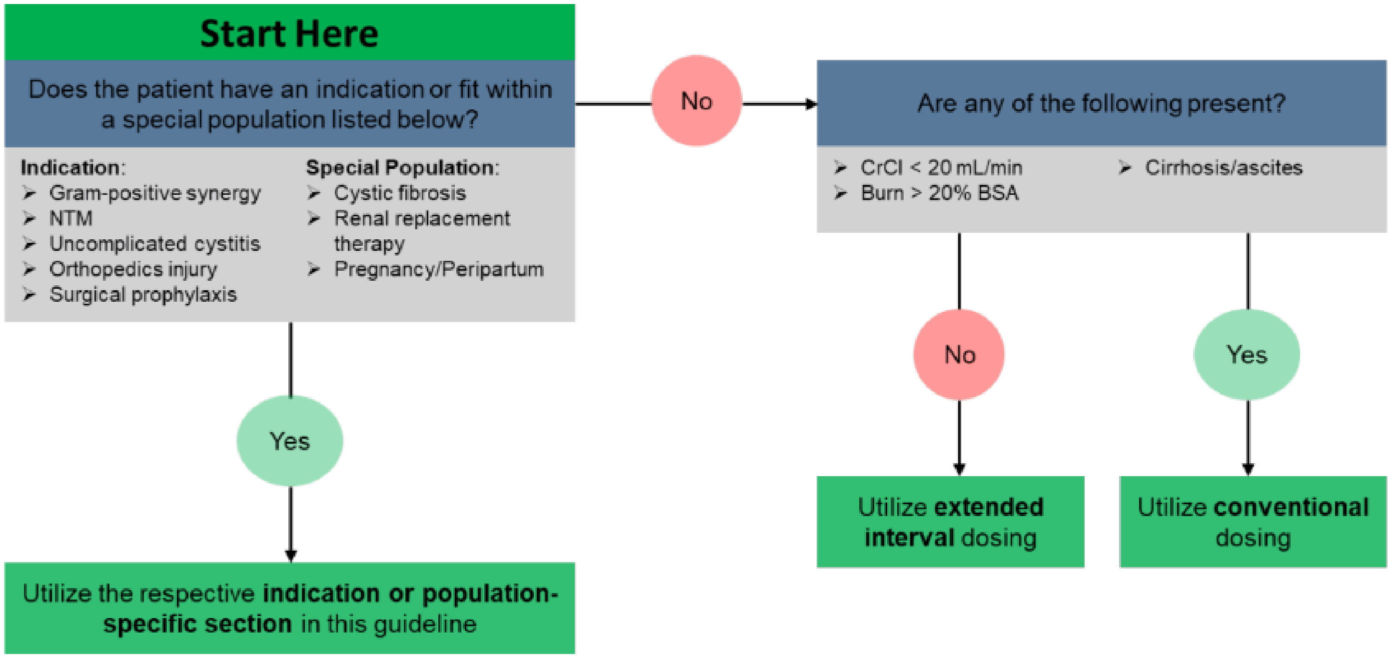
Agent	Ototoxicity		Nephrotoxicity
	Vestibular	Cochlear	
Gentamicin	++	+	++
Tobramycin	+±	+	+
Amikacin	+	++	++

ADVOCATEHEALTH

Block M, Blanchard DL. Aminoglycosides. Nih.gov. Published July 17, 2023. https://www.ncbi.nlm.nih.gov/books/NBK541105/?report=printable

Dosing Strategies

A. Aminoglycoside Dosing Method Algorithm



“Enterprise Adult Aminoglycoside Dosing & Monitoring Guidelines” Advocate Healthcare Internal Documentation. February 2025

Extended vs Conventional

- Conventional uses classical ideas of drug dosing: multiple times a day with intervals based on renal function
  - Q8hr, Q12hr, and Q24hr dosing intervals

- Extended interval dosing maximizes peak to MIC ratios to improve efficacy while minimizing toxicity
  - Q24hr, Q36hr, and Q48hr dosing intervals
  - Hartford nomogram to evaluate levels
  - Goal peak concentrations of 8 to 10 times the MIC with undetectable troughs

Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. *Antimicrobial Agents and Chemotherapy*. 1995;39(3):650-655. doi:https://doi.org/10.1128/aac.39.3.650

Hartford Nomogram

- Nomogram developed by Hartford Hospital to monitor extended interval regimens in the early 1990s
- Formulated using simulated population pharmacokinetics and collected concentration versus time data
- Collect level at ~10 hours and plot on the nomogram

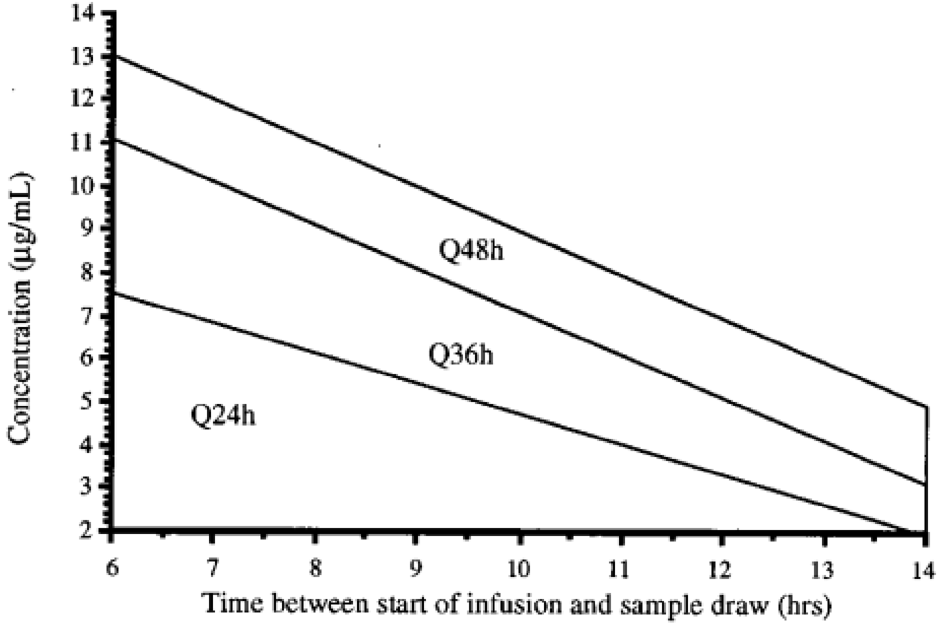


FIG. 1. ODA nomogram for gentamicin and tobramycin at 7 mg/kg.

Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. *Antimicrobial Agents and Chemotherapy*. 1995;39(3):650-655. doi:https://doi.org/10.1128/aac.39.3.650

Hartford Nomogram Limitations

- Patients with highly variable or altered kinetics were excluded from the original Hartford nomogram validation study
    - Ex: pediatrics, burn, cirrhosis, dialysis patients
- While at least one study has validated the nomogram in other populations (trauma[1]), further studies are limited
- Critical care populations have been identified as an area where individualized regimens can be superior[2,3]
    - MIC of ≥2

Finnell DL, Davis GA, Cropp CD, Ensom MH. Validation of the Hartford nomogram in trauma surgery patients. *The Annals of Pharmacotherapy*. 1998;32(4):417-421. doi:https://doi.org/10.1345/aph.17243
Wallace AW, Jones M, Bertino JS. Evaluation of Four Once-Daily Aminoglycoside Dosing Nomograms. *Pharmacotherapy*. 2002;22(9):1077-1083. doi:https://doi.org/10.1592/phco.22.13.1077.33529
He S, Cheng Z, Xie F. Pharmacokinetic/pharmacodynamic-guided gentamicin dosing in critically ill patients: a revisit of the Hartford nomogram. *International Journal of Antimicrobial Agents*. 2022;59(6):106600. doi:https://doi.org/10.1016/j.ijantimicag.2022.106600

ADVOCATE HEALTH

Individualized PK Monitoring

- When drug levels can be collected, individualized dosing regimens are thought to reduce toxicity[1]
- Based around two-point kinetics and calculating patient specific kinetic parameters
  - Elimination constants
  - Half-lives
  - Volumes of distribution
- These can be used to better inform dosing decisions

