

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 $e^{-k_{el}(t)}$ represents the fraction of the serum concentration that remains. Thus, $1 - e^{-k_{el}(t)}$ 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 $\beta t_{1/2}$ to distinguish it from the distribution half-life, $\alpha t_{1/2}$, used in two compartment modeling.¹

Peak, C max¹

- 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 Distribution¹

- 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 effect 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 greatly 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. It has been recommended in these populations to round the serum creatinine value up to 1 mg/dl.³

Aminoglycoside Overview

Background

The aminoglycoside antibiotics – gentamicin, tobramycin, amikacin, netilmicin, streptomycin, and neomycin – contain amino sugars in glycoside linkage. They are rapidly bactericidal. 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, meaning that as aminoglycoside concentration increases, the rate and extent of bacterial killing increases. Presently, investigators suggest optimizing the aminoglycoside peak serum concentration to bacterial MIC ratio (Peak/MIC) to a value $\geq 10:1$.

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.

While the post antibiotic effect (PAE) is generally thought to increase with concentration dependent antibiotics, this may not be the case with aminoglycosides. Limited data suggest that the PAE in Gram-negative bacteria may wane over time with multiple doses of aminoglycoside.

Routes of Administration

- IV, IM, IH, topical cream or ointment, and ophthalmic

Pharmacokinetic Parameters

Table 1: Key Parameters for Aminoglycoside Antibiotics

Therapeutic Serum Concentrations		
Gentamicin, tobramycin	<i>Conventional dosing</i> ¹ Peak 4-10 mcg/mL Trough < 2 mcg/mL	<i>Once-daily dosing</i> ^{5,6} Peak 20 mcg/mL Trough - undetectable
Amikacin	<i>Conventional dosing</i> ¹ Peak 15-40 mcg/mL Trough <5- 10 mcg/mL	<i>Once-daily dosing</i> Peak 40- 60 mcg/mL Trough -undetectable
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	-

- Absorption²
 - 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
- Elimination⁴
 - 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, empiric double Gram-negative coverage 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:

Enterobacteriaceae:

Escherichia coli

Proteus spp.

Enterobacter spp.

Acinetobacter spp.

Citrobacter spp.

Morganella spp.

Serratia spp. (S. marcescens)

Klebsiella spp.

Pseudomonas aeruginosa

Tobramycin is more active than gentamicin by one or two MIC tube dilutions against *Pseudomonas aeruginosa*. Gentamicin is more active by one or two MIC tube dilutions against *Serratia marcescens*. Amikacin is often held in reserve to treat resistant pathogens that develop during therapy. Other aerobic Gram-negative bacilli (*Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Haemophilus influenzae*) are susceptible but are rarely treated with aminoglycosides.

- **Gram-Positive Infections** – Aminoglycosides have activity against some Gram-positive pathogens but are not considered primary agents. *Enterococcal* infections may be treated with a combination of an aminoglycoside and a beta-lactam (e.g. penicillin, ampicillin) or vancomycin. Aminoglycosides may be used in combination with a cell wall active agent for various streptococcal infections (usually seen in *S. viridans* endocarditis). Lastly, the use of aminoglycosides as adjunctive therapy for *Staphylococcal* infections has declined due to questionable clinical benefit and increased nephrotoxicity.

Enterococci:

Enterococci are resistant to aminoglycoside monotherapy. However, use of a cell wall active agent such as penicillin G, ampicillin, or vancomycin, in combination, will break down the cell wall, 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 dosing (not extended interval aminoglycoside

dosing) should be used.

Enterococci are considered clinically resistant if their MIC is > 2000 mcg/mL. 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. This however is not the situation with tobramycin or amikacin where these are not typically recommended as adjunct therapy for *Enterococcus* infections.

Staphylococci:

The value of aminoglycosides as adjunctive therapy for staphylococci has been extensively questioned in the literature. Data suggest that the addition of an aminoglycoside to nafcillin therapy shortens the duration of bacteremia by about one-half day. No beneficial effect has been shown for a reduction in mortality. Despite these data, aminoglycosides are used by many clinicians in this situation. If an aminoglycoside is to be 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 traditional dosing. However, data are limited. Little data is available concerning once-daily dosing in *Staphylococcal* infections being primarily managed with either vancomycin or a beta-lactam antibiotic.

- **Anaerobic Infections** – Anaerobes are intrinsically resistant to aminoglycosides.

Toxicity/ Side Effects

- The two most concerning adverse effects are ototoxicity and nephrotoxicity; 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 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 rarely cause neuromuscular blockade.

