MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

PHARMACOKINETIC REVIEW:
VANCOMYCIN – PEDIATRIC PATIENTS

Abbreviations		
IBW = ideal body weight	Vd = volume of distribution	$T_{½}$ = half-life
CBW = current body weight	C_{pss} = peak serum level at steady-state	C_p = peak serum level
ABW = adjusted body weight	C_t or C_{min} = trough serum level	C_{tss} = trough, steady-state
SCr = serum creatinine	τ = Tau (dosing interval)	t_{inf} = time of infusion
k_e = elimination rate constant	t2 = time from end of infusion to blood draw	Δ t = time between levels
CrCl = creatinine clearance (see CPC renal dosing standard for additional information)		

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Aminoglycoside Overview

Pharmacokinetic Terms and Principles

Extended interval dosing

- Dosing approach using a higher total dose given less frequently in order to optimize the Peak:MIC ratio and minimize risk of toxicity
- Goal peak concentrations are higher than with traditional dosing, goal trough concentrations are lower than with traditional dosing (essentially undetectable)
- Frequency/dosing interval is variable and can range from every 12 hours to every 48 hours

K_e (or Kd or k) 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. To be accurate, at least one half-life should occur between the levels, and some suggest at least 2-4 half-lives should occur between the levels[1].

$t_{1/2}$ 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 $t_{½}$ to distinguish it from the distribution half-life, α $t_{½}$, used in two compartment modeling[1].

C_{pss} or Peak Concentration[1]

- C_{pss} is the estimated peak concentration at steady-state (i.e., back-extrapolated to 30-minutes after the end of a 30-minute infusion, or at the end of a 1-hr infusion).
- The peak is the measured drug concentration AFTER distribution

C_{min} Ct or Trough Concentration

- Concentration at the end of the dosing interval just before the next dose (within ~ 30-min of next dose).

Vd or Volume of Distribution[1]

- The volume of distribution is the 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.

Background[2,5]

The aminoglycoside antibiotics – gentamicin, tobramycin, amikacin, netilmicin, kanamycin, streptomycin, and neomycin – are bactericidal and exhibit concentration-dependent killing of susceptible bacteria. 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 that occurs at the ribosome (initiation).

You can find more information about aminoglycosides in the UMHS Antimicrobial Guidelines:
https://pharmwebsp.med.umich.edu/AC/Antimicrobial%20Use%20Guidelines/Review%20of%20antimicrobial%20agents/aminoglycosides.docx

Routes of Administration

- Given IV or IM; also available as topical cream or ointment, and ophthalmic formulations

Pharmacokinetic Parameters[1,2,5]

- Absorption
  - 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 distribute poorly into the CNS
  - There is low binding to plasma proteins
  - The volume of distribution of aminoglycosides approximates the volume of extracellular fluid
    - Neonates: 0.35-0.55 L/kg (mean 0.45 L/kg)
    - Infants/children: 0.3-0.35 L/kg
    - Adults: 0.2-0.5 L/kg (mean – 0.25 L/kg)
    - Cystic Fibrosis (CF): 0.4-0.45 L/kg
  - In patients with ascites, edema, or other enlarged "third space" the volume of distribution is increased; one approach to estimate the volume of distribution in patients with ascites or edema is to increase the volume of distribution by 1 L for each kg of fluid weight gain
  - Aminoglycosides distribute very poorly into adipose tissue

- Elimination
  - Excreted almost entirely by glomerular filtration
  - The $t_{½}$ of aminoglycosides is between ~ 1.5 – 4 hours with normal kidney function (neonates range from 2-9 hours)
  - Aminoglycosides are removed by hemodialysis (~20-30%) and CRRT (clearance dependent on filter, blood flow rate, ultrafiltration vs. dialysis vs. combination, dialysate rate), and to a lesser extent by peritoneal dialysis

Spectrum of Activity and Indications[2,5,6]

- Aminoglycosides have activity against gram-negative organisms (e.g., Enterobacterales, *Pseudomonas aeruginosa*, *Haemophilus influenzae*). While gentamicin previously was considered the first-line aminoglycoside for most indications, resistance to gentamicin in gram-negative organisms has been increasing. If an aminoglycoside is indicated, you should consider the use of tobramycin empirically for hospital-acquired infections caused by a gram-negative pathogen, depending on where the patient is located (e.g., ICU vs. floor) and other potential risk factors for resistant gram-negative pathogens. Exceptions to this are described below.

