Pharmacokinetic Training Packet for Pharmacists

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Pharmacokinetic Definitions and Principles

Kel, Ke, or Kd or Elimination Rate Constant
- The fraction or percentage of the total amount of drug in the body eliminated per unit of time.[1]
- Estimated with 2 drug levels taken between doses (the slope of the line). To be accurate, 2-4 half-lives should occur between the levels.[1]
- In pharmacokinetic calculations, the term $e^{-kel(\tau)}$ represents the fraction of the serum concentration that remains. Thus, $1 - e^{-kel(\tau)}$ represents the fraction of the serum concentration that is eliminated.

t $_{1/2}$ or Half-life
- The time required for the TOTAL amount of remaining drug in the body to decline by 50%.[1]
- Sometimes referred to as β t $_{1/2}$ to distinguish it from the distribution half-life, α t $_{1/2}$, used in two compartment modeling.[1]

Peak, C max[1]
- C max is the maximum measurable drug concentration at the end of an infusion BEFORE significant distribution occurs.

- The peak is the measured drug concentration AFTER distribution.

Vd or Volume of Distribution[1]
- The volume of distribution is the theoretical size of the compartment necessary to account for the total drug amount in the body if it were present throughout the body in the same concentration found in the plasma.
- Factors that may affect the volume of distribution include: protein binding, hydration, lean body mass, third spacing, burns, nutrition, fever, sepsis, disease states, drug-drug interactions, etc.

Creatinine Clearance – CrCl
- The renal glomerular filtration rate (GFR) is estimated by determining the CrCl.[2]

- Examination of the Cockcroft-Gault equation reveals that serum creatinine values less than 1 mg/dl will elevate the calculated creatinine clearance. This is especially true for elderly patients, malnourished patients, and spinal cord injury patients. These populations have reduced muscle mass as a fraction of total body weight and so may generate less creatinine. Caution should be used when interpreting values resulting from the Cockcroft-Gault equation in these patients, but it is not routinely recommended to round Scr values up in the elderly.

Aminoglycoside Overview

Background

The aminoglycoside antibiotics used systemically are gentamicin, tobramycin, amikacin, streptomycin, and plazomicin. Neomycin and kanamycin remain available for local applications. They are rapidly bactericidal and with less 30% of drug bound to plasma proteins. The primary intracellular site of action of aminoglycosides is the 30S ribosomal subunit. Aminoglycosides disrupt the normal cycle of ribosomal function by interfering with the first step of protein synthesis.[4]

Aminoglycosides are concentration-dependent antibiotics for Gram-negative organisms, meaning that as aminoglycoside concentration increases, the rate and extent of bacterial killing increases. Bacterial killing is thought to occur in a biphasic fashion. Initially, bacteria are killed at an extremely rapid pace in a concentration-dependent fashion. After approximately two hours and a 3 log kill (99.99% killing), the rate of bacterial killing slows. This phenomenon is thought to be due to adaptive resistance or through a down regulation of aminoglycoside transport into the bacteria through energy dependent transport processes. The post antibiotic effect (PAE) is a period of time when sub-inhibitory concentrations of antibiotics can still prevent regrowth of bacteria. This is generally thought to increase with higher doses of concentration dependent antibiotics, being up to 8 hours with extended interval dosing of aminoglycosides.

Traditionally, investigators have suggested optimizing the aminoglycoside peak serum concentration to bacterial MIC ratio (Peak/MIC) to a value ≥ 10:1, and this is the pharmacodynamic target typically utilized today. However, there is growing evidence to support utilizing area under the plasma concentration-time curve (AUC) to MIC ratio (AUC/MIC) as the preferred pharmacodynamic parameter predicting efficacy.[7-10] In studies of aminoglycosides in neutropenic mouse thigh and lung infection models, AUC_{0-24}/MIC has been found to be the parameter most strongly correlated with microbiologic efficacy.[8-9] Data from these studies demonstrated that an AUC/MIC of ~30-50 mg•hr/L may be necessary for bacterial stasis, and an AUC/MIC of ~80-100 mg•hr/L may be necessary for 1-2 log_{10} bacterial killing.[8-9] Clinical studies have also demonstrated the value of AUC/MIC in predicting therapeutic efficacy.[11-12] In a retrospective study of ICU patients receiving tobramycin monotherapy for lower respiratory or intra-abdominal infections, Smith and colleagues found that AUC_{24}/MIC was associated with clinical efficacy, and suggested a target ratio of ≥110 mg•hr/L to achieve an 80% rate of clinical cure (vs 47% for AUC_{24}/MIC < 110 mg•hr/L).[11] In another study of patients with cystic fibrosis receiving combination therapy with ticarcillin and tobramycin for infectious pulmonary exacerbation due to *Pseudomonas aeruginosa*, Mouton and colleagues found that AUC/MIC, which was corrected for protein binding, was the pharmacodynamic parameter most strongly correlated with therapeutic effect on forced expiratory volume (FEV_1). In this study, the suggested target for AUC for free drug/MIC was ~50 mg•hr/L for maximum clinical efficacy.[12] Utilizing AUC over Cmax for therapeutic drug monitoring of aminoglycosides may also have practical advantages, as AUC reflects cumulative exposure over the dosing interval rather than exposure at a single time point and is less sensitive to alterations in sample collection times, allowing for more precise estimations of drug exposure.[7,9]

Target AUC/MIC varies in the literature, as illustrated by the studies by Smith and Mouton discussed above, as well as the neutropenic mouse model data.[8-9, 11-12] Based on current data, it has been suggested that an AUC/MIC of 30-50 mg•hr/L may be adequate for treating less severe infections, such as urinary tract infections, in non-critically ill, immunocompetent patients or in patients receiving combination gram-negative therapy and that an AUC/MIC of 80-100 may be needed for more severe infections, such as pneumonia, in critically-ill patients and patients being treated with aminoglycoside monotherapy.[7] Though AUC/MIC-based monitoring for aminoglycoside therapy has not yet been widely adopted in the US, the South Australian Expert Advisory Group on Antimicrobial Resistance (SAAGAR) guidelines on the use and monitoring of aminoglycosides recommend this approach with a suggested AUC_{24}/MIC goal of 80-100 mg•hr/L.[13] Of note, literature regarding the use of AUC/MIC for aminoglycoside dosing and monitoring has been largely in relation to the treatment of infections due to gram-negative organisms. It is unknown what the optimal AUC/MIC target would be when utilizing aminoglycosides in combination therapy for synergy against gram-positive organisms.

AUC-guided dosing strategies can be implemented with equation-based, 2-level methods or Bayesian methods utilizing dosing software and 1-2 levels. Bayesian methods are preferred due to increased precision in estimation, flexibility in sampling times, ability to account for changing renal

function, and potential for reduction in number of blood samples drawn.[13-17] Nebraska Medicine currently utilizes InsightRx, a Bayesian software program, for vancomycin dosing and monitoring by AUC. This software can also be utilized for aminoglycoside dosing and monitoring the AUC as well.

Routes of Administration
- IV, IM, topical cream or ointment, and ophthalmic

Pharmacokinetic Parameters

Table 1: Key Parameters for Dosing Aminoglycoside Antibiotics

Typical Doses and Therapeutic Serum Concentrations		
	Conventional dosing[1]	*Once-daily dosing[5,6]*
Gentamicin or Tobramycin	*1.5-2 mg/kg q 8h* Peak 5-8 mcg/mL Trough < 2 mcg/mL	*5-7 mg/kg q 24h* Peak 20-30 mcg/mL Trough - undetectable
Amikacin or Plazomicin	*7.5mg/kg q 12h* Peak 15-40 mcg/mL Trough 5- 10 mcg/mL	*15-20 mg/kg q 24h* Peak 40- 60 mcg/mL Trough <5 mcg/mL
Gentamicin synergy for Gram-positive infections	*Enterococcal infections* 1 mg/kg q 8-12h Peak 3-5 mcg/mL Trough < 1 mcg/mL	*Streptococcal Infections* 3mg/kg q 24h Peak 8-12 mcg/mL Trough < 1 mcg/mL
Volume of distribution[1]	0.25 L/kg (0.1-0.5 L/kg) 0.5 L/kg (children < 5 yrs)	-
Half-life[4]	~2-3 hr – normal renal function 30-60 hr – anephric patients	-

- Absorption[2]
  - Aminoglycosides are highly polar cations and are very poorly absorbed from the intestinal tract.
  - IM – peak concentrations 30-60 minutes post-dose.
  - IV (given over 30-60 minutes) – peak concentrations 30-60 minutes post-infusion.

