Therapeutic Drug Monitoring Service

Clinical Pharmacokinetics Service Guidelines

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Disclaimer: This Manual is provided to assist with the clinical pharmacokinetic monitoring and management of selected drugs by the Department of Pharmaceutical Services at Vanderbilt University Hospital. Information contained in the manual has been derived from currently available information and reputable sources, the editors (s) do not assume any liability in connection with the use of any specific information contained herein. While great care has been taken to ensure the accuracy of the information presented, the reader is advised that is it possible that these pages contain some errors and omissions. If you find an error or omission, please contact Ben Ereshefsky at (615) 343-3478 or ben.ereshefsky@vumc.org.

The information provided in the manual is not intended to replace sound clinical judgment in the delivery of patient care. Dosing of monitored medications require independent and informed decisions by appropriate healthcare professionals. Also, the information in the manual may not be applicable to other healthcare institutions. Complete information concerning drug administration, dosage, sampling times, clinical laboratory procedures, pharmacokinetic data, and pharmacological and toxic effects of monitored medications should be assessed and contrasted with other sources prior to its clinical use.

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Pharmacists Role in Clinical Pharmacokinetic Monitoring

Am J Health Syst Pharm 1998 Aug 15; 55(16):1726-7.

- Designing patient-specific drug dosage regimens based on pharmacologic characteristics of the drugs used, the objectives of drug therapy, concurrent disease and drug therapy, and other pertinent patient factors.
- Monitoring and adjusting dosage regimens based on pharmacologic responses and on biological fluid (e.g. plasma, serum, blood, CSF) and tissue drug concentrations in conjunction with clinical signs and symptoms or other biochemical parameters.
- Evaluating unusual patient responses to drug therapy for possible pharmacokinetic and pharmacologic explanations.
- Communicating verbally and in writing, information on patient specific drug therapy to physicians, nurses, and other clinical practitioners.
- Educating pharmacists, physicians, nurses, and other clinical practitioners on pharmacokinetic principles and/or appropriate indications for clinical pharmacokinetic monitoring.
- Recommending assays or procedures for the analysis of drug concentrations in order to facilitate the evaluation of dosage regimens.
- Developing quality assurance programs to document improved patient outcomes and economic benefits from clinical pharmacokinetic monitoring.

General Procedures for Consulting the Therapeutic Drug Monitoring (TDM) Service

A. A licensed professional with prescribing privileges at Vanderbilt University Medical Center must place TDM Service consults. The consult will provide an option for the TDM Service to provide recommendations only or for the TDM Service to dose and monitor. When consulted under this provision in the Computerized Physician Order Entry System (CPOE) or by verbal or written order subsequently entered into CPOE, such requests will result in:

   a. The TDM pharmacist being authorized to write orders for the initial drug dose, laboratory tests relevant to monitoring the drug, and subsequent orders of the like for dosing adjustments. Examples of these include but are not limited to ordering drug concentrations or the equivalent for drug response (e.g. vancomycin trough), and/or assessments of renal function relative to the dosing of the drug.
   b. At any time, the medical provider may alter the dosing and/or monitoring orders that have been placed by the TDM pharmacist.
   c. At any time, the medical provider may request the TDM pharmacist discontinue the dosing/monitoring consult services being provided to a particular patient.

B. Upon receiving an order for TDM to dose and monitor, the designated pharmacist will assess the patient and review relevant information necessary to appropriately dose and monitor the specified drug to achieve therapeutic drug levels and minimize any potential risks of toxicity. Such items may include, but are not limited to:

   a. Indication for therapy, including a determination that the medication is necessary or if alternative options are more appropriate
   b. Start date and goal end date of therapy (if known)
   c. Age
   d. Gender
   e. Height/weight
   f. Renal/hepatic function
   g. Estimated pharmacokinetic parameters
   h. Medication history and/or time of last dose (if applicable)
   i. Current/last known serum drug concentration (if applicable) including collection times, relationship to steady state, and appropriateness of sample timing. If level drawn incorrectly, inclusion of the estimated level if drawn correctly when possible.
   j. Estimated pharmacokinetic parameters (e.g. Vd, Ke, $t_{1/2}$).
   k. Include other pertinent information used to assess the patient: weight (ABW, IBW, DBW), height, BSA, SCr, BUN, urine output, I/Os, cultures, Tmax, WBC, pertinent culture results, differential diagnosis, allergies, and other interacting/nephrotoxic etc. medications