- Aminoglycosides should NOT be used as monotherapy to treat infections caused by gram-positive pathogens. Aminoglycosides have bactericidal activity against *Staphylococcus* spp. They act synergistically with cell-wall active antibiotics (penicillins, vancomycin) to achieve bactericidal activity against *Enterococcus* spp. Gentamicin (and possibly streptomycin) is usually used for synergy against gram-positive organisms; tobramycin and amikacin are not typically used. Refer to the UMHS guidelines for more information.

- Aminoglycosides are indicated in the treatment of urinary tract infections, bacteremia, respiratory tract infections, gastrointestinal tract infections (including peritonitis), skin and soft tissue infections, endocarditis, osteomyelitis, and meningitis. In general, aminoglycosides are used in combination with a β-lactam antibiotic and are not used as monotherapy in the treatment of these infections (except possibly in uncomplicated cystitis).

Toxicity/ Adverse Effects[2,5,6]

- The most concerning adverse effects associated with aminoglycoside therapy are nephrotoxicity and ototoxicity; aminoglycosides can rarely cause neuromuscular blockade. They have also been associated with exacerbations of myasthenia gravis.

- Most available data correlate aminoglycoside trough concentrations with risk of nephrotoxicity. Steady-state trough concentrations above ~ 2 mcg/mL (gentamicin/tobramycin) or above ~ 8-10 mcg/mL (amikacin) are associated with increased risk of nephrotoxicity.
- There is not a clear relationship between defined aminoglycoside concentrations and ototoxicity. Clinicians should consider audiology testing (at baseline and follow-up) in all patients exposed to aminoglycosides for >2 weeks.
- Toxicity may be related to overall exposure to aminoglycosides. There have been reports of toxicities in patients with levels in the therapeutic after prolonged courses of aminoglycosides (e.g., >2 weeks), or patients with CKD (e.g., although levels are "normal", elimination is significantly prolonged, so overall exposure/AUC is increased).
- Risk factors for aminoglycoside-associated nephrotoxicity:

  1. Advanced age
  2. Previous aminoglycoside administration
  3. Concurrent use of loop diuretics or other nephrotoxic agents
  4. Chronic diuretic therapy
  5. Pre-existing kidney disease
  6. Prolonged courses of aminoglycoside therapy
  7. Administration of IV contrast

Dosing of Aminoglycosides

Traditional (TDA) versus Extended Interval Dosing (EIDA) of Aminoglycosides

- TDA: Smaller doses (e.g., 1.5 – 2.5 mg/kg (tobramycin, gentamicin)), given more often (q8 – 48h)
- EIDA: Larger doses (e.g., 7.5 mg/kg (tobramycin, gentamicin)), given less often (q24 – 48h)
- IMPORTANT NOTE:
  - "Once daily" is a confusing term, use "extended interval" instead
    - Patient on TDA may receive q24h dosing (patient with CrCl = 20 mL/min)
    - Patient on EIDA may receive q36h or q48h dosing (patient with CrCl = 50 mL/min and resultant levels were elevated. Based on these levels, it was determined that a dose of 7.5 mg/kg q36h achieved optimal peak/trough levels.)

Extended-Interval Dosing of Aminoglycosides (EIDA)[2,7-10]

- Data from randomized controlled trials suggests that extended interval administration of aminoglycosides results in similar efficacy and perhaps a decreased risk of toxicities compared to traditional dosing.
  - Aminoglycosides exhibit concentration-dependent killing of **gram-negative** bacteria. The rate of bacterial killing increases as drug concentration rises. Generally, a peak aminoglycoside concentration/MIC ratio of 10:1 needs to be achieved to maximize the bactericidal effect.
  - The combination of a high peak and a longer duration of drug free interval can minimize aminoglycoside-associated nephrotoxicity, and may help to reduce the selection and the emergence of resistant organisms.
  - A high peak concentration of aminoglycosides leads to a longer duration of post-antibiotic effect (PAE) (continued bacterial killing despite concentrations falling below the minimum inhibitory concentration).
- EIDA should NOT be utilized in patients with Infective Endocarditis due to gram-positive organisms (synergy dosing). Contrary to gram-negatives, aminoglycosides display Time Dependent killing against this organism. Smaller doses given more frequently, then, is preferred. Aminoglycosides, just like penicillins and vancomycin, are NOT bactericidal against *Enterococcus* and *Streptococcus* isolates with high penicillin MICs. However, the combination of an aminoglycoside + cell-wall active agent may result in bactericidal activity (synergy), by this proposed mechanism: the cell-wall active agent perturbs the enterococcal cell wall enough to allow the aminoglycoside to enter the cell and exert a bactericidal activity. Theoretically, then, the optimal approach would be one in which a constant concentration of aminoglycoside is available to interact with the cell-wall active agent at the site of infection. Again,

smaller doses given more frequently would be preferred. Recognize that patients may be switched to a consolidated once-daily regimen when discharged for convenience.