- Distribution
  - Aminoglycosides are poorly distributed into the CNS.[4]
  - There is negligible binding to plasma albumin.[4]
  - The volume of distribution of aminoglycosides approximates the volume of extracellular fluid. In normal volunteers, this comprises about 20 to 35% of their body weight. However, the percent of body weight attributed to extracellular fluid changes with physiologic conditions. For example, in critically ill septic patients who are fluid overloaded, the apparent volume of distribution may be increased and resulting peak serum concentrations will be decreased. Newborn infants have a large extracellular fluid volume for their weight. Thus, their distribution often approximates 50 percent of their body weight. Obese patients, because of the excess contribution of adipose tissue to the body weight but not to the overall distribution volume, will have a normal value of 10 to 20% of their body weight. In patients with ascites, edema, or other enlarged "third space", the volume of distribution is increased. To estimate the volume of distribution of patients with ascites or edema one approach is to increase the volume of distribution by 1 L for each kg of fluid weight gain.[1]
  Any situation resulting in a distribution volume of > 35% for a patient at lean body weight or > 20% for an obese patient should be thoroughly investigated for both biologic and artifactual causes. Once Vd is determined for a specific patient, it may still change during the course of therapy.
  - Aminoglycosides distribute very poorly into adipose tissue.[1]

- Elimination[4]

- Excreted almost entirely by glomerular filtration
- The t $_{1/2}$ of aminoglycosides is ~2-3 hours with normal renal function
- Aminoglycosides are removed by hemodialysis and, to a lesser extent, by peritoneal dialysis.

Indications and Spectrum of Activity

- Aminoglycosides may be used for a variety of infections but are typically reserved for the treatment multidrug-resistant organisms, including empiric double coverage for Gram-negative infections in critically ill septic patients, and combination therapy with a beta-lactam for Enterococcal endocarditis.

- **Gram-negative Infections** – Aminoglycoside antibiotics are useful for Gram-negative infections. The primary pathogens they are used to treat include:
  Enterobacterales (formerly *Enterobacteriaceae*):
  Escherichia coli
  Proteus spp.
  Enterobacter spp.
  Citrobacter spp.
  Morganella spp.
  Serratia spp. (S. marcescens)
  Klebsiella spp.
  Multidrug-resistant organisms:
  Pseudomonas aeruginosa
  Acinetobacter spp.

  Tobramycin is more potent than gentamicin against *Pseudomonas aeruginosa* (MIC half as much and therefore gentamicin is no longer recommended for systemic infections with Pseudomonas). Amikacin is often held in reserve to treat pathogens resistant to other therapy, including non-tuberculous Mycobacteria. Other aerobic Gram-negative bacteria (*Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Haemophilus influenzae*) are susceptible but are rarely treated with aminoglycosides.

- **Gram-Positive Infections –** Aminoglycosides, in particular gentamicin, can have activity against some Gram-positive pathogens but are not considered primary agents. Low doses are used for synergy to enhance the bactericidal activity of cell wall agents administered concomitantly.

  <u>Enterococci:</u>

  Enterococci are resistant to aminoglycoside monotherapy. However, use of an agent active against the cell wall or membrane such as penicillin G, ampicillin, vancomycin or daptomycin, in combination, will break down the cell wall or membrane, allowing the aminoglycoside to gain access to the 30S ribosomal subunit. Generally, the combination of a beta-lactam antibiotic or vancomycin with either gentamicin or streptomycin is considered to be synergistic in killing the bacterial organism. If aminoglycosides are to be used, current recommendations suggest peak gentamicin concentrations of 3 to 5 mcg/mL for gentamicin and 20 mcg/mL for streptomycin. However, these goals are based on expert opinion. For enterococcal infections, traditional synergy dosing of 1mg/kg q 8-12h (not extended interval aminoglycoside dosing) should be used for patients with normal renal function. Patients with enterococcal endocarditis often have co-morbidities including renal compromise and therefore a starting dose of 1 mg/kg q 12-24h is recommended empirically.

  Enterococci are considered clinically resistant to synergy dosing if their MIC is > 500 for gentamicin or 2000 mcg/mL for streptomycin. In this situation, not only is there the problem of antibiotic penetration but also the enterococci have likely acquired (through a plasmid) the ability to enzymatically inactivate the aminoglycoside. There are approximately 5 aminoglycoside inactivating enzymes that are of clinical importance. Fortunately, when enterococci are gentamicin-resistant, they are generally streptomycin-susceptible and vice versa. Tobramycin and amikacin are not recommended as adjunct therapy for *Enterococcus* infections due

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unreliable activity. As an alternative, studies have shown the combination of ceftriaxone (2g q12h) with ampicillin is non-inferior to gentamicin for synergy in patients with enterococcal endocarditis and is associated with fewer adverse effects.

<u>Staphylococci:</u>

The value of aminoglycosides as adjunctive therapy for staphylococci has been questioned in the literature. While data suggest that the addition of an aminoglycoside to nafcillin therapy shortens duration of bacteremia by about one-half day, no beneficial effect has been shown for a reduction in mortality. Aminoglycosides are primarily used in this situation for patients with prosthetic valve infective endocarditis and gentamicin is preferred. If used, the clinician should recognize that extending aminoglycoside therapy beyond five days may place the patient at risk of aminoglycoside toxicity. Thus far, peak gentamicin concentrations of 3 to 5 mcg/mL seem adequate for adjunctive therapy when using synergy dosing. However, data are limited. Little data is available concerning once-daily gentamicin dosing in staphylococcal infections being primarily managed with either vancomycin or a beta-lactam antibiotic.

<u>Streptococci:</u>

Aminoglycosides may be used in combination with a cell wall active agent for various streptococcal infections (usually endocarditis from viridans group streptococci). This is the one Gram-positive infection where once-daily dosing (3mg/kg/d) of gentamicin has been shown to be equally effective to traditional synergy dosing.

- **Anaerobic Infections –** Anaerobes are intrinsically resistant to aminoglycosides. Aminoglycosides are also inactivated by the acidic environment in abscesses.

Toxicity/Side Effects
- The two most concerning adverse effects are nephrotoxicity and ototoxicity; both reportedly occur in approximately < 2 to 10% of patients.
- **Nephrotoxicity risk is significantly decreased with extended-interval dosing, rarely occurs before 5 days of aminoglycoside exposure, and is reversible**
- Auditory toxicity is typically a bilateral high frequency loss that generally will not greatly affect most patients' lifestyle but will likely be a permanent effect.
  - There also have been rare cases of significant auditory toxicity resulting in permanent deafness and/or vestibular toxicity that affects the patients' ability to balance. These are rare and have been associated with persistently elevated aminoglycoside troughs and cumulative lifetime aminoglycoside exposure.
- Aminoglycosides can also rarely cause neuromuscular blockade, especially if administered rapidly.

Dosing

Traditional/conventional dosing refers to multiple daily doses of aminoglycosides (e.g. gentamicin or tobramycin dosed 80mg every 8 hours or 1.5-2.5 mg/kg every 8 hours).