Wallace AW, Jones M, Bertino JS. Evaluation of Four Once-Daily Aminoglycoside Dosing Nomograms. *Pharmacotherapy.* 2002;22(9):1077-1083. doi:https://doi.org/10.1592/phco.22.13.1077.33529

Example Walk through

- JW is a 49-year-old female being treated with amikacin for a pulmonary MAC infection
- After her first dose of Amikacin 1000mg (15mg/kg), we collect a peak and a trough
    - Peak = 19 mcg/mL drawn at 1.5 hours, Trough = 3 mcg/mL drawn at 9 hours
- We can use these values to calculate her elimination rate constant and then a true peak and compare it to our desired peak

Table 9. Amikacin Dosing Methods for NTM[3]

Dosing Strategy	Creatinine Clearance	Recommended Initial Dose	Expected/Goal Peak[2]	Goal Trough
Daily Dosing[1]	≥ 60 mL/min	Age < 50y: 10-15 mg/kg q24h Age ≥ 50y: 10-12 mg/kg q24h	35-45 mcg/mL	< 5 mcg/mL
	40-59 mL/min	10-12 mg/kg q36h		
	20-39 mL/min	10-12 mg/kg q48h		

“Enterprise Adult Aminoglycoside Dosing & Monitoring Guidelines” Advocate Healthcare Internal Documentation. February 2025

Example Walk through

Definitions:
T = dosing interval (hr)
t' = infusion duration (hr)
t''= time since completion of infusion when C1 drawn (hr)
C1 = first level drawn off dose: higher level (mcg/mL)
C2 = second level drawn off dose: lower level (mcg/mL)
Δt = the time difference between C1 and C2 (hr)

- $Ke = \frac{\ln C1 - \ln C2}{\Delta t}$ ➡ $= \frac{\ln(19) - \ln(3)}{7.5} = 0.3025$
- $C\ max = \frac{C1}{e^{-Ke\,(t'')}}$ ➡ $= \frac{19}{e^{-0.3025\,(1.5)}} = 29.9$
- We see that our true peak is lower than what we want (35-45)
  - Now we can calculate a volume of distribution and new maintenance dose

Example Walk through

Definitions:
τ = dosing interval (hr)
t' = infusion duration (hr)
t"= time since completion of infusion when C1 drawn (hr)
C1 = first level drawn off dose: higher level (mcg/mL)
C2 = second level drawn off dose: lower level (mcg/mL)
Δt = the time difference between C1 and C2 (hr)

- $V_d = \frac{Dose}{True\ Cmax}$ → $V_d = \frac{1000}{29.9} = 33.44L$
- Now we can calculate our new maintenance dose
- $MD = \frac{C_{\max(desired)} * K_e * V_d * [1 - e^{(-K_e * \tau)}] * t'}{[1 - e^{(-K_e * t')}]}$
- $MD = \frac{40 * 0.3025 * 33.445 * [1 - e^{(-0.3025 * 24)}] * 1}{[1 - e^{(-0.3025 * 1)}]} = 1549$
- We can now consider increasing our maintenance dose to 1500mg daily

Assessment Question - AG

GM is a 55-year-old male being treated for VAP with Gentamicin 7mg/kg. A level is drawn at 10 hours and comes back at **6 mcg/mL**. What would be the recommended dosing interval to use based on the Hartford nomogram?

A. Every 24 hours
B. Every 36 hours
C. Every 48 hours
D. Convert to conventional dosing

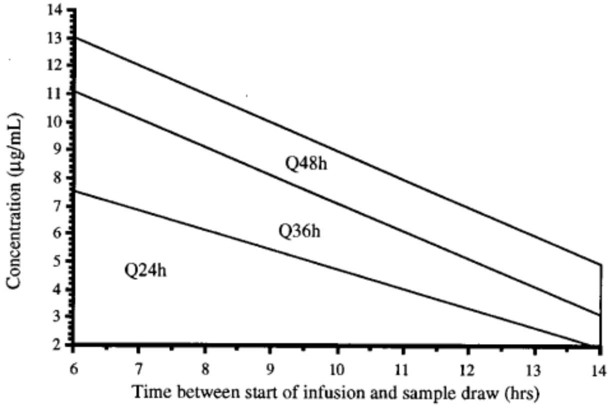


FIG. 1. ODA nomogram for gentamicin and tobramycin at 7 mg/kg.