- In addition, select patients may not be able to safely achieve an appropriate peak and trough concentration using the extended-interval approach (for example, a patient with a CrCl of 10 mL/min would not achieve a trough <2 for several days after a single dose). A general rule is that if a patient would require >48h dosing in order to meet peak/trough goals with EIDA dosing, then the patient should be converted to TDA. In these scenarios, consider changing to **traditional dosing of Aminoglycosides (see recommendations below).**
- The below patient populations may require more frequent monitoring and should be expected to have unpredictable pharmacokinetics:
  - Renal dysfunction (CrCl <40 mL/min): Most patients with renal dysfunction should receive traditional dosing; extended-interval dosing may be considered in very specific patient scenarios (ICU patients with severe sepsis/shock possibly colonized with/infected with multi-drug resistant gram-negative organisms). These patients should be given a single dose, with subsequent doses based on levels (see section on dosing in critically ill patients below).
  - Critically-ill patients (see separate section concerning ICU patients below)
  - Morbid obesity (≥200% IBW)
  - Anasarca
  - Meningitis
  - >20% BSA burns
  - Pregnancy
  - End Stage Liver Disease or Ascites
  - Cystic Fibrosis

Dosing Recommendations:

See Pediatric Aminoglycoside Dosing and Monitoring Guideline

Serum concentration monitoring with Extended Interval Dosing of Aminoglycosides:

- Monitor for signs/symptoms of infection (e.g., T_{max}, WBC, cultures and sensitivities)
- Monitor kidney function (BUN/SCr at least 2 – 3 times/week, UOP daily)
- Serum concentrations should be monitored in all patients receiving aminoglycosides for a duration of therapy projected to exceed 48 hours
- Please be purposeful in selecting between "trough", "random", and "peak" orders. In many settings, levels should be termed "random", such as pre- HD levels, levels in patients being dosed by level, and 18-, 2-, and 12- hour levels in patients receiving extended-interval aminoglycoside dosing. Ordering a "trough" in a patient who is being dosed by levels will lead to unnecessary actions by the lab and service caring for the patient.
- After the 1st dose: Obtain 2 **random** levels at least one half-life apart (e.g., ~ 2-3 hours after start of infusion, and then ~ 6 – 10 hours later (or, ~ 8 – 12 hours after the start of infusion)); calculate PK parameters and back-extrapolate peak concentration (back-calculate to the time at the end of the 1-hour infusion) and 18-hour and/or trough concentrations (there should not be significant accumulation with multiple dosing, therefore, levels can be obtained after the 1st dose).
  - Select patients with CrCl >60 mL/min and with none of the above criteria associated with unpredictable pharmacokinetics may be monitored solely with an initial 18-hour level
- Subsequent monitoring of levels depends on the indication for aminoglycoside therapy, patient clinical status, renal function, and initial serum concentrations. The following provides guidance on frequency of monitoring serum concentrations:

Significant dosing changes after the initial level(s), significant changes in serum concentration, changes in fluid status, or changes in renal function	Every 2 – 3 days

Stable ICU patients, or patients with mild-moderate changes in dose, renal function or fluid status	Every 3 – 5 days
Floor patient with at least 2 consecutive levels within goal range and stable renal function and fluid status	Every 5 – 7 days

- In ALL cases, dosing and frequency of monitoring requires assessment of the patient (e.g., clinical status, renal function, serum concentrations), indication for therapy, assessment of potential risk factors for treatment failure and/or toxicity, and good clinical judgment
- In **stable** patients, may consider monitoring 18-hour levels, with goals as listed below.

Serum concentration monitoring with Traditional Dosing of Aminoglycosides:

- Monitor for signs/symptoms of infection (e.g., T_{max}, WBC, cultures and sensitivities)
- Monitor kidney function (BUN/SCr at least 2 – 3 times/week, UOP daily)
- Serum concentrations should be monitored in all patients receiving aminoglycosides for a duration of therapy projected to exceed 48 hours
- Peak and trough concentrations should be monitored in patients receiving Traditional Dosing of Aminoglycosides. Order peak and trough around the 4th dose.
- Subsequent monitoring of levels depends on the indication for aminoglycoside therapy, patient clinical status, renal function, and initial serum concentrations; serum concentrations should be monitored every 3 – 7 days.
  - In ALL cases, dosing and frequency of monitoring requires assessment of the patient, indication for therapy, assessment of potential risk factors for treatment failure and/or toxicity, and clinical judgment
  - In stable patients, may consider monitoring 18-hour levels, with goals as listed below.