Extended interval aminoglycoside dosing (EIAD) is preferred over traditional dosing in patients that meet EIAD eligibility criteria. EIAD typically employs a daily dose of 7 mg/kg (5 mg/kg/day for UTI is reasonable) and is usually dosed q24h in patients with normal renal function. This approach is designed to produce higher peak concentrations than seen with conventional dosing strategies and thus increase the Cp-max/MIC ratio. The use of the 24-hour dosing interval is designed to create an "aminoglycoside-free" period during the dosage interval. This period will reduce accumulation of aminoglycosides in tissues such as the inner ear and kidney and will thus reduce drug-related toxicity. The "aminoglycoside-free" period takes advantage of the post-antibiotic effect for these concentration-dependent agents and should also assist in preventing the development of adaptive resistance. The precise timeframe for this period is presently unknown, but is thought to be 6-8 hours with EIAD.

Uptake of aminoglycosides by tissues (e.g. nephron) is a saturable process. One large aminoglycoside dose given once daily rather than several doses divided daily may result in less net transfer of aminoglycoside from the blood into renal tissue. Smaller but more frequent doses are not believed to saturate drug transport into the tissue and ultimately produce higher tissue concentrations than EIAD. Thus, between saturation of the amount of aminoglycoside moving into the tissue and the use of an "aminoglycoside-free" period, EIAD strategies are noted to be less toxic to the patient through a reduction in aminoglycoside tissue accumulation.

Laboratory Monitoring of Therapy

Table 2: Serum Concentration Sampling Times for Traditional and Extended-Interval Dosing of Aminoglycosides

	Peak Sample Time	Trough Sample Time	Hospital Cost	Comments
Traditional Dosing[1]	1hour post IM injection or 30-60 min after 30-60 min infusion	≤ 30 min before dose (IM and IVPB)	G: $10.43 T: $13.75 A: $15.78	Obtain levels after 3-4 doses (after ~5 half-lives). Most patients should be at steady-state at this time.
Extended Interval Dosing[5,6] (once-daily in patients with normal renal function)	Not indicated. Obtain random level instead, typically with AM labs 6-14 hours after the infusion.	Not routinely indicated. Trough often undetectable and no significant accumulation should occur.	G: $10.43 T: $13.75 A: $15.78	Levels can be obtained after the first dose as patient should be at steady state immediately.

Extended-Interval Aminoglycoside Dosing (EIAD) or Once Daily Dosing [5,6]

- The benefits of EIAD include:
  - <u>Aminoglycosides have concentration dependent activity</u>. The rate of bacterial killing increases as drug concentration is increased. As stated previously, investigators suggest optimizing the aminoglycoside peak serum concentration to bacterial MIC ratio (Peak/MIC) to a value ≥ 10:1 or AUC:MIC 80-100 to maximize bacterial killing.
  - The combination of a high peak and an "aminoglycoside-free" interval <u>will help to reduce the selection and the emergence of resistant organisms (</u>by eliminating the adaptive resistance phenomena) and minimize aminoglycoside-associated toxicity.
    A high aminoglycoside peak concentration leads to a longer duration of <u>post-antibiotic effect (PAE).</u>

- **Exclusion criteria** – pregnancy (although 5mg/kg/d has been studied for chorioamnionitis), burns (>20%), ascites, enterococcal endocarditis, or HD/CrCl < 20 mL/min.
- PLEASE NOTE: Extended interval aminoglycoside dosing should be considered in all patients for which an aminoglycoside is ordered for a suspected or documented <u>Gram-negative bacilli</u> infection, except for those that meet the exclusion criteria.
- For pulmonary exacerbations of Cystic Fibrosis, see the EIAD protocol specific to those patients in the next section

- Dosing
  - Use Actual Body Weight (ABW) unless the patient is obese
  - If patient is >20% over ideal body weight (IBW) use an adjusted body weight (AdjBW)

    AdjW = IBW + [0.4 (ABW - IBW)]

    Note that "Dosing Weight" in Epic OneChart is not the same as Adjusted Body Weight. Dosing weight in that context is the first weight used after admission when establishing the weight to be used for consistency in protocols such as those for heparin or chemotherapy

  - Tobramycin/ gentamicin - dose at 7 mg/kg (may use 5 mg/kg for UTI)
  - Amikacin - dose at 15 mg/kg, or 20mg/kg for multi-drug resistant organisms (nosocomial pneumonia)

Table 3: Extended-Interval Aminoglycoside Dosing

Estimated CrCl (mL/min)	Initial Dosing Interval
> 60 mL/min	Q24H
40-59 mL/min	Q36H
20-39 mL/min	Q48H
< 20 mL/min	Not recommended

- Therapeutic monitoring and dose adjustment
  - Levels should be obtained in the following situations:
    - Random serum level with morning labs, Ideally 6-14 hours **AFTER THE START** of the infusion for the first dose to confirm appropriate serum level.
    - Confirm an appropriate serum concentration after dosage adjustment.
    - Suspected toxicity (oto- or nephro-) or when there is a change in or impaired renal function while on maintenance therapy.
    - Reaffirm a seriously abnormal or unusual serum concentration (i.e., potential line draws as inappropriate draw times can usually be adjusted and used by software.)
    - Weekly monitoring of stable patients on prolonged course of aminoglycosides
    - Twice weekly monitoring recommended for unstable patients

- Dosage adjustments should be made according to the Hartford Nomogram (Figure 1).
    - **Important Notes:**
        - Because the Hartford Nomogram was based on a dose of 7mg/kg, if a lower dose is being used, the resultant level should be multiplied by a factor equal to 7 mg divided by the dose used. Example: If a patient is receiving 5mg/kg/day and the post-dose level after 10 hours was 2 mcg/mL, you would multiply the level by 1.4 (7/5) to give a level of 2.8 mcg/mL. This adjusted level is the one you would plot on the Hartford Nomogram.
        - If using amikacin, a trough serum concentration can be drawn and should be less than 5.
        - If the level falls on the line, choose the longer interval for administration.
        - If the aminoglycoside level falls off the nomogram, traditional dosing should be used and adjusted for renal function.
            - A dose of 3mg/kg q24h can be considered in these cases to achieve a peak of approximately 10 mcg/mL.
            - This is also where using Bayesian software to calculate a predicted AUC can be helpful
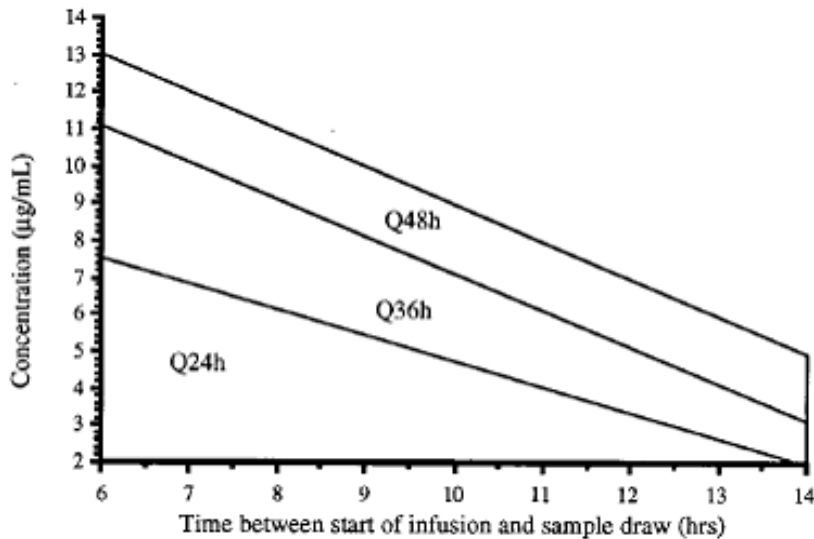
Figure 1. Hartford Nomogram

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

Aminoglycoside Pharmacokinetic Calculations – Traditional Dosing
(Traditional dosing is only to be used if patient does not meet criteria for EIAD)

Desired Levels for Various Infections with Traditional Dosing

Medical Condition	Desired Peak	Desired Trough
Gentamicin/ Tobramycin		
Synergy (Gram-positives) 1mg/kg	3-5	<1
UTI, endometriosis, pyelonephritis 1.5 mg/kg	4-6	<1-1.5
Pneumonia, sepsis, necrotizing infection 2-2.5 mg/kg	8-10	<2
Cystic Fibrosis 2.5-3 mg/kg	10-12	<1
Amikacin		
Moderate Infections 5 mg/kg	15-25	<5
Severe Infections 7.5 mg/kg	25-40	<10

Guidelines for Aminoglycoside Serum Levels for Individualized Dosing (not EIAD)
Levels should be obtained according to the following guidelines:
- A. Patient not responding to therapy as expected.
- B. Suspected toxicity (oto- or nephro-) or patient has a change in or impaired renal function while on maintenance therapy.
- C. Reaffirm a seriously abnormal or unusual serum concentration (i.e., potential line draws, inappropriate times, etc.)
- D. To determine that a therapeutic level has been achieved after culture results have been reported and the decision to continue the aminoglycoside has been made.
- E. Initial dosage check for empiric therapy in neutropenic patients or suspected *Pseudomonas* infections (i.e., cystic fibrosis or ventilator-dependent patients).
- F. Weekly monitoring of prolonged therapy with aminoglycosides.