ADVOCATE HEALTH

Pearls

Therapeutic Drug Monitoring

- Tacrolimus
- Phenytoin
- Triazole antifungals
- Albumin

Tacrolimus

- Mechanism:
    - Immunosuppression via inhibition of T-cell activation/proliferation. Achieved by binding to intracellular FKBP and blocking calcineurin.
- Narrow therapeutic index requiring therapeutic drug monitoring
- Variable trough goals
    - Dependent on type of organ transplant, and time from transplant
    - Typically 5 - 12 mcg/mL

ADVOCATE HEALTH

Henkel L, Jehn U, Thölking G and Reuter S (2023) Tacrolimus—why pharmacokinetics matter in the clinic.
Front. Transplant. 2:1160752. doi: 10.3389/frtra.2023.1160752/

Tacrolimus

- Absorption:
  - Variable bioavailability based on form, food intake, time of administration, and genetics
- Distribution:
  - Primarily bound to red blood cells through FKBPs
- Metabolism:
  - First-pass metabolism via cytochrome P450 enzymes (CYP3A4 and CYP3A5), and P-glycoprotein (P-gp)
  - Major DDI concerns
- Elimination:
  - T ½ = typically 12 hours
  - Significantly increased half-life in liver impairment or with CYP inhibitors
  - Not removed by hemodialysis

Patel P, Rout P. Tacrolimus. [Updated 2026 Jan 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan. ncbi.nlm.nih.gov/books/NBK544318/
Park SI, Felipe CR, Pinheiro-Machado PG, Garcia R, Tedesco-Silva H Jr, Medina-Pestana JO. Circadian and time-dependent variability in tacrolimus pharmacokinetics. Fundam Clin Pharmacol. 2007;21(2):191-197. doi:10.1111/j.1472-8206.2007.00468.

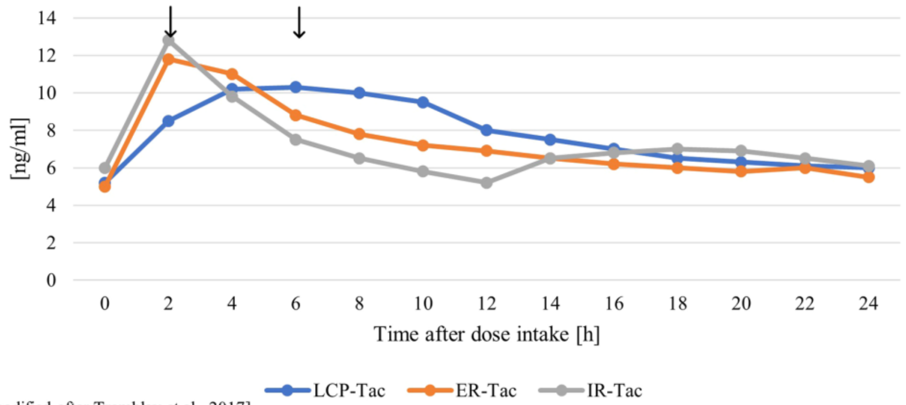
Tacrolimus Pearls

Formulations:

- IR capsules, ER capsules/tablets, oral suspension granules, IV solution, sublingual tablet
- IV form typically avoided due to nephrotoxicity, anaphylaxis risk, cost
- Not interchangeable due to variable PK profiles

Formulations	Conversion Ratio
PO IR capsule to PO solution	1 : 1
PO IR capsule to PO XL capsule	1 : 1
PO IR capsule to PO XR capsule	1 : 0.8
PO IR capsule to SL tablet	2 : 1
PO to IV	4 : 1

(AUC)-normalized mean whole blood concentrations of tacrolimus based on conversion factors of 1:1.08:0.70 IR-Tac:ER-Tac:LCP-Tac



[modified after Tremblay et al., 2017]