C. For consult patients, the designated pharmacist will provide daily progress notes in the electronic chart to provide information regarding the course of the dosing and/or monitoring services in accordance with the following:

   a. The designated pharmacist will document a progress note in the patient's chart within the same calendar day for any consults received prior to 2230, otherwise a note will be placed in the patient's chart the following day. A pharmacist will be covering the evening "PK assignment" (from 1500-2230) as indicated on the inpatient pharmacist schedule. Consult orders placed between 2230 and 0630 will be addressed the following shift. Until the consult is cancelled by a provider, the applicable medication is discontinued, or the patient is discharged, a consultation note is required to be placed in the patient's chart **daily**.
   b. For supratherapeutic concentrations above two times the upper limit of the goal therapeutic range, the medical team is required to be notified, and a chart note should be written as soon as possible, but no more than 12 hours after the concentration was reported.
   c. The chart note should contain all relevant patient information and pharmacokinetic parameters necessary to support the dosing and monitoring recommendations.
   d. Notes written by students or pharmacists unlicensed in the state of Tennessee must be co-signed on the same day by a Tennessee licensed pharmacist qualified by the TDM service. Pharmacists who are licensed in the state of Tennessee, but who have not completed the VUH pharmacokinetics training program must have their note reviewed by a Tennessee licensed pharmacist qualified by the TDM service.
   e. Documentation of pharmacokinetic evaluations by the TDM service follows the standardized template format in eStar.

D. The designated pharmacist will be responsible for follow-up monitoring and/or dose adjustments if the pharmacist deems such actions necessary as documented in the progress notes.

E. Upon selecting a dosing and/or monitoring plan, the pharmacist will enter applicable orders into the CPOE system. Any orders written by the pharmacist in response to a TDM to dose order will be entered under the **requesting/attending physician** with the specified type of "Per activated protocol".

F. Refer to this manual, including Appendix A, to guide empiric dosing of aminoglycosides. Use the vancomycin dosing advisor in CPOE and this manual for vancomycin dosing guidance. Calls received by the inpatient pharmacy regarding dosing and monitoring of medications under a TDM consult order should be forwarded to the appropriate pharmacist covering that patient or the TDM pager. If outside of TDM Service hours, an available pharmacist may assist the caller to the best of their ability until further follow up can be conducted.

General Guidelines for Pharmacokinetic Monitoring

1. When a patient is on a monitored drug
    a. Assess the necessity for serum drug concentrations and address this issue with the medical team/physician when appropriate
    b. Assess the patient's clinical course and microbiologic results to determine if further administration of a monitored drug is necessary or if alternative options are more appropriate
    c. Avoid problems with interpretation of upcoming concentrations by:
        i. Obtaining the concentration at steady-state, whenever possible
        ii. Avoiding ordering drug levels between the hours of 2100 and 0400, if possible.
        iii. Adjusting timing of concentrations as needed for interruptions or changes in dosing schedule
2. When a concentration is obtained
    a. Use the time reported on the lab report and the MAR to verify that the concentration is a peak, trough, or random level.
    b. Document that the doses preceding the concentrations were administered on-time to verify that the concentration represents steady state conditions.
    c. As necessary, calculate the appropriate pharmacokinetic parameters on concentrations obtained
    d. Determine if a drug concentration is subtherapeutic, therapeutic, or supratherapeutic and document this assessment in the progress note.
    e. Document any information, not retrievable from the medical record, that was used in your calculation or recommendations (e.g. information directly from the patient or another health care professional).

Basic Equations and Principles Applicable to Pharmacokinetic Monitoring:

- Ideal Body Weight (IBW)
  Male, kg = 50 + (2.3 x each inch over 60")
  Female, kg = 45.5 + (2.3 x each inch over 60")
  (Devine; Drug Intell Clin pharm 1974; 6:650)

- Actual Body Weight (ABW)

- Adjusted Weight (AdjBW) *Used when patient weight is greater than 125% of IBW*
  (ABW - IBW) * 0.4 + IBW

- Estimation of renal function using serum creatinine (SCr):