Definitions

IBW	=	ideal body weight
ABW	=	actual body weight
DBW	=	dosing body weight
kel	=	elimination rate constant
Vd	=	volume of distribution
τ	=	dosing interval
t	=	time of infusion
t_{before}	=	time between blood draw and start of infusion
t_{end}	=	time from end of infusion to blood draw
$t_{1/2}$	=	half-life
C_{max}	=	peak serum level at steady-state
C_{min}	=	trough serum level at steady-state
SCr	=	serum creatinine

Empiric Dosing – No Levels

1. $CrCl = \dfrac{(140-age) \times AdjBW}{72 \times SCr}$ (x 0.85 if female)

Ideal Body Weight (IBW)
Males: 50 kg + 2.3 kg per inch > 60 inches
Females: 45.5 kg + 2.3 kg per inch > 60 inches
Adjusted Body Weight (AdjBW)
AdjBW = IBW + [0.4(ABW – IBW)]

2. Use population kinetics to calculate a dosing regimen (see Pharmacokinetic Pocket Card and use "empiric" formulas). Use ABW unless patient's ABW >20% over IBW, then switch to AdjBW. A loading dose should be considered in severe infections.

Individualized Dosing (levels obtained) – Calculate patient-specific kel and Vd

1. $kel = \dfrac{\ln(C_{max}/C_{min})}{\tau - (t + t_{end} + t_{before})}$

2. $Cmax_{actual} = \dfrac{C_{max}}{e^{-kel(tend)}}$

3. See Pharmacokinetic Pocket Card for specific Vd formulas under "After levels."
4. If you want to adjust the dose, plug patient-specific kel and Vd into dose equations and verify appropriate levels with the equations for estimated peak and trough at steady state.

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Extended interval aminoglycoside dosing in patients with cystic fibrosis at Nebraska Medicine

The optimal dosing of aminoglycosides in patients with cystic fibrosis (CF) exacerbations has been explored in numerous studies.[1-3] Studies in CF and non-CF patients have found that extended interval aminoglycoside dosing is at least as effective as traditional dosing and may be associated with less toxicity.[1-8] The largest controlled trial in patients with CF randomized 219 patients with exacerbations into one of two study arms: tobramycin 10 mg/kg once daily, or 10 mg/kg divided three times daily.[1] All patients received ceftazidime in addition to tobramycin. There was no difference in the primary endpoint, the mean change in % predicted FEV_1 during the 14 days of treatment between the once daily (10.4%) and three times daily (10%) groups (0.4%; 95% CI -3.3 to 4.1). Furthermore, a meta-analysis that included four studies and 328 subjects found no differences in CF exacerbation clinical outcomes between once and thrice-daily dosing and found significantly less nephrotoxicity with once daily dosing in pediatric patients.[2] Based on these data, the Cystic Fibrosis consensus guidelines recommend extended interval dosing as the preferred method.[6] The recommendation for the use of extended interval dosing is based on:

1. Equivalent efficacy[1-5]
2. Potential for decreased toxicity, with specific evidence for decreased nephrotoxicity in children[1, 7, 8]
3. Increased ease of dosing, particularly where extended/continuous infusion of antimicrobials are used concomitantly or the aminoglycoside is administered in the outpatient setting

The development of aminoglycoside resistance is of particular concern for patients with cystic fibrosis as these patients are frequently colonized with multidrug-resistant pathogens such as *P. aeruginosa*. Based on pharmacokinetic/pharmacodynamic rationale, extended interval dosing may promote less resistance, given favorable peak:MIC ratios are achieved and a drug-free interval has been shown to decrease adaptive resistance.[9] However, in patients with very rapid renal elimination, a prolonged drug-free interval may occur which is longer than the duration of the aminoglycoside post-antibiotic effect. Aminoglycoside resistance development during extended interval dosing has been assessed on a limited extent basis.[10, 11] Burkhardt, et al. examined *P. aeruginosa* resistance trends in 33 cystic fibrosis patients receiving once or thrice daily tobramycin.[10] They found an increase in tobramycin MIC after therapy in 47% (8/17) and 38% (6/16) of patients in the once and thrice-daily groups, respectively. A two-year study of tobramycin monotherapy in 44 patients found the tobramycin logarithmic geometric mean MIC increased from 13.2 mg/L to 18.4 mg/L (p=0.076) and 11.5 mg/L to 19.4 mg/L (p=0.014) in patients receiving once or thrice daily tobramycin, respectively.[11] It is difficult to draw conclusions as these studies are limited by the very small study population and the lack of isolate typing before and after therapy.

The pharmacodynamic goals of therapy with aminoglycosides relate to total exposure and pathogen MIC, frequently represented by a peak:MIC ratio of 8-12:1 for maximal clinical response.[12, 13] Most studies evaluating once daily dosing of aminoglycosides in cystic fibrosis have used daily doses of 8-10 mg/kg and have consistently resulted in tobramycin peaks of 20-30 mg/L.[1, 14-17] Based on these data, the following dosing algorithm was developed.

Recommendation*: All patients with CF should receive aminoglycosides per the extended-interval dosing protocol outlined below unless meeting exclusion criteria.

Exclusion: Pregnant patients or those with CrCl of <20 mL/min: dose via traditional dosing*

1. Determine dosing body weight (kg)
-Dose based on actual body weight (ABW), unless:
-If patient is >20% over ideal body weight (IBW) use adjusted body weight (AdjBW)

$$IBW_{Male} = 50 + (2.3 \times inches\ over\ 5\ ft) \qquad IBW_{Female} = 45.5 + (2.3 \times inches\ over\ 5\ ft)$$
$$AdjBW = IBW + [0.4 (ABW - IBW)]$$

2. Determine initial dose
Check past dosing in electronic medical record (Search "my iVents") for previous doses. If none, then:
Tobramycin: 10 mg/kg
Amikacin: 20 mg/kg
> *Note: If patients are unable to receive their first dose by 3pm then the dose should be held and administered at 8am the following day unless otherwise requested by the prescriber*

3. Obtain two serum concentrations with first dose and as indicated
Obtain two serum concentrations 1 & 5 hours after the end of the one-hour infusion.
(This typically allows for 2 half-lives to pass between levels. For patients with compromised renal function, the second serum concentration may be timed later.)
- Bayesian software will perform the calculations below and determine the dose needed to achieve an AUC goal near 100 mg*h/L. InsightRX® is set to recommend dosing every 24h by default so an alternative interval will need to be entered, if needed.