Renal Function Calculations:

- Pediatric - Bedside Schwartz: $estimated\ GFR\ \left(\frac{\frac{mL}{min}}{1.73\ m^2}\right) = \frac{0.413 * height\ (cm)}{SCr\ (\frac{mg}{dL})}$
- Adult - Cockcroft-Gault: $Estimated\ CrCl\ \left(\frac{mL}{min}\right) = \frac{(140 - age) * IBW\ (kg)}{72 * SCr\ (\frac{mg}{dL})}$
- Calculate GFR from CRRT clearance: $Estimated\ GFR\ \left(\frac{mL}{min}\right) = D\ rate\ \left(\frac{mL}{hr}\right) * \frac{1\ hr}{60\ min} * \frac{1.73\ m^2}{BSA\ m^2}$

Administration Notes:

- Gentamicin/tobramycin doses <300 mg – Infused over 30 minutes
- Gentamicin/tobramycin doses ≥300 mg – Infused over 60 minutes
- Amikacin doses <1000 mg – Infused over 30 minutes
- Amikacin doses ≥1000 mg – Infused over 60 minutes

Assessing and/or Adjusting a dose based on 2 serum concentrations (traditional dosing and extended-interval dosing):

Option 1: PK Calculator

https://www.med.umich.edu/asp/misc/UMich_PK_Calculator.xlsx

Option 2: Manual Calculation

τ = dosing interval (hours)
k_e = elimination rate constant (hr^{-1})
t_{inf} = time of infusion (hours)

Step 1: Calculate k_e and half-life using patient-specific data/levels

$$k_e(hr^{-1}) = \frac{\ln\left(\frac{C_1}{C_2}\right)}{\Delta t} \qquad t_{1/2} = \frac{0.693}{k_e}$$

Step 2: Back-calculate C_{pss} and C_{min} (remember, C_{pss} is concentration at 30-minutes after 30-minute infusion, or at the end of a 1-hour infusion). The below equation can be utilized to calculate any concentration (including peak, trough, 18-hour, etc.).

$$C_2 = C_1 e^{-k_e(\Delta t)}; \qquad \Delta t = time\ between\ C_1\ and\ C_2\ (hours)$$

IMPORTANT: C_1 MUST be a HIGHER concentration than C_2 for this equation to be accurate.

Step 3: If levels are within desired ranges, no changes needed. If not, calculate a new dose and/or interval using patient-specific data.

Step 4: Calculate Vd_{ss} for use in subsequent equations

$$Vd_{ss} = \frac{Dose*(1-e^{-k_e*t_{inf}})}{t_{inf}*k_e*(C_{max}-\left[C_{min}*e^{-k_e*t_{inf}}\right])}$$

Step 5: Calculate new dosing interval (τ)

$$\tau(hr) = \frac{ln\left(\frac{C_1}{C_2}\right)}{k_e} + t_{inf}; \qquad C_1 = Goal\ peak; \quad C_2 = Goal\ trough$$

Step 6: Calculate new dose

$$Dose\ (mg) = \frac{t_{inf}*k_e*Vd*C_1*(1-e^{-k_e(\tau)})}{(1-e^{-k_e\left(t_{inf}\right)})}; \qquad C_1 = Goal\ peak$$

Step 7: Calculate new C_{pss} and C_{min}

$$C_{pss}(\frac{mcg}{mL}) = \frac{Dose * (1 - e^{-k_e(t_{inf})})}{k_e * t_{inf} * Vd * (1 - e^{-k_e(\tau)})}$$

$$C_{min} = C_{pss} * e^{-k_e(\Delta t)}; \qquad \Delta t = time\ between\ C_{pss}\ and\ C_{min}\ (hours)$$

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UMHS Antimicrobial Guidelines - Aminoglycosides:
https://pharmwebsp.med.umich.edu/AC/Antimicrobial%20Use%20Guidelines/Review%20of%20antimicrobial%20agents/aminoglycosides.docx

UMHS Guidelines for Antimicrobial Use

Vancomycin Overview

Background[1,2]

Vancomycin is a tricyclic glycopeptide antibiotic that exhibits exposure-dependent (AUC-dependent) killing of susceptible bacteria by blocking peptidoglycan polymerase (glycopeptide polymerization) in the bacterial cell wall, resulting in inhibition of cell wall synthesis and secondary damage to the cytoplasmic membrane. Vancomycin exhibits bactericidal activity against most gram-positive pathogens, except for Enterococcus sp. (bacteriostatic activity).