  Cockcroft-Gault Equation: Creatinine Clearance (CrCl)

  $$\text{Est. CrCl} = \frac{(140-\text{age})*\text{ABW}^{*}}{72 * \text{SCr}} \quad \text{(multiply by 0.85 if female)}$$

  *ABW if patient is not obese, AdjBW if patient is >125% above IBW

  - Above equation may over-estimate CrCl in obese patients, use clinical judgement to adjust dosing as necessary
  - The CrCl equation is not an accurate measure of renal function when SCr is fluctuating
  - Creatinine is an endogenous substance derived from muscle metabolism, small and not bound to plasma proteins, maintains a fairly constant level, and is predominantly filtered ~85% (~155 TS) with minimal non-renal elimination.
  - Proportional to muscle mass and body weight
  - Normal 24-hour excretion: 20-25mg/kg IBW (males) and 15-20mg/kg (females)
  - Creatinine production decreases with age: 2mg/kg/24hours per decade.
  - Altered creatinine clearance found with:
    - Patients who are either small, frail, or elderly
    - Cerebral palsy
    - Poor nutrition

General Pharmacokinetics/Pharmacodynamic Terms for Antibiotics:

Cmax/Cpk = maximum serum concentration
Cmin/Ctr = minimum serum concentration
MIC = minimum inhibitory concentration
AUC = area under the curve
HDEI = high-dose extended interval in reference to aminoglycoside dosing also known as ODA (once daily aminoglycoside)

PAE = post antibiotic effect
SS = steady state

Contrast-Induced Nephrotoxicity

- Proposed mechanism includes renal artery vasoconstriction, thereby precipitating renal medulla hypoxia, coupled with direct cytotoxicity.
- Risk factors include older age, concurrent nephrotoxic agents, pre-existing CKD, anemia, heart failure, larger contrast doses, and higher osmolarity contrast agents (i.e. > 1,000 mOsm/kg).
- Occurs with increase in SCr of ≥ 25% or 0.5 mg/dL from baseline within 48-72 hrs from time of administration (World J Nephrol. 2017 May 6(6): 86-99).

Iodinated Contrast Agent Properties[¥]		
Contrast Agent	Osmolarity (mOsm/L)	Acute Kidney Injury Risk
Diatrizoate (Hypaque)[*]	1400-2400	+++
Iothalamate (Conray)[*]	1000	+++
Ioxglate (Hexabrix)	600	++
Iohexol (Omnipaque)[*]	290-860	++
Iodixanol (Visipaque)[#]	280	+

[¥]Mayo Clin Proc. 2012; 87: 390-402.
[*]VUH Formulary Agent
[#] VUH Formulary Agent - Restricted

Aminoglycoside Dosing and Associated Equations:

Overview

- Primarily used as double coverage with ß-lactams for aerobic gram-negative infections outside of the urinary tract such as *Pseudomonas aeruginosa, Enterobacter* spp.*, Proteus* spp.*, E. coli, Klebsiella* spp.*, Acinetobacter* spp.*,* and *Serratia marcescens*
    - Based on the institutional antibiogram, it is not recommended to routinely double cover for gram-negative bacteria
    - Aminoglycoside monotherapy should only be used for uncomplicated infections involving the urinary tract.
- Can be used for synergy with some gram-positive bacterial infections (e.g.endocarditis)
- Exhibit concentration-dependent killing for gram-negative bacteria (possibly time dependent for gram positive bacteria)
- C_{pk}/MIC ratio is most commonly linked to clinical outcomes but AUC/MIC has been shown equal or better in animal studies
- To obtain >90% clinical response for gram-negative infections, it is suggested that C_{pk} exceed the MIC by ~10X.
  This is the rationale for administering higher doses (7mg/kg tobramycin/gentamicin and 20mg/kg amikacin) with an extended interval (q24hrs).
  HDEI dosing of aminoglycosides was originally based on *Pseudomonas aeruginosa* MIC ~ 2, goal C_{pk} ~20mcg/ml and C_{pk}/MIC ratio = 10:1 based on 7 mg/kg dosing for gentamicin and tobramycin (Antimicrob Agents Chemother. 1995 Mar; 39(3):650-5).
- Larger doses (7mg/kg) have an extended volume of distribution
- Exhibit concentration-dependent killing with a post-antibiotic effect (PAE) for gram negative bacteria ranging from 2-10 hours (animal models)
- Subject to adaptive resistance, short-term decrease or down-regulation in drug uptake & subsequent reduction in bactericidal activity after prolonged exposure to low drug concentrations.
    - Extended interval administration (EIA) dosing may reduce adaptive resistance by saturating drug uptake
    - AUC 0-24hr of 70-100mcg/ml*hr has been proposed as "therapeutic" range to prevent toxicity
- Tobramycin is the only aminoglycoside recommended to treat *Pseudomonas aeruginosa* infections outside of the urinary tract.