4. Determine elimination rate and half-life

$$kel = \frac{\ln (C_{1\,hr}/C_{5\,hr})}{\text{time (hr) between the two levels}}$$

$$\text{Half-life} = \frac{\ln(2)}{kel}$$

5. Determine dosing interval according to half-life
(Dosed no more frequently than every six half-lives, serum concentrations will be <1 mcg/mL for at least one half-life with this dosing)

Half-life	Dosing interval
<4 hours	Q24h
4 to 6 hours	Q36h
>6 to 8 hours	Q48h
>8 hours	Convert to traditional dosing*

*Traditional dosing goals: -tobramycin (3mg/kg) peaks of 10-12 mcg/mL & troughs <1 mcg/mL
 -amikacin (7.5mg/kg) peaks of 25-40 mcg/mL & troughs of 4-8 mcg/mL

6. Determine Cmax (back-extrapolated to 30 minutes after the end of the one-hour infusion)

$$Cmax_{(30\text{ minutes after end of infusion})} = \frac{C_{1\,hr}}{e^{-kel(t,end)}}$$

t,end = typically 0.5 h if the first level is drawn 1 h after end of infusion

Goal Cmax$_{(30\text{ minutes after end of infusion})}$ is 20-30 mcg/mL for tobramycin & 30-45 mcg/mL for amikacin

7. If Cmax$_{(30\text{ minutes after end of infusion})}$ is outside goal range, increase or decrease dose by 10% and repeat steps 3-7 with next dose.

8. Inpatient monitoring:
-Pharmacist will obtain either a random level with AM labs, trough (goal <1 mcg/mL) OR two serum concentrations as described in step 3 at least every five days to verify appropriateness of dosing and make recommendations as needed.
-More frequent serum concentrations are indicated in patients with changing clinical status (changes in renal function/creatinine, clinical response, toxicity, etc.).
-Serum creatinine will be obtained on Mondays and Thursdays.

9. Outpatient monitoring:
-Troughs and serum creatinine drawn twice weekly, starting within four days, or earlier as clinically indicated. If the trough is elevated (detectable) or renal function changes then two serum concentrations will need to be obtained to determine the appropriate interval.

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Vancomycin Overview

Background

Vancomycin is a tricyclic glycopeptide antibiotic that exhibits bactericidal activity by blockage of the glycopeptide polymerization in the bacterial cell wall. This produces an immediate inhibition of cell wall synthesis and secondary damage to the cytoplasmic membrane.[1] Vancomycin exposure represented by area under the curve to minimum inhibitory concentration ($AUC_{0-24hrs}$:MIC) ratio has been suggested to be the best pharmacodynamic predictor of outcomes, however trough was used as a surrogate . Vancomycin is used most widely for the treatment of severe staphylococcal infections (including empiric therapy for methicillin-resistant staphylococci), The oral formulation is only effective in the treatment of pseudomembranous colitis caused by C. *difficile*.[2]

Vancomycin is also utilized for infections caused by ampicillin-resistant Enterococci or penicillin-susceptible pathogens in patients who are severely allergic to beta-lactam antibiotics. Several studies have shown that with both staphylococci and enterococci, vancomycin does not kill the bacteria as quickly or sterilize the blood as rapidly as nafcillin/oxacillin or cefazolin. For this reason, many authors suggest that unless the patient has a severe allergy to beta-lactam antibiotics or has a methicillin(oxacillin)-resistant staphylococcal infection, the patient would be better served using a beta-lactam agent rather than vancomycin.

Concern over the increasing problems with vancomycin resistant enterococci (VRE) prompted the Center for Disease Control to issue a statement suggesting appropriate prescribing criteria for vancomycin.[3]

Vancomycin is <u>not</u> recommended for:
Routine surgical prophylaxis
Treatment of a single positive blood culture for coagulase-negative staphylococci
Empiric therapy of febrile neutropenia where no evidence of Gram-positive infection exists
Prolonged empiric therapy
MRSA colonization
Treatment of MSSA or other beta-lactam susceptible Gram-positive infections, especially in dialysis patients
Prophylaxis in hemodialysis or CAPD patients
Prophylaxis in low birth weight infants
Systemic or local prophylaxis for indwelling central or local catheters
Selective gut decontamination
Topical application or irrigation

Pharmacokinetic Parameters[1,4,5]

<u>Absorption</u> – Oral absorption is negligible, however, when given orally, high vancomycin concentrations are achieved in the colon (for treatment of C. difficile).

<u>Distribution</u> – Penetration into tissues varies depending on inflammation and disease state. Penetration into the CSF is enhanced with inflamed meninges (e.g., meningitis). Penetration into lung tissue ranges from 5-41%. Volume of distribution is ~0.7 L/kg and does not significantly change for most disease states or conditions.

<u>Elimination</u> – When given IV, primarily excreted via kidneys. Oral doses are excreted primarily in the feces. Clearance = CrCl. Elimination half-life = 6-7 hrs in those with normal renal function. This is prolonged in patients with renal insufficiency.

<u>Therapeutic Plasma Concentrations</u> – peak = 30-40 mcg/mL, trough = 10-20 mcg/mL to achieve an AUC between 400-600 mg mg*hr/L

Concentration-toxicity Relationship

Shortly following the release of vancomycin to the market in 1956, reports began to surface describing ototoxicity secondary to vancomycin therapy, with serum concentrations ranging from 80-100 mcg/mL.[6] Based on this, authors recommended therapeutic drug monitoring of vancomycin to reduce the risk of ototoxicity. This side effect, however, has been seen in only 2% of patients who

receive vancomycin. Cantu and colleagues performed a literature search that yielded 53 reported cases of ototoxicity over a 30-year period.[7] Of these cases, only 17 were patients receiving monotherapy, all of which were reversible. Vancomycin levels ranged from 17-62 mcg/mL, so no specific threshold level was found. Vancomycin-associated ototoxicity is likely to be exacerbated by concomitant aminoglycoside therapy. It is manifested by vestibular damage and/or cochlear damage, which leads to sensory hearing loss and tinnitus.[8]

The other reported toxicity associated with vancomycin use is nephrotoxicity. The incidence of nephrotoxicity secondary to vancomycin monotherapy is estimated to be 5-7% but increases to 43% in patients receiving concomitant nephrotoxic drugs (e.g., aminoglycosides, amphotericin B).[7,8] When reviewing cases, it is difficult to establish with certainty whether vancomycin is always the cause of impaired renal function or whether vancomycin accumulation has occurred as a consequence of decreased renal function for other reasons.[9] Many of the early reported cases of nephrotoxicity occurred with impure preparations of vancomycin. Since the introduction of vancomycin and through the mid-1980's, early lots of vancomycin contained large amounts of fermentation broth impurities. The preparation was brown and was dubbed "Mississippi mud" because of its appearance.[10] Modern formulations have excellent safety profiles; however, reports of vancomycin-related nephrotoxicity still surface, particularly with the recommendations to increase vancomycin trough concentrations from the typical range of 5-15 mg/L to 10-20 mg/L.[4]

Studies have been performed trying to establish a link between higher vancomycin trough concentrations and the risk for nephrotoxicity. Four recent studies found a greater risk of nephrotoxicity at trough levels ≥ 15 mcg/mL as compared to trough levels less than 15 mcg/mL.[11-14] A recent meta-analysis reported that the relative risk of AKI with vancomycin was 2.45 (95% confidence interval, 1.69-3.55), with most episodes of AKI developing between 4 and 17 days of therapy.[23] Another recent study has identified the total daily dose as a potential factor in nephrotoxicity, suggesting that daily doses of 4g or more are significantly associated with an increased risk of nephrotoxicity, even after controlling for potential confounding factors in a multivariate analysis.[15] No correlation has been found between nephrotoxicity and peak vancomycin levels.