ADVOCATE HEALTH

Patel P, Rout P. Tacrolimus. [Updated 2026 Jan 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan. https://www.ncbi.nlm.nih.gov/books/NBK544318/

Tacrolimus Pearls

- Patient factors with influence on dosing:
  - Female patients require higher doses and have a higher risk of experiencing adverse effects
  - African American patients require higher doses
  - Native American patients typically require lower doses

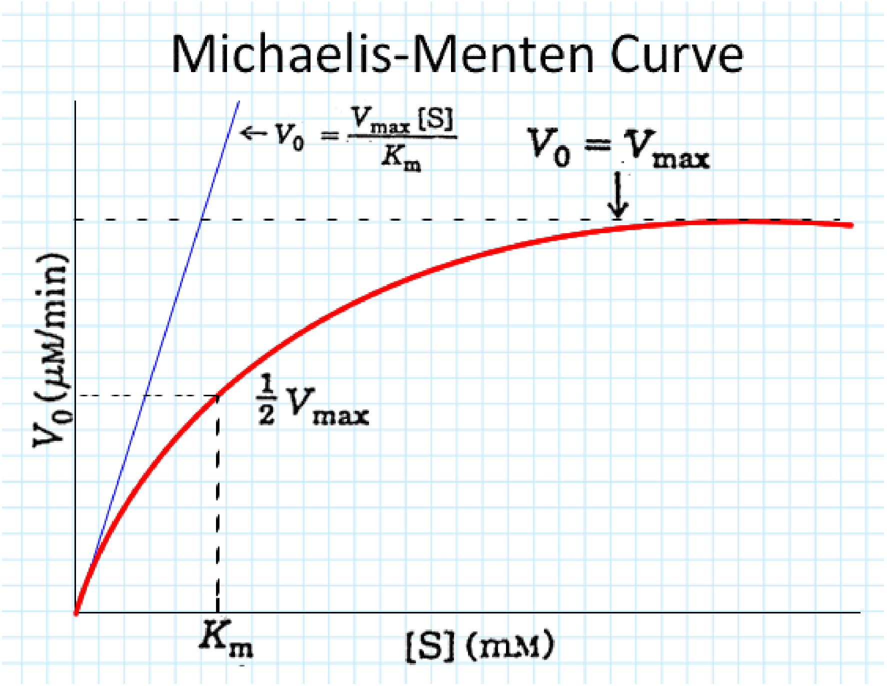
- Post-transplant dosing considerations:
  - Large steroid doses induce CYP3A4 activity

- Elevated levels in HF exacerbation

Patel P, Rout P. Tacrolimus. [Updated 2026 Jan 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK544318/

Phenytoin

- Non-linear kinetics:
  - Follows first-order kinetics at low concentrations
- Free vs bound
  - Impact of albumin
- CYP metabolized, CYP inducer
- Variable T1/2



Rodriguez-Vera L, Yin X, Almoslem M, et al. Comprehensive Physiologically Based Pharmacokinetic Model to Assess Drug-Drug Interactions of Phenytoin. Pharmaceutics. 2023;15(10):2486. Published 2023 Oct 18. doi:10.3390/pharmaceutics15102486
"Team:FSU/Model - 2021.Igem.org." Igem.org, 2021, 2021.igem.org/Team:FSU/Model.

Triazole Antifungals

	Voriconazole	Posaconazole
Absorption	• 96% oral bioavailability • Bioavailability is greatly reduced with food • Must be taken on empty stomach	• Formulation dependent absorption: • Suspension: required high-fat meal or supplement and proper gastric acidity • DR tablet and IV: more consistent absorption
Distribution	• Protein binding: 58% • Extensive tissue penetration (CNS, lungs) • Large volume of distribution	• Highly protein bound (>98%) • Large volume of distribution
Metabolism	• Hepatic: primarily CYP2C19, CYP2C9, CYP3A4 • Nonlinear kinetics (Michaelis-Menten)	• Primarily glucuronidation (UGT1A4) • Minimal CYP metabolism
Elimination	• Less than 2% unchanged drug in urine	• Mostly fecal
TDM	• Treatment goal: indication specific (typically trough 1-5 mcg/mL)	• Prophylaxis: > 0.7 mg/L • Treatment: > 1 – 1.25 mg/L