Routes of Administration

- IV for systemic infections; should not be given IM
- Oral or rectal for the treatment of Clostridium difficile infection

Pharmacokinetic Parameters[1-5]

Absorption – Oral absorption is negligible under normal conditions, and it does appear to concentrate in the colon (e.g., for treatment of infection caused by C. difficile). However, patients with significant inflammation of the colon can have absorption and detectable serum concentrations. Per the package insert for oral vancomycin, clinically significant serum concentrations have been reported in some patients who have taken multiple oral doses of vancomycin for treatment of C. difficile colitis. Therefore, monitoring of serum vancomycin concentrations may be appropriate in some clinical situations (e.g., patients with impaired kidney function receiving PO vancomycin, especially for longer courses of therapy).

Distribution – Widely distributed into body tissues, with limited distribution into CSF. Penetration into the CSF is enhanced with inflamed meninges (e.g., meningitis). Volume of distribution ~ 0.5-0.6 L/kg in children and does not significantly change for most disease states or conditions.

Elimination – When given IV, vancomycin is primarily excreted via kidneys. Oral doses are excreted primarily in the feces. Estimated clearance ~ 0.65 * CrCl. Elimination half-life is ~ 2-3 hours in infants, children, and adolescents with normal renal function. This is prolonged in patients with varying degrees of renal insufficiency.

Spectrum of Activity and Indications[1,3,4]

Vancomycin is indicated for the treatment of documented infections caused by gram-positive pathogens (Staphylococcus sp., Enterococcus sp., Streptococcus sp.) with resistance to beta-lactam antibiotics, or in patients with serious allergic reactions (e.g., anaphylaxis-type reactions) to penicillins and/or cephalosporins. Vancomycin may be used empirically in select patient populations or when MRSA is suspected (e.g., sepsis, healthcare-associated pneumonia, ventilator-associated pneumonia, endocarditis, meningitis, septic arthritis, skin and soft-tissue infections, select febrile neutropenia patients). Oral vancomycin may be used in the treatment of pseudomembranous colitis caused by C. difficile in select patients. However, vancomycin is effective for the treatment of *C. difficile* ONLY when given orally/enterally/rectally. Intravenous vancomycin is NOT effective for the treatment of *C. difficile* colitis.

Toxicity/Adverse Effects[3,6-8]

- Many of the early data/reports of toxicity associated with vancomycin therapy were thought to be due to impurities in the preparation, and it was referred to as “Mississippi Mud” because of its appearance
- When modern formulations are administered properly, vancomycin has a much better safety profile and compares with safety profiles of other antimicrobial agents; however, vancomycin-related adverse effects can still occur, and therapeutic monitoring or serum trough concentrations is warranted
- The most concerning adverse effect associated with vancomycin therapy is nephrotoxicity, although the incidence appears to be low when vancomycin is used appropriately and when not administered with other medications that could increase the risk for nephrotoxicity

- Risk of nephrotoxicity may be increased in patients who are receiving concomitant nephrotoxic medications (e.g., aminoglycosides, amphotericin B), when patients have elevated trough or AUC concentrations of vancomycin, or in patients with reduced kidney function
- Other adverse effects include thrombophlebitis (especially via peripheral IV administration), hypersensitivity (rash, drug fever), neutropenia (usually with prolonged treatment) and thrombocytopenia
- Infusion-related reactions (e.g., "Red Man's Syndrome") can also occur, and are typically associated with rapid infusion; extending the duration of infusion (e.g., from 2 to 4 hours) and pre-medicating with diphenhydramine 1 mg/kg/dose may help to prevent or minimize infusion-related reactions

Dosing

- Vancomycin exhibits exposure-dependent killing (or AUC-dependent killing) of bacteria at therapeutic concentrations, and dosing should target an AUC of 400-600.
- The AUC target for dosing and monitoring is 400-600, regardless of site of infection or organism MIC to vancomycin
- Utilize the Initial dosing of vancomycin in pediatric patients guideline
- If patient recently received vancomycin, review the previous regimen and patient information to initiate the most recent therapeutic dose
- Doses should be based on actual body weight
- Avoid initial doses >3600 mg/DAY in children