As more data become available, it is increasingly clear that the risk of AKI increases along a spectrum of AUC values as well, with AUC's greater than 650 to 1300 mg•hr/L being associated with significant increases in risk of AKI.[24-26] Suzuki et al. found that most patients who developed an AKI in their study had AUC values between 600 and 800 mg•hr/L compared with 400 to 600 mg•hr/L in those without AKI.[27] These findings are supported by numerous other human and animal studies evaluating the relationship between vancomycin AUC and nephrotoxicity.[28-31]

Concentration-efficacy Relationship
Vancomycin has been shown to demonstrate concentration-independent killing against Gram-positive pathogens. A close relationship between drug dosage and resultant serum concentration and their relationship to minimum inhibitory concentration (MIC) and therapeutic outcome is ideal. Although the area under the curve (AUC) to MIC ratio has been shown to be the pharmacodynamic parameter that best correlates with vancomycin activity and a target AUC/MIC ratio of at least 400 is recommended, limited human data are available to suggest better clinical outcomes with attainment of such a target.[4]

Because obtaining multiple serum vancomycin concentrations for the calculation of the AUC is difficult in the clinical setting, vancomycin trough concentrations have historically been used as a surrogate marker for monitoring vancomycin therapy. Previous vancomycin guidelines from 2009 recommended that vancomycin trough concentrations always be maintained above 10 mcg/mL and between 15-20 mcg/mL for complicated infections (e.g., bacteremia, endocarditis, osteomyelitis, meningitis, pneumonia).[4, 23] Since the release of those guidelines, however, numerous studies have shown that troughs may not be ideal surrogates for AUC values. Neely et al. conducted a study to assess the ability of trough concentrations to predict AUC values and found that troughs significantly underestimate AUC. Over half of the patients in this study with a therapeutic AUC (>400 mg•hr/L) actually had troughs <15 mg/L, highlighting an opportunity to decrease vancomycin exposure (and therefore toxicity).[24] Based on this study and many like it, 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 released joint guidelines for the monitoring of vancomycin in March of 2020.[32]

In these new guidelines, the authors recommend a shift away from trough-based dosing of vancomycin in favor of an AUC-based approach, with an AUC goal of **400-600 mg•hr/L**. To achieve AUC's in this range, doses of 15 to 20 mg/kg (based on actual body weight) administered every 12 hours as an intermittent infusion are recommended for most patients with normal renal function. It is recommended that AUC monitoring be accomplished through one of two methods:

1. (Preferred) Using Bayesian software programs, embedded with a PK model based on richly sampled vancomycin data as the Bayesian prior, to optimize the delivery of vancomycin based on the collection of 1 or 2 vancomycin concentrations, with at least 1 trough. It is preferred to obtain 2 PK samples (ie, at 1 to 2 hours post infusion and at end of the dosing interval) to estimate the AUC with the Bayesian approach. A trough concentration alone may be sufficient to estimate the AUC with the Bayesian approach in some patients, but more data are needed across different patient populations to confirm the viability of using trough-only data.

2. Utilizing first-order PK equations to estimate the AUC based on 2 concentrations (obtained near steady-state, post-distributional peak concentration [Cmax] at 1 to 2 hours after infusion and trough concentration [Cmin] at the end of the dosing interval), preferably but not required during the same dosing interval (if possible).

Using Bayesian calculators is the preferred method based on accuracy, convenience, and the ability to calculate dosages with dynamic renal function when not at steady state concentrations.[32-33] Neely et al. implemented a Bayesian software program and found similar efficacy to trough-based dosing with lower troughs and less nephrotoxicity.[34] Recent data suggest that it is important to achieve therapeutic AUC values within the first 24-48 hours of therapy. Nebraska Medicine now uses InsightRX as a Bayesian software program to dose vancomycin based on AUC.

Sampling considerations

- Vancomycin serum trough concentrations should be monitored in most patients with the 4th dose if therapy is expected to continue.
- For patients with a severe infection and/or changing renal function, order a trough or random serum concentration with AM labs after the first or second dose. An advantage of using Bayesian dosing software is that it can adjust for levels that are drawn prior to steady-state and make a recommendation that will result in a therapeutic AUC. An additional serum concentration is recommended in a few days if therapy is continued.
  - *Since software can adjust for levels at any time during the dosing interval, serum concentrations should not be redrawn if the timing of lab draw and doses are not ideal*.
- Monitoring peak concentrations with vancomycin is not needed for most populations. However, a second level can useful for determining a more accurate clearance for patients with changing renal function or other pharmacokinetic parameters. If peak concentrations are obtained, a few points must be kept in mind:

  (1) Vancomycin pharmacokinetics have been described by 1, 2 and 3 compartmental models; InsightRX offers several two-compartment models that allow the user to find one with better fit for complex patients. For example, the modified Thomsen and Colin models work well on the majority of patients at Nebraska Medicine, while modified Goti model is designed for patients with diminished renal function. This model performs best in this situation with more than one serum concentration.

  (2) The vancomycin concentration at 1 hr may be more than double that taken at 2 hr and still be within the recommended target range;

  (3) To get accurate levels, one must be certain that the distribution phase is complete before the peak serum level is drawn.

  - In order to interpret peak levels appropriately, the infusion duration and draw time for the lab must be properly documented. If the lab value is reported during the infusion, the software will attempt to adjust based on what it thinks the value should be. However the recommendation may not be entirely accurate until an additional level is drawn.
  - For the average patient, if the trough concentration is within recommended limits, the peak and AUC is unlikely to reach a potentially toxic range.[20]

Indications for Monitoring Serum Vancomycin Concentrations[9,21,22]

- Monitoring is NOT needed in the following settings:
    - Patients expected to be treated for less than five days
    - Patients receiving oral vancomycin.

- Vancomycin serum levels ARE recommended in the following settings:
    - Patients with severe (life-threatening) infection. TROUGH or RANDOM (easiest with AM labs) in 1st 24-48 hours. Consider TWO LEVELS with in patients with diminished or changing renal function. Recommend using the modified Goti model
    - Patients requiring aggressive vancomycin dosing. TWICE WEEKLY for patients on q8h dosing until stable with two similar levels, then once weekly.
    - Patients receiving vancomycin with an aminoglycoside, amphotericin B or other concomitant nephrotoxins.
    - Anephric patients undergoing hemodialysis and receiving infrequent doses of vancomycin for serious systemic infections. RANDOM TROUGH with AM LABS prior to dialysis per the Nephrology protocol (preferred) or 4 hours after dialysis.
    - Patients with rapidly changing renal function*.
    - Patients receiving prolonged (>5 days) vancomycin therapy.
    - Patients receiving higher than usual doses of vancomycin (adults: > 20 mg/kg/dose, pediatrics: > 60 mg/kg/day).
    - Morbidly obese patients. Use OBESITY (ENHANCED) model in patients > 100 kg and consider TWO levels
    - Reaffirm a seriously abnormal or unusual serum concentration (i.e., line draws, inappropriate drawn during infusion time, etc.).
    - Neonates: a) determine a therapeutic level has been achieved after culture results have been reported and b) monitor serum levels with prolonged therapy >10 days. INITIAL: PEAK AND TROUGH; TROUGH ONLY after therapeutic levels achieved for prolonged administration with stable renal function.

*Rapidly changing renal function = 33% increase/decrease in CrCl or 0.3 mg/dl increase/decrease in SCr over 24-48 hours.

Serum Drug Levels				
Drug		**Time to Obtain**	**Therapeutic Range**	**Hospital Cost**
Vancomycin	Trough	½ hour before infusion begins	10-20 mcg/mL	$9.71
	Peak*	1 hour after infusion ends	30-40 mcg/mL	$9.71

*Not routinely recommended

Vancomycin Pharmacokinetic Calculations

Note: Nebraska Medicine now uses InsightRX as a software program to perform Bayesian-derived dosing for vancomycin based on AUC targets. It is recommended to use this, along with clinical judgment, to create and implement vancomycin dosing and monitoring plans. To help check your work, the equations below describe dosing without Bayesian software based on first-order pharmacokinetic equations.