Extended Interval Aminoglycoside Dosing (HDEI): [aka Once Daily Aminoglycosides (ODA)]
GENTAMICIN; TOBRAMYCIN; AMIKACIN

There are several studies suggesting that larger doses of aminoglycosides given once daily are just as effective, and less toxic than conventional dosing given multiple times a day. HDEI regimens take advantage of concentration-dependent killing through the optimization of Cpk/MIC ratios. .

- Inclusion Criteria: All patients ordered aminoglycosides for prophylaxis, empiric therapy, or documented infection.

- Exclusion Criteria:
  Pregnant patients (exception is for treatment of endometritis)
  Patients on dialysis
  Patients with an estimated CrCl < 30 ml/min

    - Initial Dose: Doses should be based on adjusted body weight (AdjBW) for obese patients and ABW for non-obese patients. Patients with estimated CrCl $\geq$ 40 ml/min will receive gentamicin/tobramycin 7-10 mg/kg or amikacin 20 mg/kg, infused over 30-60 minutes.

      INITIAL DOSING GUIDELINES FOR ADULTS:
        - Estimate CrCl using Cockroft-Gault Equation
        - Calculate Dosing Body Weight for Patients
        - Calculate Dosage (gentamicin and tobramycin)
            - Dose 7 mg/kg DBW (CF: 10 mg/kg DBW)
            - UTI/chorioamnionitis/endometritis: 5 mg/kg
            - Streptococcal endocarditis (synergy): 3 mg/kg
            - Maintain trough $\leq$ 0.5 mcg/ml
        - Calculate Dosage (amikacin)
            - 20 mg/kg/day
            - Maintain trough $\leq$ 2.3 mcg/ml
        - If CrCl <40 mL/min may give a single first dose of 3mg/kg gentamicin or tobramycin

    - Subsequent doses: The goal of the initial concentration after the 1st dose is to verify that the drug is eliminated appropriately to establish the appropriate dosing interval. The interval may need to be extended beyond 24 hours to

achieve trough levels of ≤ 0.5 mcg/ml (or ≤2.3mcg/ml for amikacin). Appropriate dosing intervals include every 24, 36, 48 hours. SCr/BUN should be measured at baseline and at least twice weekly thereafter.

- Patients with normal renal function will usually have a "drug-free" period with an undetectable trough concentration (≤ 0.5 mcg/ml or ≤2.3 mcg/ml).
- For patients with trough concentrations ≥ 0.5 mcg/ml (or ≥2.3 mcg/mL), renal function should be monitored closely and risks of nephrotoxicity and ototoxicity evaluated carefully.
- If a gentamicin/tobramycin trough level following a 7 or 10 mg/kg dose requires >48 hours to decline to <1 mcg/ml, conventional dosing or 3mg/kg dosing may be warranted.
- If an amikacin trough level following a 20 mg/kg dose requires > 48 hours to decline to <8 mcg/ml, conventional dosing may be warranted.
- Patients should not receive more than one dose within a 24-hour period with extended interval dosing.

- Follow-up monitoring: If HDEI is continued >4 days, a trough concentration and a BUN/SCr should be obtained twice weekly to check for drug accumulation and assess risk of nephrotoxicity. Concomitant nephrotoxic medications should be avoided if possible. If a patient continues on an aminoglycoside for >1 week and SCr remains stable, the pharmacist may change to checking troughs weekly with close daily monitoring. Presence of nephrotoxic drugs that may alter CrCl may warrant more frequent monitoring. Such medications may include:

  a. Amphotericin B
  b. Loop diuretics
  c. Vasopressor agents
  d. IV contrast
  e. Acyclovir
  f. Vancomycin
  g. Ketorolac/NSAIDS