Pediatric Monitoring

Goals of therapy for vancomycin:

	Therapeutic Goals

Vancomycin	• AUC is the preferred method of vancomycin monitoring (goal 400-600)
	• Open chest prophylaxis:
	  ○ trough of 5-10 mcg/mL
	• Pre-dialysis:
	  ○ trough <15 mcg/mL
	• Dosing by levels:
	  ○ trough <15 mcg/mL

Monitoring within 48 hours of vancomycin initiation:

- Vancomycin levels should be unnecessary if therapy not anticipated to exceed 48 hours.
- Do not check vancomycin concentrations within the first 48 hours except in the following situations:

Clinical Situation	**Monitoring Recommendation**
The majority of patients will have vancomycin discontinued within 48-72 hours and do not require levels	
Documented gram positive infection	• Obtain 2 vancomycin levels at steady state and calculate AUC to achieve goal AUC of 400-600 • Obtain a random level ~2 hours post-infusion and a trough prior to the next dose for most patients
Septic shock	
Weight >100 kg	
Children with low muscle mass (e.g., muscular dystrophy, cerebral palsy, spinal muscular atrophy)	
Significant acute changes in renal function, CrCl <30 mL/min, therapeutic hypothermia, ECMO, AKI, or neonates <72 hours old whose mothers received peri-partum vancomycin	• Obtain a vancomycin level and dose per level • Monitor random levels in patients and re-dose when level <15 mcg/mL

Monitoring after 48 hours of vancomycin initiation;

- Use the following table to guide monitoring of vancomycin based on the patient's clinical status:

Clinical Situation	Monitoring Recommendation
Patients with stable renal function (including patients with CKD and receiving CRRT)	• Obtain 2 vancomycin levels at steady state and calculate AUC to achieve goal AUC of 400-600 • Obtain a random level ~2 hours post-infusion and a trough prior to the next dose for most patients to calculate AUC • Document individualized trough range that corresponds to AUC of 400-600 for that patient
Patients on conventional dialysis	• Check pre-HD level • Target pre-HD levels of <15
CHC patients within 72 hours of surgery	• Check trough concentration • Redose for trough <10 (for open chest prophylaxis)
Patients who have fluctuating fluid and/or renal status	• Use clinical judgement to determine monitoring strategy • It is reasonable to perform AUC or trough-based monitoring. The instability of renal clearance or volume of distribution should be taken into account when evaluating levels and subsequent dosing

- Doses should not exceed 100 mg/kg/day for most patients.
- Refer to the following table for recommendations on frequency of ordering vancomycin levels and serum creatinine:

Clinical Situation	Monitoring Recommendation
Subsequent levels should be drawn every 1-7 days, and serum creatinine should be monitored at least every 48 hours during entire course of vancomycin therapy. Avoid evening and overnight levels if clinically stable.	
Patients with changing fluid status or renal function	• Obtain levels every 1-3 days • Monitor 2 vancomycin levels to facilitate AUC calculation, when possible • In patients receiving one-time doses (i.e., dosing by level), monitor random levels and re-dose when level <15 mcg/mL
Patients with stable fluid status and renal function requiring long-term therapy	• Obtain levels every 5-7 days, after initial level(s) are therapeutic • Once a patient is on a stable dose with an AUC between 400 and 600, monitoring of vancomycin troughs may be acceptable in patients with stable fluid status and renal function

Additional Monitoring Considerations

- Details on monitoring and re-dosing in intermittent hemodialysis are listed below:
    - If pre-HD level checked: A general rule of thumb is to expect a 10% reduction in vancomycin level for every 1 hour of dialysis. So, in a "standard" 4-hour HD session, one can assume ~30-40% decrease from the pre-HD level. As such:
        - Re-dose after HD if pre-HD level <20. If level >20, consider dose reduction, and if level <10, consider dose increase.
        - If pre-HD level exceeds concentrations listed above, do not administer a dose post-HD
- In general, monitoring of vancomycin serum concentrations is not necessary in patients receiving oral vancomycin therapy; however, patients with inflammation of the colon could have some systemic absorption and detectable serum concentrations of vancomycin. Monitoring of serum concentrations in patients receiving oral vancomycin may be warranted in selected patients (e.g., patients with inflammation of the colon and impaired kidney function, especially those receiving higher doses (e.g., 250 – 500 mg PO q6h) and/or a prolonged duration of therapy).