Sienkiewicz BM, Łapiński Ł, Wiela-Hojeńska A. Comparison of clinical pharmacology of voriconazole and posaconazole. Contemp Oncol (Pozn). 2016;20(5):365-373. doi:10.5114/wo.2016.64594

Albumin

- Primary plasma binding protein for a wide range of drugs
- Hypoalbuminemia (< 2.5 g/dL) is common in the critically ill population
- Low albumin = more free (unbound) drug concentration fraction
- Total drug levels may lead to clinical misinterpretation
- Clinical risks: altered clearance, toxicity, and/or therapeutic failure

Idasiak-Piechocka, Ilona, et al. "Effect of Hypoalbuminemia on Drug Pharmacokinetics." Frontiers in Pharmacology, vol. 16, 20 Feb. 2025, https://doi.org/10.3389/fphar.2025.1546465.
Heffernan AJ,Sime FB, Kumta N, Wallis SC, McWhinney B, Ungerer J,Wong G, Joynt GM, Lipman J, Roberts JA,2022. Multicenter Population Pharmacokinetic Study of Unbound Ceftriaxone in Critically Ill Patients. Antimicrob Agents Chemother66:e02189-21.https://doi.org/10.1128/aac.02189-21

Albumin Impact on Antibiotics

- Ceftriaxone:
  - ~85–95% protein bound
  - Levels not routinely collected
  - Reduced albumin levels are associated with a lower probability of achieving target attainment
  - A 1 g/dL reduction in albumin reduces probability of achieving the target by up to 20%

Idasiak-Piechocka, Ilona, et al. “Effect of Hypoalbuminemia on Drug Pharmacokinetics.” Frontiers in Pharmacology, vol. 16, 20 Feb. 2025, https://doi.org/10.3389/fphar.2025.1546465.
Heffernan AJ,Sime FB, Kumta N, Wallis SC, McWhinney B, Ungerer J,Wong G, Joynt GM, Lipman J, Roberts JA,2022. Multicenter Population Pharmacokinetic Study of Unbound Ceftriaxone in Critically Ill Patients. Antimicrob Agents Chemother66:e02189-21.https://doi.org/10.1128/aac.02189-21

Albumin Impact on Warfarin

- 99% protein bound
- Hypoalbuminemia may lead to high INR variance and bleed risk with dose adjustments
- Routine dose decreases in setting of hypoalbuminemia not recommended

ADVOCATE HEALTH

Idasiak-Piechocka, Ilona, et al. “Effect of Hypoalbuminemia on Drug Pharmacokinetics.” Frontiers in Pharmacology, vol. 16, 20 Feb. 2025, https://doi.org/10.3389/fphar.2025.1546465.

Assessment Question - Pearls

Which of the medications discussed today have saturable clearance?

A. Tacrolimus
B. Warfarin
C. Posaconazole
D. Phenytoin and Voriconazole

Summary/Conclusion

- Monte Carlo simulations have many useful applications in pharmacy research and practice
- Vancomycin AUC monitoring requires more resources, but may be beneficial for patients with a serious MRSA infection or an increased risk of AKI
- Utilizing appropriate dosing strategies and calculations can help formulate therapeutic regimens for aminoglycosides
- Drugs with variable pharmacokinetic profiles and/or narrow therapeutic indices may benefit from therapeutic drug monitoring and dose adjustments

References

1. Liu J. Post Antibiotic Effect: The Importance of Assessing Microbial Response After an Initial Antimicrobial Challenge - Emery Pharma. Emery Pharma. Published March 20, 2025. https://emerypharma.com/blog/post-antibiotic-effect-the-importance-of-assessing-microbial-response-after-an-initial-antimicrobial-challenge/

2. Moore RD, Lietman PS, Smith CR. Clinical Response to Aminoglycoside Therapy: Importance of the Ratio of Peak Concentration to Minimal Inhibitory Concentration. *Journal of Infectious Diseases*. 1987;155(1):93-99. doi:https://doi.org/10.1093/infdis/155.1.93

