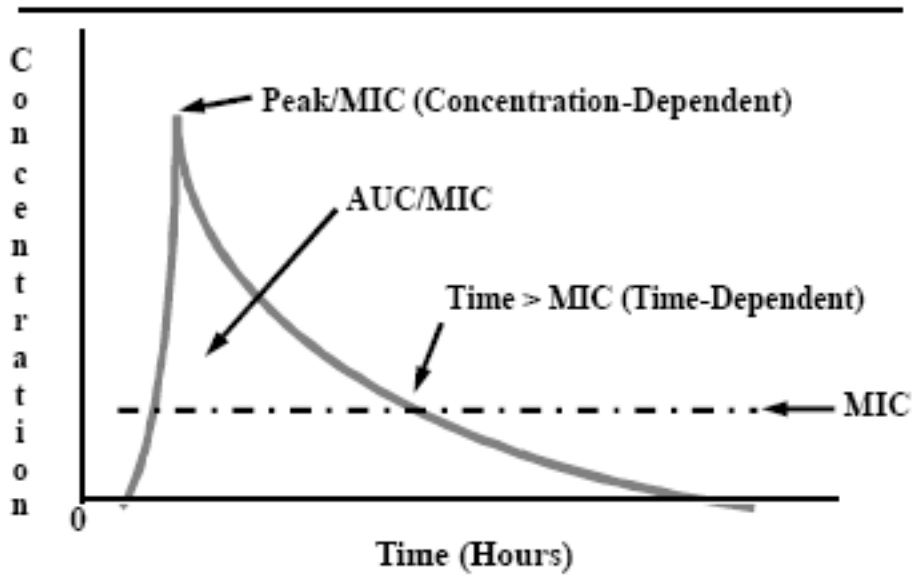
Antibiotic Pharmacokinetic Monitoring
Sandeep Devabhakthuni, PharmD, BCPS, Last updated: May 2011

What is the difference between concentration-dependent killing and time-dependent killing?

Certain classes of antibiotics like aminoglycosides and fluoroquinolones eradicate bacteria by achieving high concentrations at the binding site. This concept is called concentration-dependent killing, and the pharmacodynamics parameter can be simplified as peak/Minimum Inhibitory Concentration (MIC) ratio (Figure 1).[1,2] The best responses occur when the concentrations are ≥ 10 times above the MIC for their target organism at the site of infection. For classes of antibiotics that demonstrate time-dependent killing (e.g., beta-lactams [penicillins, cephalosporings, carbapenems, monobactams], clindamycin, and linezolid), the optimal response occurs when the time that the drug remains above the MIC is ≥ 50% of the dosing interval (Figure 1). [1,2]

Figure 1. Pharmacokinetic and Pharmacodynamic Parameters for Antibiotic Efficacy[1]



Vancomycin

What is the best pharmacodynamic parameter to optimize bacterial killing for vancomycin?

Vancomycin is a tricyclic glycopeptide that inhibits bacterial cell wall synthesis. It is considered to be bactericidal against most Gram-positive organisms, except *Enterococcus* species. Vancomycin has bot time-dependent killing and moderate persistent effects that is dependent on concentration (i.e., peak). Persistent effects include the Post-Antibiotic Effect (PAE), which is the persistent suppression of bacterial growth following antibiotic exposure. The ideal dosing regimen is to maximize the amount of drug received. Thus, the appropriate pharmacodynamics parameter that correlates with efficacy is the 24H-Area Under the Curve (AUC)/MIC ratio. [2,3]

How should vancomycin be dosed?

1) Dosing weight: actual body weight unless morbidly obese (use adjusted body weight instead)
2) Loading dose (if appropriate): 25-30 mg/kg (one-time dose)
   a) Use: seriously ill patients (e.g., requiring intensive care) and patients with complicated infections (e.g., bacteremia or pneumonia).
3) Initial or maintenance dose[4]: 15-20 mg/kg
4) Dosing interval: (Table 1)
   a) Determine creatinine clearance (based on Cockroft-Gault equation)

Table 1. Vancomycin Dosing Interval Based on Renal Clearance[4]

Creatinine Clearance (mL/min)	Dosing Interval (hours)
> 75	Q8-12H
50-74	Q12H
35-50	Q24H
25-34	Q48H
< 25	Dose by daily level
Intermittent Hemodialysis	Dose after dialysis
CRRT	Q24H

CRRT, continuous renal replacement therapy

When should vancomycin monitoring be performed?