Definitions

IBW	=	ideal body weight
ABW	=	actual body weight
AdjBW	=	adjusted body weight
DBW	=	dosing body weight
kel	=	elimination rate constant
Vd	=	volume of distribution
τ	=	dosing interval
t	=	time of infusion
t_{before}	=	time between blood draw and start of infusion
t_{end}	=	time from end of infusion to blood draw
$t_{1/2}$	=	half-life
C_{max}	=	peak serum level at steady-state
C_{min}	=	trough serum level at steady-state
SCr	=	Serum creatinine

Empiric Dosing – No Levels

1. Total daily dose = Cl x AUC goal.
    a. An AUC of 450 is our standard goal.
    b. Cl = ke x Vd

$$CrCl = \frac{(140-age) \times IBW}{72 \times SCr} (\times 0.85 \text{ if female})$$

Ideal Body Weight (IBW)
Males: 50 kg + 2.3 kg per inch > 60 inches
Females: 45.5 kg + 2.3 kg per inch > 60 inches

2. Use InsightRX to determine a starting dose based on population kinetics

3. A loading dose of 25-30 mg/kg (Use AdjBW for obese patients) may be considered for more rapid attainment of target trough concentrations in seriously ill patients.[4] Based on an average Vd of 0.7 L/kg this will achieve a serum concentration of 17.5-21 mg/L. Early attainment of AUC > 400 (serum concentrations ≥15 mcg/mL) have been associated with improved patient outcomes in patients with MRSA bloodstream infections.[23] Keep in mind that the infusion rate for vancomycin is 1g/hr, so large doses may require long infusion periods.

Individualized Dosing (trough only obtained)
1. Because vancomycin exhibits linear pharmacokinetics, increases or decreases in total daily dose have a corresponding proportional increase or decrease in AUC values. Set up a proportional relationship to estimate the actual trough based on new dose.

$$\frac{AUC (actual)}{x} = \frac{Current\ total\ daily\ dose}{New\ total\ daily\ dose}$$

x = estimated new AUC based on new dose

Ex. Pt. receiving 1000mg IV q12h and resulting AUC is 300 mg•hr/L with a goal level between 400-600 mg•hr/L . You determine that you want to increase the dose to 1500mg IV q12h (a 50% increase in total daily dose). Accordingly, the resulting trough should increase by approximately 50%.

$$\frac{300 \text{ mg·hr/L}}{x \text{ mg·hr/L}} = \frac{2000 \text{ mg}}{3000 \text{ mg}}$$ Therefore,   x = 450 mg·hr/L

Thus, the new dose of 1500mg IV q12h would be expected to produce a therapeutic AUC of ~450 mg·hr/L.

Note: <u>Altering the dosing frequency will have larger effects on the resulting trough than suggested by the proportion.</u> For example, if in the above example the dosing frequency (and not the dose) was changed to q8h (this results in the same 50% increase in total daily dose), then the resulting AUC would likely be higher than 450 mg·hr/L as suggested by the proportion due to accumulation. Similarly, in instances where the dosing frequency is being decreased, the resulting trough will be lower than the proportion suggests.

Individualized Dosing (Utilizing 2 levels and based on a 2-compartment elimination model)

Step	Description	Equation
1	Verify that doses were given on time and drawn appropriately	
2	Calculate the patient's observed k_e from 2 levels	$k_e = \dfrac{ln\frac{C_1}{C_2}}{t_2 - t_1}$ where C_1 usually is the peak, C_2 is usually the trough
3	Calculate half-life, $t_{1/2}$	$t_{1/2} = \dfrac{0.693}{k}$
4	Calculate true peak, C_{max}	$C_{max} = \dfrac{C_1}{e^{-k\,\Delta t}}$, Δt = time between end of infusion and time level drawn
5	Calculate true trough, C_{min}	$C_{min} = C_{max} \times e^{-k_e \times (tau - t)}$ where t = infusion time
6	Calculate V_d (steady state conditions) *optional step: not required to determine AUC*	$V_d = \dfrac{Dose \times (1 - e^{-k \cdot t})}{t \times k_e\,(C_{max} - [C_{min} \times e^{-k \cdot t}])}$ where t = infusion time
7	Calculate vancomycin clearance *optional step: not required to determine AUC*	$CL_{van} = V_d \times k_e$
8	If C_{min} is high, calculate the time needed to reach desired range	Time for C_{min} to reach $C_{desired} = \dfrac{ln\frac{C_{min}}{C_{desired}}}{k_e}$
9	Calculate AUC during infusion using linear trapezoidal rule	$AUC_{inf} = t \times \dfrac{(C_{max} + C_{min})}{2}$
10	Calculate AUC during elimination using logarithmic trapezoidal rule	$AUC_{elim} = \dfrac{(C_{max} - C_{min})}{k_e}$
11	Calculate AUC$_{24}$	$AUC_{0-24} = (AUC_{inf} + AUC_{elim}) \times \dfrac{24}{tau}$
12	Estimate total daily dose need to achieve target AUC$_{24}$ *Tip: new tau = 1 to 1.5x the half-life*	$New\ TDD = Current\ TDD \times \dfrac{AUC_{0-24}\ (desired)}{AUC_{0-24}\ (calculated)}$
13	Calculate predicted steady state C$_{max}$ for new dosing regimen	$C_{ss,max} = \dfrac{New\ dose}{CL \times t} \times \dfrac{1 - e^{-k \cdot t}}{1 - e^{-k \cdot tau}}$
14	Calculate predicted steady state C$_{min}$ for new dosing regimen	Same as step 5
15	Calculate predicted AUC based on new dosing regimen	Same as steps 9-11

Source: *[Stanford Health Care Vancomycin Dosing Guide](#)*

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Clinical Pearls for Aminoglycosides and Vancomycin

Dialysis Considerations

Aminoglycosides
- o We assume that approximately 50% of the drug is removed by a standard hemodialysis session. For example, if the serum concentration prior to dialysis is 2.4 mcg/mL, we assume that it would be around 1.2 mcg/mL after dialysis.
- o When indicated, we recommend obtaining a random level prior to dialysis or at least 2 hours after the end of a hemodialysis session to allow for redistribution. If levels are obtained sooner than this, especially immediately post-dialysis, the resultant level will be lower than the actual level because dialysis removes the drugs from the blood faster than it can redistribute from the tissues back into the bloodstream.

Vancomycin
- o We assume that approximately 30-40% of the drug is removed by a standard hemodialysis session (10% per hour). For example, if the serum concentration prior to dialysis is 18 mcg/mL, we assume that would be around 13.5 mcg/mL after dialysis.
- o **We recommend following the nephrology dosing strategy outlined below for adults with ESRD on hemodialysis.** If unable to use this protocol, serum concentration monitoring may be obtained when indicated via a random level at least 4 hours after the end of a hemodialysis session to allow for redistribution. If levels are obtained sooner than this, especially immediately post-dialysis, the resultant level will be lower than the actual level because dialysis removes vancomycin from the blood faster than it can redistribute from the tissues back into the bloodstream.

TNMC Nephrology preferred dosing strategy: Adult hemodialysis patients receiving vancomycin

The following preferred dosing strategy applies to adult patients with chronic kidney disease receiving hemodialysis who receive vancomycin for confirmed or suspected infection.

Excluded patients include chronic kidney disease patients receiving SLED or peritoneal dialysis, patients receiving vancomycin antibiotic lock therapy, and pediatric patients.

The targets of pre-HD vancomycin serum concentration for this protocol are 15-20 mcg/mL. This will ensure AUC_{24} >360-480 mg*hr/L

Loading Dose of vancomycin: 20 mg/kg IV once (Minimum: 1000mg and Maximum: 2000mg)

Maintenance Dosing: 750 mg (7-10 mg/kg) IV with each dialysis until dosage changed or discontinued (administered after dialysis in hospital but can be during the last hour of outpatient dialysis).

Prior to the second (2nd) post-load dialysis session, a pre-dialysis vancomycin trough level will be drawn: therapeutic goal 15 – 20 mcg/mL.

The dialysis dose is based upon this level:

Predialysis serum concentration	Supplemental vancomycin dose with dialysis session
> 20 mcg/mL	vancomycin 500 mg IV
15 – 20 mcg/mL	vancomycin 750 mg IV
< 15 mcg/mL	lesser of vancomycin 15 mg/kg or 1000 mg IV

Prior to the <u>third</u> (3rd) post-load dialysis session, a pre-dialysis vancomycin trough level can be drawn if there are uncertainties: therapeutic goal 15-20 mcg/mL. If this level is within range, continue with dosing and draw weekly vancomycin level (prior to dialysis).