3. Block M, Blanchard DL. Aminoglycosides. PubMed. Published July 19, 2022. https://www.ncbi.nlm.nih.gov/books/NBK541105/

4. Susa ST, Preuss CV, Hussain A. Drug Metabolism. Nih.gov. Published August 17, 2023. https://www.ncbi.nlm.nih.gov/books/NBK442023/

5. Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. *Antimicrobial Agents and Chemotherapy*. 1995;39(3):650-655. doi:https://doi.org/10.1128/aac.39.3.650

6. Morales Castro D, Dresser L, Granton J, Fan E. Pharmacokinetic alterations associated with critical Illness. *Clinical Pharmacokinetics*. 2023;62(2):209-220. doi:https://doi.org/10.1007/s40262-023-01213-x

7. Porter RS. *The Merck Manual of Diagnosis and Therapy.* 20th ed. Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc; 2018.

8. Lodise TP, Lomaestro BM, Drusano GL. Application of Antimicrobial Pharmacodynamic Concepts into Clinical Practice: Focus on β-Lactam Antibiotics: Insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy*. 2006;26(9):1320-1332. doi:https://doi.org/10.1592/phco.26.9.1320

9. Ngcobo NN. Influence of Ageing on the Pharmacodynamics and Pharmacokinetics of Chronically Administered Medicines in Geriatric Patients: A Review. *Clinical Pharmacokinetics*. 2025;64(1):335-367. doi:https://doi.org/10.1007/s40262-024-01466-0

10. Stark J. *Two Compartment Body Model and v D Terms*.; 2013. https://pharmacy.ufl.edu/files/2013/01/two-compartment-model.pdf

11. Talevi A, Bellera CL. Two-Compartment Pharmacokinetic Model. *The ADME Encyclopedia*. Published online 2022:1167-1174. doi:https://doi.org/10.1007/978-3-030-84860-6_59

12. Pharmaceutical Press. What is pharmacokinetics? Pharmaceutical Press. Published May 2024. https://www.pharmaceuticalpress.com/resources/article/what-is-pharmacokinetics/

References

13. Wallace AW, Jones M, Bertino JS. Evaluation of Four Once-Daily Aminoglycoside Dosing Nomograms. *Pharmacotherapy*. 2002;22(9):1077-1083. doi:https://doi.org/10.1592/phco.22.13.1077.33529

14. He S, Cheng Z, Xie F. Pharmacokinetic/pharmacodynamic-guided gentamicin dosing in critically ill patients: a revisit of the Hartford nomogram. *International Journal of Antimicrobial Agents*. 2022;59(6):106600. doi:https://doi.org/10.1016/j.ijantimicag.2022.106600

15. Gilani B, Cassagnol M. Biochemistry, cytochrome P450. PubMed. Published April 24, 2023. https://www.ncbi.nlm.nih.gov/books/NBK557698/

16. Prasad V, Makary MA. One Pivotal Trial, the New Default Option for FDA Approval — Ending the Two-Trial Dogma. *New England Journal of Medicine*. 2026;394(8):815-817. doi:https://doi.org/10.1056/nejmsb2517623

17. Alagga AA, Gupta V, Pellegrini MV. Drug Absorption. PubMed. Published February 27, 2024. https://www.ncbi.nlm.nih.gov/books/NBK557405/

18. Onetto AJ, Sharif S. Drug distribution. PubMed. Published June 26, 2023. https://www.ncbi.nlm.nih.gov/books/NBK567736/

19. Tsvetelina Velikova, Niya Mileva, Naseva EK. Method “Monte Carlo” in Healthcare. *World Journal of Methodology*. 2024;14(3):93930. doi:https://doi.org/10.5662/wjm.v14.i3.93930

20. Toropova MA. Drug Metabolism as an Object of Computational Analysis by the Monte Carlo Method. *Current Drug Metabolism*. 2018;18(12):1123-1131. doi:https://doi.org/10.2174/1389200218666171010124733

21. Finnell DL, Davis GA, Cropp CD, Ensom MH. Validation of the Hartford nomogram in trauma surgery patients. *The Annals of Pharmacotherapy*. 1998;32(4):417-421. doi:https://doi.org/10.1345/aph.17243

22. Le, J. (2024). *Drug Excretion*. In **The Merck Manual of diagnosis and therapy** (Section 22: Administration and kinetics of drugs). Merck Sharp & Dohme. https://www.merckmanuals.com/home/drugs/administration-and-kinetics-of-drugs/drug-elimination

23. “What Is Monte Carlo Simulation?” GeeksforGeeks, 17 July 2025, www.geeksforgeeks.org/artificial-intelligence/what-is-monte-carlo-simulation/.