Peak serum concentration is not necessary because it does not correlate well with vancomycin toxicity (e.g., nephrotoxicity or ototoxicity). Only the trough concentration monitoring is needed in order to assess efficacy. For patients with normal renal function, it takes approximately 4 doses for vancomycin to reach steady state. As such, trough concentrations should be drawn before the 4th dose. Trough concentrations may be drawn earlier in critically ill patients, patients with unstable renal function, and patients on vancomycin dosing interval ≥ 24 hours. However, these trough concentrations must be interpreted with caution since additional doses will continue to accumulate until steady state is reached. Trough concentrations should be drawn right before the next dose (within 2 hours prior to administration). If vancomycin is being dosed by level (patients with creatinine clearance < 25 mL/min, hemodialysis, or CRRT), it should be redosed if the level is < 20 mg/L.[4]

Once the target trough concentration has been achieved, routine monitoring on a weekly basis at minimum is recommended for patients with stable renal function. For patients with unstable renal function, hemodynamically compromised or at risk for nephrotoxicity, monitoring should be at least 2-3 times weekly.

What trough concentrations should I target?

The target trough concentration is dependent on the type of infection as reported in Table 2.[5]

Table 2. Vancomycin Target Trough Monitoring[5]

Type of Infection	Target Trough Concentration
Soft and skin tissue infections, abscess, cellulitis **(MIC < 1 mg/L)**	10-15 mg/L
Soft and skin tissue infections, abscess, cellulitis **(MIC > 1 mg/L)**	15-20 mg/L
Complicated infections (endocarditis, osteomyelitis, bacteremia, prosthetic joint infection, or pneumonia)	15-20 mg/L
Infections involving central nervous system (meningitis)	20-25 mg/L

Aminoglycosides

What is the best pharmacodynamic parameter to optimize bacterial killing for aminoglycosides?

Aminoglycosides fight against bacteria by interfering with bacterial protein synthesis, which is achieved through irreversible binding to 30S ribosomal subunit. Aminoglycosides have bactericidal activity against aerobic Gram-negative infections and demonstrates concentration-dependent killing with a prolonged PAE (~4-6 hours). The best pharmacodynamics parameter to determine the ideal dosing regimen is peak/MIC ratio.[1,2]

How should aminoglycoside dosing be approached?

1) Dosing weight:[6] ideal body weight (IBW) unless 20% over IBW (use adjusted body weight instead)
2) Initial dosing:[6,7] dependent on traditional versus extended interval dosing
   a) Extended interval dosing in all patients
      i) Rationale: maximize concentration-dependent killing and minimize toxicity (i.e., nephrotoxicity and ototoxicity), ease of administration and monitoring, reductions in administration and monitoring-related costs.
      ii) Exceptions: patients with altered pharmacokinetics: burns > 20%, morbidly obese, pregnancy, ascites or significant third spacing, hemodynamic instability, unstable renal function, or cystic fibrosis; patients being treated for Gram-positive synergy.
         - Use traditional dosing instead
   b) See Table 3 for initial dosing recommendations
3) Dosing interval:[6,7] (Table 4)
   a) Determine creatinine clearance (Cockroft-Gault equation)

Table 3. Aminoglycoside Initial Dosing Recommendations[6,7]

Site of Infection or Indication	Gram-positive infections (synergy)	Gram-negative infections (sepsis/pneumonia)
Gentamicin/Tobramycin		
Traditional initial dose	**1 mg/kg/dose**	**1.5-2 mg/kg/dose**
Desired peak	3-5 mg/L	8-10 mg/L (10-12 times MIC of infecting organism)
Desired trough	< 1 mg/L	< 2 mg/L
Extended interval dose	NA	**7 mg/kg/dose**
Desired peak	NA	10-12 times MIC of infecting organisms
Desired trough	NA	< 1 mg/L
Amikacin		
Traditional initial dose	NA	**7.5 mg/kg/dose**
Desired peak	NA	30-40 mg/L
Desired trough	NA	< 7 mg/L
Extended interval dose	NA	**15 mg/kg/dose**
Desired peak	NA	10-12 times MIC of infecting organisms
Desired trough	NA	< 7 mg/L

NA, not applicable

Table 4. Aminoglycoside Dosing Interval Based on Renal Clearance[6,7]

Creatinine Clearance (mL/min)	Traditional/Synergy Dosing Interval (hours)	Extended Dosing Interval (hours)
> 60	Q8H	Q24H
40-60	Q12H	Single dose
< 40	Individualized	Single dose

When should aminoglycoside monitoring be performed?