- In ALL cases, dosing and frequency of monitoring requires assessment of the patient, indication for therapy, assessment of potential risk factors for treatment failure and/or toxicity, and clinical judgment. UMHS vancomycin dosing tables are an excellent resource, however, these should augment good clinical evaluation, and doses should be rounded up or down based on the patient specific factors, specific examples are detailed below.
  - **Be VERY cautious with using aggressive doses in critically ill patients, as most do not clear vancomycin as quickly as would be predicted based on their calculated creatinine clearance.**
  - **Patients with history of acute kidney injury, vasopressor therapy, multiple comorbidities, concomitant nephrotoxic agents, obesity, daily vancomycin dose of ≥3 g are at risk of supratherapeutic levels and toxicity. Conservative dosing and frequent monitoring are warranted in these patients**
  - **Malnourished patients and patients with very low muscle mass commonly have very low baseline serum creatinine (typically <0.5 mg/dL). If you observe a patient with a SCr >0.5 mg/dL, evaluate the patient's history for the baseline SCr, as a "normal" SCr value in these patients could be an indication of renal insufficiency (e.g., if baseline SCr is ~ 0.3 mg/dL and the patient has a measured SCr of 1 mg/dL, this is ~ 3-times higher than baseline)**
  - **Obese patients and patients with large volumes of distribution (CHF, pregnancy, cirrhotic patients with ascites, obesity, septic patient with large volume fluid resuscitation) may need larger initial doses, but are at risk for rapid vancomycin accumulation. Please monitor frequently and don't be afraid to reduce the dose if accumulation is occurring (even if level is within goal range).**

AUC Calculations

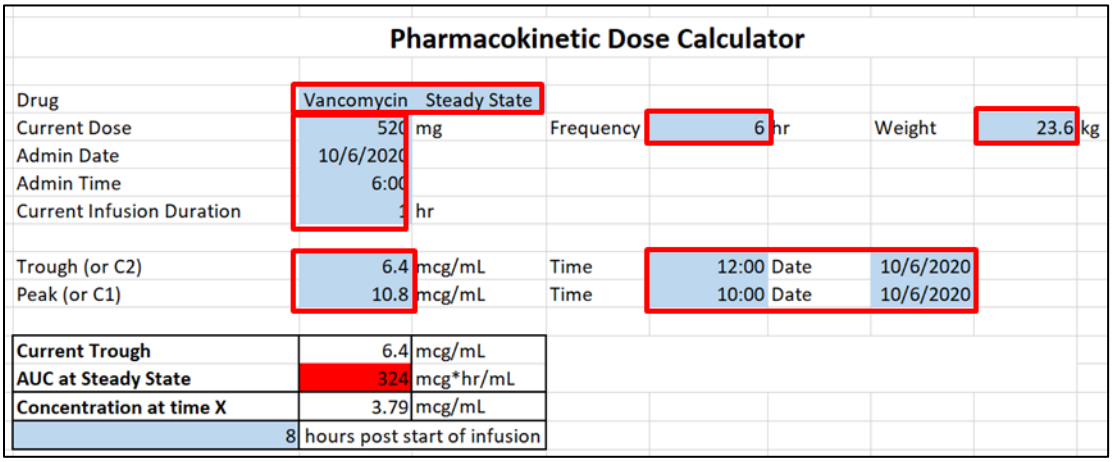
- For patients receiving meet criteria for vancomycin monitoring and have two levels drawn, AUC calculations should be performed using the approved UMHS pharmacokinetic calculator

  https://www.med.umich.edu/asp/misc/UMich_PK_Calculator.xlsx

- Example: Patient RS is a 6-year-old male (dosing weight 23.6 kg) with a MRSA epidural abscess on a vancomycin regimen on 520 mg q6h. At steady state (after the 3rd dose), the following levels are drawn in relation to vancomycin doses:

Vancomycin:	Serum levels:
520 mg x1 18:05 10/5/2020	6.4 mcg/mL 12:01 10/6/2020
520 mg x1 23:45 10/5/2020	10.8 mcg/mL 09:57 10/6/2020
520 mg x1 06:06 10/6/2020	
520 mg x1 12:10 10/6/2020	

Step 1: Insert drug, if monitoring is performed at steady state or after first dose, current vancomycin regimen, weight, and serum level information. Be mindful to select the appropriate infusion duration is selected and that dates and times of levels are accurate.