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	1 hour post IM injection 30 min post 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 (once-daily) Dosing ^{5,6}	Not indicated.	Not indicated	G: \$10.43 T: \$13.75 A: \$15.78	Obtain random level 6-14 hours after the start of infusion. No significant accumulation with multiple dosing; therefore, levels can be obtained after the first dose.

Dosing

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 or individualized dosing strategies and thus increase the $C_p\text{-max}/\text{MIC}$ 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 should also assist in preventing the development of adaptive resistance. The optimal timeframe for this period is presently unknown.

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 the tissue. Uptake of aminoglycosides by tissues (e.g. nephron) is a saturable process. 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.

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

Of the two approaches, EIAD is preferred over traditional dosing in patients that meet EIAD eligibility criteria.

Extended-Interval Aminoglycoside Dosing (EIAD) or Once Daily Dosing ^{5,6}

- The benefits of EIAD include:
 - Aminoglycosides have concentration dependent activity. 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 $\geq 10:1$ to maximize bacterial killing.
 - The combination of a high peak and an “aminoglycoside-free” interval will help to reduce the selection and the emergence of resistant organisms (by eliminating the adaptive resistance phenomena) and minimize aminoglycoside-associated toxicity. A high aminoglycoside peak concentration leads to a longer duration of post-antibiotic effect (PAE).
- **Exclusion criteria** - pregnancy, breastfeeding, burns (>20%), ascites, *Enterococcal* endocarditis, and 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 Gram-negative bacilli infection, except for those that meet the exclusion criteria.
- See the EIAD protocol specific to patients with Cystic Fibrosis in the next section
- Dosing
 - Use Actual body weight (ABW)
 - If patient is obese (>20% over ideal body weight - IBW) use dosing body weight (DBW)
$$DBW = IBW + [0.4 (ABW - IBW)]$$
 - Tobramycin/ gentamicin - dose at 7 mg/kg (may use 5 mg/kg for UTI)
 - Amikacin - dose at 15 mg/kg

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 only in the following situations:
 - Random serum level 6-14 hours **AFTER THE START** of the infusion of 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, inappropriate times, etc.)
 - Weekly monitoring of prolonged therapy with aminoglycosides
 - 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 10h post-dose level 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, plot $\frac{1}{2}$ of the serum concentration on the nomogram.
 - 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.

Figure 1. Hartford Nomogram

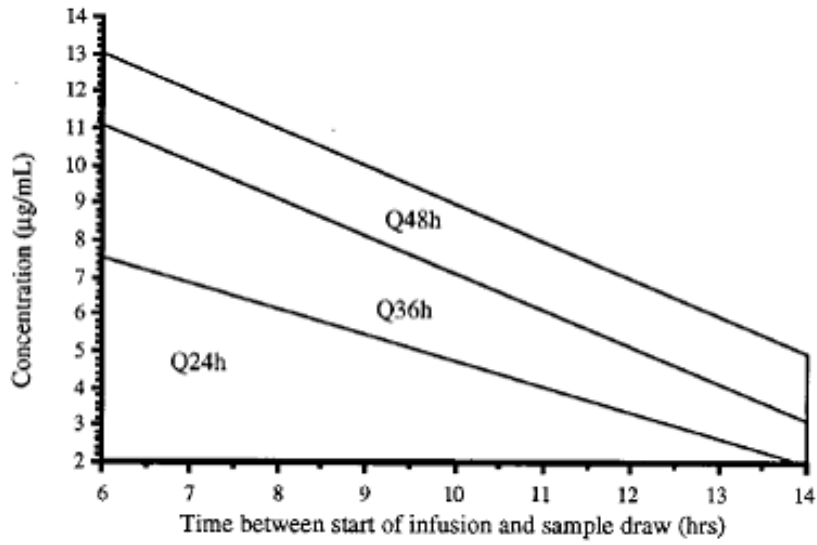


FIG. 1. ODA nomogram for gentamicin and tobramycin at 7 mg/kg.

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

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

$$1. \text{ CrCl} = \frac{(140 - \text{age}) \times \text{IBW}}{72 \times \text{SCr}} \quad (\times 0.85 \text{ if female})$$

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 population kinetics to calculate a dosing regimen (see Pharmacokinetic Pocket Card and use “empiric” formulas). Use DBW = IBW + [0.4(ABW – IBW)] if patient ABW >20% over IBW. A loading dose should be considered in severe infections.

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

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

$$2. \text{ C}_{\text{max actual}} = \frac{C_{\text{max}}}{e^{-\text{kel}(t_{\text{end}})}}$$

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.