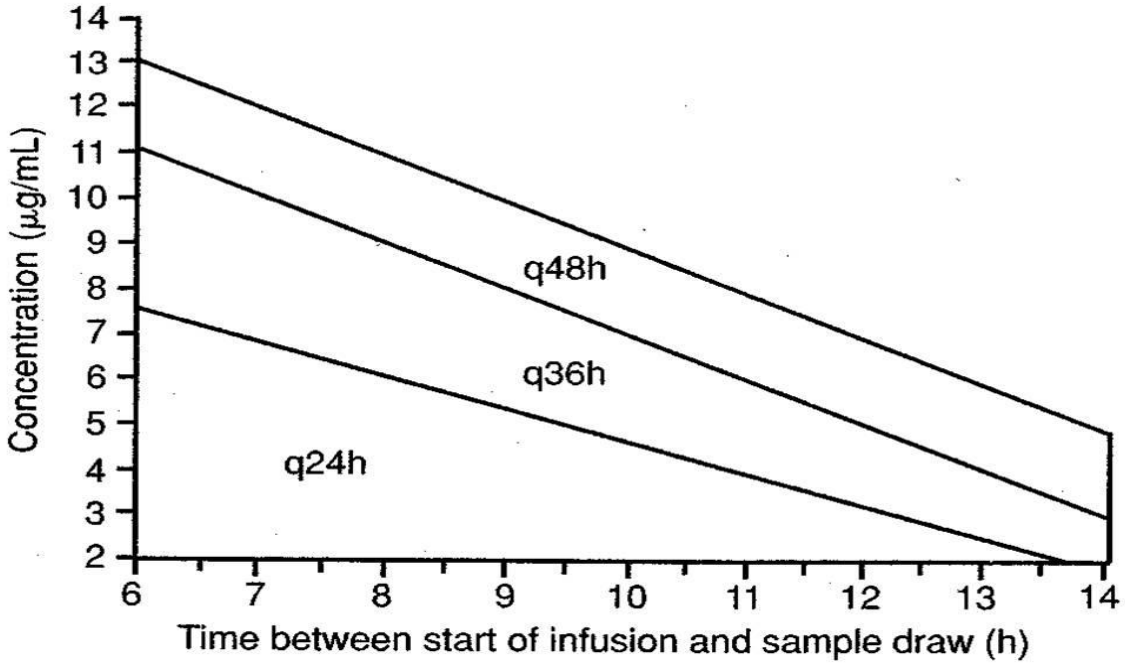
Traditional Dosing:[6]

1) Obtain serum peak and trough concentrations after 3rd dose following initiation of therapy and any dosing adjustments in therapy.
2) Draw trough concentration just prior to next dose.
3) Draw peak concentration 30-45 minutes after the end of an intravenous infusion.
4) Once achieved, monitor periodically (e.g., 2-3 times weekly) throughout therapy wit changes in renal function.
5) If stable renal function, monitor at least once weekly.

Extended Interval Dosing:[7]

1) Random serum concentration monitoring approximately 6-12 hours after 1st dose.
2) Interpret by using an established nomogram (Figure 2) or based on MIC data. For amikacin therapy, divide serum concentration by 2 before using nomogram.
3) Monitor periodically if unstable renal function or prolonged therapy (> 7-10 days).

Figure 2. Hartford nomogram (based on 7 mg/kg dosing)[7]



References

1. Quintiliani R. Using pharmacodynamics and pharmacokinetics concepts to optimize treatment of infectious diseases. *Infect Med.* 2004; 21: 219-32.
2. McKinnon PS, Davis SL. Pharmacokinetic and pharmacodynamics issues in the treatment of bacterial infectious diseases. *Eur J Clin Microbiol Infect Dis.* 2004. 23: 271-88.
3. Rodvold KA. Pharmacodynamics of anti-infective therapy: taking what we know to the patient's bedside. *Pharmacotherapy*; 2001; 21: 319S-330S.
4. Matzke GR, Zhanel GG, Guay DR. Clinical pharmacokinetics of vancomycin. *Clin Pharmacokinet*.1986; 11:257-82.
5. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2009; 66: 82-98.
6. Murphy JE, editor. Clinical Pharmacokinetics, Bethesda, MD: American Society of Health-System Pharmacists; 1993.
7. Nicolau DP, Freeman CD, Belliveau PP, et al. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. *Antimicrob Agents Chemother*. 1995; 39: 650-55.

Please direct any questions or feedback regarding this resource to newpractitioners@ashp.org. We appreciate your comments, feedback and suggestions as we strive to capture issues and challenges affecting New Practitioners.