Pharmacokinetic Dose Calculator

Drug	Vancomycin	Steady State					
Current Dose	520	mg	Frequency	6	hr	Weight	23.6 kg
Admin Date	10/6/2020						
Admin Time	6:00						
Current Infusion Duration	1	hr					
Trough (or C2)	6.4	mcg/mL	Time	12:00	Date	10/6/2020	
Peak (or C1)	10.8	mcg/mL	Time	10:00	Date	10/6/2020	

Current Trough	6.4	mcg/mL
AUC at Steady State	324	mcg*hr/mL
Concentration at time X	3.79	mcg/mL
8	hours post start of infusion	

Step 2: Interpret AUC. The calculator will populate an estimated AUC on the current regimen. Goal AUC is 400-600.

Pharmacokinetic Dose Calculator

Drug	Vancomycin	Steady State					
Current Dose	520	mg	Frequency	6	hr	Weight	23.6 kg
Admin Date	10/6/2020						
Admin Time	6:00						
Current Infusion Duration	1	hr					
Trough (or C2)	6.4	mcg/mL	Time	12:00	Date	10/6/2020	
Peak (or C1)	10.8	mcg/mL	Time	10:00	Date	10/6/2020	
Current Trough	6.4	mcg/mL					
AUC at Steady State	324	mcg*hr/mL					
Concentration at time X	3.79	mcg/mL					
8	hours post start of infusion						

For this patient, the calculated AUC is sub-therapeutic (<400 mcg*hr/mL). Evaluation of AUC should also include an assessment of renal and fluid status as significant shifts in either parameter can result in sub- or supra-therapeutic levels. For this patient, a dose adjustment is indicated.

Step 3: Determine new dosing regimen to obtain a goal AUC of 400-600 by inputting values for “new dose,” “new interval,” and “new infusion duration,” if needed.

New Dose	650	mg	27.5	mg/kg
New Interval	6	hr		
New Infusion Duration	1	hr		
New Trough	8.0	mcg/mL		
New Steady State AUC	407	mcg*hr/mL		
Trough Range for AUC goal*	7.9 - 11.8	mcg/mL	* based on new infusion duration	

The dosing regimen should achieve a new steady state AUC of 400-600 and will display the corresponding predicted new trough. Additionally, the calculator will automatically populate a trough range corresponding to an AUC of 400-600 and the dose in mg/kg.

Additional components of the AUC calculator:

- Patient-specific pharmacokinetic parameters including k_e, $t_{½}$, and Vd are calculated and displayed on the right-hand side of the calculator
- The “concentration at time X” function can be used to determine a concentration at any time post-start of infusion to guide timing of next dose

Equations:

Rate elimination constant	$k_e = \frac{\ln\left(\frac{C_1}{C_2}\right)}{\Delta t}$; $\Delta t = \tau - t_{inf} - t_{pk} - t_{tr}$ $\tau = dosing\ interval$; $t_{inf} = time\ of\ infusion$; $t_{pk} = time\ from\ end\ of\ infusion\ to\ peak\ drawn$; $t_{tr} = time\ from\ trough\ to\ next\ dose$
Half-life	$t_{1/2} = \frac{0.693}{k_e}$
Maximum serum concentration	$C_{max} = \frac{C_1}{e^{-k_e * t_{pk}}}$
Minimum serum concentration	$C_{min} = C_1 * e^{-k_e * t_{tr}}$
Volume of distribution (1st dose)	$Vd\ (1^{st}\ dose) = \frac{Dose * (1 - e^{-k_e * t_{inf}})}{t_{inf} * k_e * C_{max}}$
Volume of distribution (steady state)	$Vd_{ss} = \frac{Dose * (1 - e^{-k_e * t_{inf}})}{t_{inf} * k_e * (C_{max} - [C_{min} * e^{-k_e * t_{inf}}])}$
24 hour Area-under-the-curve	$AUC_{24} = (AUC_{inf} + AUC_{elim}) * \frac{24}{\tau}$; $AUC_{inf} = \frac{(C_{max} + C_{min})}{2} * t_{inf}$ $AUC_{elim} = \frac{(C_{max} - C_{min})}{k_e}$
New total daily dose for target AUC	$TDD\ (mg) = k_e * Vd * AUC_{goal}$
New dose	$Dose\ (mg) = \frac{TDD}{\left(\frac{24}{\tau}\right)}$
New trough	$C_{min} = \frac{Dose * e^{-k_e * (\tau - t_{inf})}}{Vd * (1 - e^{-k_e * \tau})}$

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