Desired Levels for Various Infections

Medical Condition	Desired Peak	Desired Trough
<i>Gentamicin/ Tobramycin</i>		
Synergy (Gram-positives)	3-5	<1
UTI, endometriosis, pyelonephritis	4-6	<1
Tissue Infections, pneumonia, sepsis	8-10	<2
Cystic Fibrosis	10-12	<1
<i>Amikacin</i>		
Moderate Infections	15-25	<5
Severe Infections	25-40	<10

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Extended interval aminoglycoside dosing in patients with cystic fibrosis at TNMC

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 nephrotoxicity.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 FEV₁ 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 efficacy¹⁻⁵
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 O, 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, 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 with the intention of approximating these exposure goals while limiting prolonged drug-free intervals in patients with very rapid renal elimination.

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

Exclusion: CrCl of <20 mL/min should be dosed 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 dosing body weight (DBW)

$$IBW_{Male} = 50 + (2.3 \times \text{inches over 5 ft}) \quad IBW_{Female} = 45.5 + (2.3 \times \text{inches over 5 ft})$$

$$DBW = IBW + [0.4 (ABW - IBW)]$$

2. Determine initial dose

Tobramycin: 10 mg/kg

Amikacin: 20 mg/kg

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.

4. Determine elimination rate and half-life

$$kel = \frac{\ln(C_{2 \text{ hr}}/C_{6 \text{ hr}})}{\text{time (hr) between the two levels}}$$

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

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
<2 hours	See note below [§]
2 to 4 hours	Q24h
>4 to 6 hours	Q36h
>6 to 8 hours	Q48h
>8 hours	Convert to traditional dosing [‡]

[§]**Note:** Due to rapid clearance, patients with a half-life of <2hrs may not receive adequate aminoglycoside exposure and will also have a prolonged drug-free period. Consider switching to a flat dose of 7mg/kg q12h for tobramycin and 15 mg/kg q12h for amikacin. For this regimen, continue to monitor serum levels at 1 and 5 hrs after end of 1 hr infusion to verify half-life remains <2hrs.

[#]Twice daily regimen not recommended for outpatient therapy

[‡]Traditional dosing goals: -tobramycin peaks of 10-12 mcg/mL & troughs <1 mcg/mL
-amikacin peaks of 15-25 mcg/mL & troughs of <5 mcg/mL

6. Determine Cmax (back-extrapolated to end of one-hour infusion)

$$C_{max(\text{end of infusion})} = \frac{C_{max}}{e^{-kel(t_{end})}}$$

Goal Cmax 20-30 mcg/mL for tobramycin and 30-45 mcg/mL for amikacin

7. If Cmax_(end of infusion) is outside goal range, increase or decrease dose by 10% and repeat steps 3-7 with next dose.

Continued on next page

8: Inpatient monitoring:

-Pharmacist will obtain either a 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.

Outpatient monitoring:

-Troughs and serum creatinine drawn every four days or earlier as clinically indicated. If the trough is elevated or renal function changes than 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 pharmacodynamics predictor of outcomes, however data are limited. Vancomycin is indicated for the treatment of severe staphylococcal infections (including methicillin-resistant staphylococci), endocarditis (including staphylococcal, streptococcal), and in the treatment of pseudomembranous colitis caused by *C. difficile* (given orally only).²

Vancomycin is also utilized for infections caused by penicillin-susceptible pathogens in patients who are penicillin-allergic. 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 ampicillin, respectively. For this reason, many authors suggest that unless the patient has an allergy to beta-lactams or has a methicillin-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 not 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

Continued empiric therapy

Selective gut decontamination

MRSA colonization

Primary therapy for pseudomembranous colitis

Topical application or irrigation

Treatment of MSSA or other beta-lactam susceptible Gram-positive infections 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

Pharmacokinetic Parameters^{1,4,5}

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

Distribution – 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.

Elimination – 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.

Therapeutic Plasma Concentrations – peak = 30-40 mcg/mL, trough = 10-20 mcg/mL .

Troughs of 15-20 mcg/mL are indicated for patients being treated for documented or suspected *Staphylococcus aureus* bloodstream infections, endocarditis, pneumonia, meningitis, and osteoarticular infections.

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, the 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 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. This effect, however, seems to be relatively rare when vancomycin is used as monotherapy. 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 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 However, the causal relationship is difficult to discern from these studies because of small sample sizes, retrospective study design (for all but one), and a number of potential confounding factors including concomitant nephrotoxins. 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.

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,⁴ limited human data are available to suggest better clinical outcomes with attainment of such a target.