24. “Enterprise Adult Aminoglycoside Dosing & Monitoring Guidelines” Advocate Healthcare Internal Documentation. February 202

ADVOCATE HEALTH

References

25. Patel, Shivali, et al. "Vancomycin." National Library of Medicine, StatPearls Publishing, 29 Oct. 2024, www.ncbi.nlm.nih.gov/books/NBK459263/.

26. Loll, Patrick. "PDB101: Global Health: Antimicrobial Resistance: Undefined: Vancomycin." RCSB: PDB-101, 2016, pdb101.rcsb.org/global-health/antimicrobial-resistance/drugs/antibiotics/cell-wall-biosynthesis/transpeptidase-substrate/glycopeptide-antibiotics/vancomycin/vancomycin.

27. Tharp, Rick. "PK/PD Approach to Antibiotic Therapy Review." Www.rxkinetics.com, www.rxkinetics.com/antibiotic_pk_pd.html.

28. Rybak, Michael J, et al. "Therapeutic Monitoring of Vancomycin for Serious Methicillin-Resistant Staphylococcus Aureus Infections: A Revised Consensus Guideline and Review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists." American Journal of Health-System Pharmacy, vol. 77, no. 11, 19 Mar. 2020, https://doi.org/10.1093/ajhp/zxaa036.

29. Abdelmessih, Emily, et al. "Vancomycin Area under the Curve versus Trough Only Guided Dosing and the Risk of Acute Kidney Injury: Systematic Review and Meta-Analysis." Pharmacotherapy, vol. 42, no. 9, 5 Aug. 2022, pp. 741–753, https://doi.org/10.1002/phar.2722.

30. Lim AS, Seng JJB, Ng TTM, Chng HT, Han Z. 1097. A Comparison of Area-Under Curve (AUC)-Guided vs Trough-Guided Monitoring of Vancomycin and Its Impact on Nephrotoxicity: A SystematicReview and Meta-analysis. *Open Forum Infect Dis*. 2021;8(Suppl 1):S640-S641. Published 2021 Dec 4. doi:10.1093/ofid/ofab466.1291

31. Henkel L, Jehn U, Thölking G and Reuter S (2023) Tacrolimus—why pharmacokinetics matter in the clinic. Front. Transplant. 2:1160752. doi:10.3389/frtra.2023.1160752

32. Patel P, Rout P. Tacrolimus. [Updated 2026 Jan 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK544318/

33. Park SI, Felipe CR, Pinheiro-Machado PG, Garcia R, Tedesco-Silva H Jr, Medina-Pestana JO. Circadian and time-dependent variability in tacrolimus pharmacokinetics. Fundam Clin Pharmacol. 2007;21(2):191-197. doi:10.1111/j.1472-8206.2007.00468.

34. Rodriguez-Vera L, Yin X, Almoslem M, et al. Comprehensive Physiologically Based Pharmacokinetic Model to Assess Drug-Drug Interactions ofPhenytoin. Pharmaceutics. 2023;15(10):2486. Published 2023 Oct 18. doi:10.3390/pharmaceutics15102486

35. "Team:FSU/Model - 2021.Igem.org." Igem.org, 2021, 2021.igem.org/Team:FSU/Model.

36. Sienkiewicz BM, Łapiński Ł, Wiela-Hojeńska A. Comparison of clinical pharmacology of voriconazole and posaconazole. Contemp Oncol (Pozn).2016;20(5):365-373. doi:10.5114/wo.2016.64594

Questions?

Jeremy Theis
Jeremy.theis@aah.org

Alex Heringer
Alexander.heringer@aah.org