Following a dose adjustment, vancomycin level should be checked prior to the next dialysis session to ensure level is stable, then weekly.

<u>General dosing strategy:</u>

Load (20 mg/kg)⟶HD plus 750 mg⟶Level prior to next dialysis ⟶HD plus dose based on level⟶Level prior to next dialysis ⟶HD plus dose based on level

Check level prior to 2nd hemodialysis following load.
Check level prior to the next two dialysis sessions following any dosage change.
If no dose changes following two levels, decrease to weekly levels.

<u>Examples:</u>

1)   If patient is loaded with vancomycin (20mg/kg) on Sunday, the patient would receive 750 mg of vancomycin with dialysis on Monday. Patient would return for dialysis on Wednesday, at which time a pre-dialysis vancomycin level would be drawn. If the level was 15-20 mcg/mL, then the patient would receive 750 mg of vancomycin after that dialysis session. Prior to the Friday dialysis session a vancomycin level would be drawn and if the level was again between 15 – 20 mcg/mL the patient would receive 750 mg of vancomycin on Friday and with each subsequent dialysis session, and the vancomycin levels would be drawn weekly.

2)   Patient loaded with vancomycin (20mg/kg) on Sunday, the patient would receive 750 mg of vancomycin with dialysis on Monday. Patient would return for dialysis on Wednesday, at which time a pre-dialysis vancomycin level would be drawn. If the level was <15 mcg/mL then the patient would receive 1000 mg of vancomycin. Patient would have a level checked on Friday prior to dialysis. If therapeutic (between 15-20 mcg/mL), continue with 1000 mg per treatment and check level the next Monday (or with the next dialysis session). **If the level on Friday is still less than 14 mcg/mL then the post-dialysis dose should be increased to vancomycin 1250 mg. With any dose adjustment, check level with next dialysis sessions until dose and level are stable x 2 then decrease frequency of vancomycin level to weekly.

3)   Patient loaded with vancomycin (20mg/kg) on Sunday, the patient would receive 750 mg of vancomycin with dialysis on Monday. Patient would return for dialysis on Wednesday, at which time a pre-dialysis vancomycin level would be drawn. If the level was >20 mcg/mL, then the patient would receive 500mg of vancomycin. Patient would have a level checked on Friday prior to dialysis. If therapeutic, continue with 500 mg with dialysis and check level the next Monday (or with the next dialysis session). If therapeutic, continue with vancomycin 500 mg infused during the last hour of dialysis and decrease frequency of vancomycin level to weekly. At this point, if vancomycin level is not therapeutic, contact the prescriber.

CLINICAL PHARMACOKINETIC CONSULTS

- A consult for pharmacy dosing should be included automatically on all aminoglycoside and vancomycin orders beyond one-time doses. Prescribers need to opt-out, which they rarely do on purpose.
- Consults are also available on any other therapeutically monitored drug by request.
- Initial note – All new orders need to have an initial PK note written, including our recommendations and predicting levels based on Bayesian software or empiric (population) PK parameters. The ONLY exceptions to writing a note with the 1st dose are NICU, CF, and post-op (x $\leq$ 3 doses). **However, ALL new orders still need to be checked for appropriateness**
    - NICU doses are based on the nomogram in NEOFAX according to gestational age and weight that is part of their order sets. Changes are based on levels and should have notes if therapy is continued past 36 hours.
    - Doses for patients with CF should be based on past regimens (search "My iVents" for patient's last admission) and/or a mg/kg basis with two levels drawn post-dose to establish clearance,
    - Post-op doses's (esp AG's) need to be changed if interval is not appropriate for patient's age/renal function, but are rarely continued long enough to need levels.
- Whenever levels are obtained or a dose is changed, a note should be written in the chart. It is our job to interpret the levels. NOTE: When making a recommendation on whether or not to obtain levels, please
    - Unless the patient has an urgent need (severe infection, or changing renal function) levels can be obtained near steady state (at 4 to 5 half-lives). This can help you figure out which dose to obtain levels with (usually the third dose for aminoglycosides (traditional dosing) and the fourth dose with vancomycin).
- Interventions: These require contact with the physician to inform them of your recommendations. Document the interaction in EPIC/OneChart via I-Vents.)
    - Drastic change in dose/regimen
    - Questionable levels – need to redraw
    - Potentially toxic or subtherapeutic levels
- We need to associate a prescriber with the order to change or order anything related to dose or monitoring. This can be done "Within scope"; no co-sign is required
    - You can use the prescriber who specifically consulted or the physician/APP you communicated with
- Every patient should be assessed EVERY DAY, and the monitoring iVent should be updated daily. (WBC, BUN, SCr, Tmax, cultures, etc.)
    - Scr should be drawn at least twice weekly, ideally every other day
    - It is very important to document the microbiology reports and reassess whether therapy remains necessary.
- Communicate with the next pharmacist when levels are due, length of therapy, etc. This includes the central pharmacists, when necessary, on weekends and holidays.

NOTE WRITING
Examples (There are many ways to write these notes.)

- Initial note:
  Gentamicin started for Pseudomonas UTI. Based on population pharmacokinetics and the patient's estimated CrCl, recommend 300 mg (5 mg/kg) IV q24h with predicted steady-state peak and trough to be ~16-20 mcg/mL and < 1 mcg/mL, respectively. (If more aggressive therapy desired for systemic infection/sepsis, consider 420 mg (7mg/kg) IV q24h for predicted peak and trough of ~24-30 mcg/mL and < 2 mcg/mL, respectively.) Will check random level after first dose and adjust as needed. Thank you for the consult. Pharmacy will continue to follow.

- Follow-up note:

Gentamicin day #3 for synergy of Enterococcal endocarditis. Currently on 80 mg (1mg/kg) q12h. Peak level drawn 2 hours after end of infusion, therefore actual peak ~6 mcg/mL. Trough is 0.8 mcg/mL To minimize risk of oto/nephrotoxicity,recommend adjusting dose to 60 mg q12h and checking another trough in ~3-4 doses. Thank you. Pharmacy will continue to follow.

OBJECTIVE OF NOTES
- Initial assessment using population parameters or previous dosing
- Interpret levels (e.g., peak level of 10.2 mcg/mL appears to have been drawn early, therefore pre-distributional and falsely high)
- Correspond levels to calculated AUC's for vancomycin (e.g., "trough of 13.4 mcg/mL should yield an AUC of approximately 440 mg•hr/L")
- Recommend new regimen and when to start it, or continuing present dose
- Monitoring/follow-up (next levels, if any, SCr if necessary)
- Education – teaching hospital

TIPS
- Give yourself some room when predicting levels (e.g., vancomycin AUC 425-450 mg•hr/L). Don't put an exact number on the consult note when estimating AUC's or levels. For example, if you calculate an expected vancomycin AUC of 410, reaffirm that this is approximate or put a range of 25-50 ("an AUC of approximately 410 mg•hr/L" or "400-425 mg•hr/L") on the form. This is not an exact science and should not be purported as such!
- If you calculated the estimated creatinine clearance via Cockroft-Gault and it is > 120 ml/min, put ">120 ml/min" in the blank for CrCl
- Avoid blaming (e.g., "The level was drawn 1.5 h post-dose, estimate actual peak to be…" rather than, "The nurse drew the peak 1 hour late.")
- Suggest/recommend (e.g., "if plan to continue, recommend checking a trough in ~3-5 days).
- Identify indication. Think about the infection, not just an organism (e.g., Write *S. aureus* bacteremia, or empiric treatment s/p abdominal abscess drainage rather than *S. aureus* or empiric treatment)
- Assess the patient, don't just trust the indication used when antibiotic first started (e.g., writing that the antibiotic is being used for "bacteremia/fungemia" when no cultures are positive is a contradiction)
- Limit liability, and Be professional

- *ALWAYS READ CHART BEFORE WRITING NOTE*