Because obtaining multiple serum vancomycin concentrations for the calculation of the AUC is difficult in the clinical setting, vancomycin trough concentrations are used as a surrogate marker for monitoring vancomycin therapy. A consensus paper on therapeutic monitoring of vancomycin recommends 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} Recent evidence has provided some support for targeting troughs of 15-20 mcg/mL in patients with MRSA bloodstream infections. Kullar et al found that failing to obtain a first trough concentration of at least 15 mcg/mL was independently associated with higher rates of treatment failure.²³ However, a clear correlation between achievement of such trough concentrations and clinical outcomes has not been consistently demonstrated; patient severity of illness, source of infection, and vancomycin MIC are frequently confounding variables.¹⁶ This range of trough concentrations is recommended in order to prevent the development of resistance¹⁷⁻¹⁹ and increase the probability of attaining the target AUC/MIC ratio.⁴

Sampling considerations

Justification for monitoring peak concentrations with vancomycin is lacking for most populations. 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; (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 exact infusion time and exact draw time for the lab must be documented and reported. Given that peak levels have not been clearly correlated with efficacy or toxicity, abandoning the measurement of peak vancomycin concentrations would eliminate the confusion surrounding their interpretation. Furthermore, Sanders has suggested that, provided the trough concentration is within recommended limits, the peak level is unlikely to reach a potentially toxic range.²⁰

Indications for Monitoring Serum Vancomycin Concentrations^{9,21,22}

- Monitoring is NOT recommended in the following settings:
 - Patients treated for less than five days with target trough levels <15 mcg/mL.
 - Patients receiving oral vancomycin.

- Vancomycin serum levels ARE recommended in the following settings:
 - Patients requiring aggressive vancomycin dosing with target trough concentrations between 15-20 mcg/mL. TROUGH ONLY.
 - Patients receiving vancomycin/aminoglycoside or vancomycin/amphotericin B combination therapy or other concomitant nephrotoxins. TROUGH ONLY.
 - Anephric patients undergoing hemodialysis and receiving infrequent doses of vancomycin for serious systemic infections. RANDOM TROUGH prior to dialysis per the Nephrology protocol (preferred) or 4 hours after dialysis.
 - Patients with rapidly changing renal function*. TROUGH ONLY.
 - Patients receiving prolonged (>5 days) vancomycin therapy. TROUGH ONLY.
 - Patients receiving higher than usual doses of vancomycin (adults: > 20 mg/kg/dose, pediatrics: > 60 mg/kg/day). TROUGH ONLY.
 - Morbidly obese patients. TROUGH ONLY.
 - Reaffirm a seriously abnormal or unusual serum concentration (i.e., line draws, inappropriate times, 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 = 50% increase/decrease or 0.5 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

*Troughs of 15-20 mcg/mL are indicated for patients being treated for documented or suspected *S. aureus* bloodstream infections, endocarditis, pneumonia, meningitis, and osteoarticular infections.

*Not routinely recommended

Vancomycin Pharmacokinetic Calculations

Definitions

IBW	=	ideal body weight
ABW	=	actual body weight
DBW	=	dosing body weight
k _{el}	=	elimination rate constant
V _d	=	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

$$1. CrCl = \frac{(140 - \text{age}) \times IBW}{72 \times SCr} \quad (\times 0.85 \text{ if female})$$

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

- Use population kinetics to calculate a dosing regimen (see Pharmacokinetic Pocket Card and use “empiric” formulas). Use ABW, even for obese patients.
- A loading dose of 25-30 mg/kg (based on ABW) may be considered for more rapid attainment of target trough concentrations in seriously ill patients.⁴ Early attainment of 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 trough values. Set up a proportional relationship to estimate the actual trough based on new dose.

$$\frac{C_{min}(\text{actual})}{x} = \frac{\text{Current total daily dose}}{\text{New total daily dose}}$$

x = estimated new trough based on new dose

Ex. Pt. receiving 1000mg IV q12h and resulting trough is 11 mcg/mL with a goal level between 15-20 mcg/mL. 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%.

$$\frac{11 \text{ mcg/mL}}{x \text{ mcg/mL}} = \frac{2000 \text{ mg}}{3000 \text{ mg}} \quad \text{Therefore, } x = 16.5 \text{ mcg/mL}$$

Thus, the new dose of 1500mg IV q12h would be expected to produce a trough of ~16.5 mcg/mL.

Note: Altering the dosing frequency will have larger effects on the resulting trough than suggested by the proportion. 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 trough would be higher than 16.5 mcg/mL as suggested by the proportion. Similarly, in instances where the dosing frequency is being decreased, the resulting trough will be lower than the proportion suggests.

Individualized Dosing (peak/trough obtained) – Calculate patient-specific kel and Vd

Note: Peak rarely indicated, see indications for monitoring above.

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

2. $C_{max_{actual}} = \frac{C_{max}}{e^{-kel(t_{end})}}$

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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Clinical Pearls for Aminoglycosides and Vancomycin

Dialysis Considerations

Aminoglycosides

- 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.
- When indicated, we recommend obtaining a random level 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 they can redistribute from the tissues back into the bloodstream.

Vancomycin

- We assume that approximately 20-30% of the drug is removed by a standard hemodialysis session. 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.
- **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 will 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 pre-HD vancomycin serum concentration targets of this protocol are 15-20 mcg/mL.

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

Maintenance Dosing: 750 mg IV with each dialysis until dosage changed or discontinued (administered during the last hour of 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 third (3rd) post-load dialysis session, a pre-dialysis vancomycin trough level will be drawn: 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 two dialysis sessions to ensure level is stable, then weekly.

General dosing strategy:

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.

Examples:

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 during the last hour of 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 CONSULT SERVICE

- Automatically consult on all aminoglycoside and vancomycin orders.
- Consult on any other therapeutically monitored drug on request.
- Initial note – All new orders need to have an initial PK note written, predicting levels based on empiric (population) PK parameters, including our recommendations. The ONLY exceptions to 1st note are NICU, CF, and post-op ($x \leq 3$ doses). **However, ALL new orders still need to be checked for appropriateness** (e.g., the NICU is based on a nomogram, CF patients' doses are based on past doses and/or a mg/kg basis, post-op's (esp AG's) need to be changed if interval is not appropriate for patient's age/renal function).
- Whenever levels are obtained, a note should be written (even if the levels weren't ordered or the patient is not at steady-state). It is our job to interpret the levels. NOTE: When making a recommendation on whether or not to obtain levels, please refer to the guidelines on the bottom of the kinetics consult sheets (vancomycin and aminoglycosides). Levels should be obtained near steady state (at 4 to 5 half-lives). Thus, this can help you figure out with which dose to obtain levels (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 and document the interaction in EPIC/OneChart via I-Vents.)
 - Inappropriate initial dose regimen
 - Questionable levels – need to redraw
 - Potentially toxic or subtherapeutic levels
- We need to have a physician's order to change or order anything.
 - If we are specifically consulted by a physician (i.e., they write, "gentamicin, pharmacy to dose"), sometimes it is not necessary to call when changing the dose and ordering levels – depending on physician and patient (i.e., write order as a verbal order from Dr. _____).
- Every patient should be monitored EVERY DAY, and the monitoring calendar should be updated every day. (WBC, BUN, SCr, Tmax, cultures, etc.) NOTE: It is very important to document the microbiology reports on the back of the calendar.
- Communicate with the next pharmacist when levels are due, length of therapy, etc. This includes the central pharmacists, when necessary, on weekends and holidays (i.e., bring a consult form that has been started down to the central pharmacy).

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, would predict steady-state peak and trough on 120 mg IV q12h to be ~3-4 mcg/mL and < 2 mcg/mL, respectively. If desire more aggressive therapy, may consider 140 mg IV q12h for predicted peak and trough of ~5-6 mcg/mL and < 2 mcg/mL, respectively. Suggest checking levels around 3rd dose (when the drug will be at steady-state). Thank you for the consult. Pharmacy will continue to follow.
- Follow-up note:
Gentamicin day #3. Peak level drawn 2 hours after end of infusion, therefore actual peak ~6 mcg/mL. Trough of 0.8 mcg/mL is optimal to minimize risk of oto/nephrotoxicity. Recommend continuing current dose and checking another trough in ~3 days. 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)
- 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 trough 12-15 mcg/mL). Never put an exact number on the consult form when estimating levels. For example, if you calculate an expected vancomycin trough of 11.8 mcg/mL, put a range of +/- 1 (11-13 mcg/mL) on the form. This is not an exact science and should not be purported as such!
- If you calculated the estimated creatinine clearance via Cockcroft-Gault and it is > 100 ml/min, we round down to 100 ml/min (i.e., we do not use a value greater than 100 ml/min in our calculations) because this is typically the maximum value for adult men and women. Put ">100 ml/min" in the blank for CrCl, and use 100 ml/min in your calculations.
- 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 (e.g., *S. aureus* bacteremia, empiric treatment s/p abdominal abscess drainage rather than *S. aureus* or empiric treatment)
- Don't diagnose (e.g., "possible pneumonia")
- Limit liability
- Be professional
- *ALWAYS READ CHART BEFORE WRITING NOTE*