- Monitoring for ototoxicity should be performed, especially for patients receiving aminoglycosides for more than two weeks. Ototoxicity results from damage to the vestibular and cochlear portions of the eighth cranial nerve. Auditory symptoms included tinnitus, roaring, ringing, or "buzzing" in the ears, and varying degrees of hearing impairment. Loss of high-frequency perception is only detectable by audiometric testing and usually occurs before clinical hearing loss. Vestibular symptoms include nausea, vomiting, dizziness, vertigo, nystagmus, oscillopsia, and ataxia. A feeling of fullness in the ears and tinnitus are early signs of ototoxicity. Symptoms are exacerbated in the dark. Hearing loss may be irreversible, but patients usually retain normal conversational hearing. Other ototoxic drugs (e.g. furosemide) should be avoided, if possible.

Aminoglycosides: Traditional/Conventional Dosing
GENTAMICIN; TOBRAMYCIN; AMIKACIN

This dosing method will be used for patients that do not meet the HDEI Dosing Criteria.

1. General dosing guidelines
   a. Initial Dosing
      i. Select desired C_{pk} and C_{tr} based on site and severity of infections, organism, MIC, and immunocompetence of patient (see Appendix A).
      ii. Estimate CrCl
      iii. NOTE: the breakpoints for gram-negative organisms are based on HDEI dosing (see previous section). It is unclear if traditional dosing of aminoglycosides will achieve adequate concentrations to meet desired PK/PD parameters. Consideration should be given to alternative antibiotic options.

   Patients with normal renal function
   a. Gentamicin and tobramycin 1-2.5mg/kg DBW/dose every 8/12/24 hours
   b. Amikacin 5-7.5mg/kg DBW/dose every 8/12/24 hours.
   c. Note: elderly patients often require a 12- or 24-hour dosing interval.

2. Time of Sampling
   a. Relative to Dose
      i. Cpk 30min after end of 30min infusion (IV); 1 hour after IM injection
      ii. Ctr within 30min prior to dose
      iii. At steady state (levels before and after3rd dose)
3. Recommended frequency of sampling

a. Routine use in "uncomplicated" patients
    i. Initial Cpk and Ctr (3rd dose)
    ii. If regimen is adjusted, repeat Cpk and Ctr, at new steady state, if initial values differ ≥25% from predicted (i.e. suggestive of unusual kinetic parameters or deviation from sampling guidelines)
    iii. SCr and BUN at least 2x week; monitor other signs of renal function
    iv. Repeat Ctr once during the first week when duration of therapy >4 days. If a patient continues on an aminoglycoside for >1 week and SCr remains stable, the pharmacist may change to weekly troughs with close daily monitoring.
b. Gram-positive endocarditis synergy
    i. Routine monitoring of Cpk is not recommended. Ctr is the only level needed for monitoring.
c. Use in "complicated" patients (e.g. diminished or changing hydration status and/or renal function, concurrent ototoxic or nephrotoxic drugs)
    i. Initial Cpk and Ctr at steady state
    ii. SCr and BUN daily
    iii. Repeat Cpk and/or Ctr twice weekly (or as dictated by clinical condition)

Therapeutic Range (Traditional Dosing)

Desired Cpk and Ctr concentrations for traditional aminoglycoside dosing should be determined clinically by site and severity of infection, causative organism and its MIC, immunocompetence of patient, intent of therapy, etc.

Concentration	Gentamicin, tobramycin	Amikacin
Cpk (mcg/ml)	5-10	25-35
Ctr (mcg/ml)	<2	<8

See table below for general recommendations for desired Cpk based on site of infection.

Site/Type of infection	**Target C_{pk} (mcg/ml) (gentamicin/tobramycin)**
Abdominal	6-8
Bacteremia	6-8
Endocarditis, Gram positive (1mg/kg/dose) **SYNERGY** Gram negative	 3-5 8-10
Eye	6-8
Meningitis	8-10
Neutropenia	6-10
Peritonitis	6-8
Pneumonia	8-10
Skin and soft tissue	6-8
Urinary tract	4-6
C_{min} (mcg/ml) (gent/tobra)	**< 2 (< 1 for synergy)**

Aminoglycoside: Empiric Calculations:

- IBW unless >125% IBW then use DBW
- DBW = [ABW-IBW] x 0.4 +IBW
- Vd
  0.20 L/kg (dehydrated)
  0.25 L/kg (average)
  0.35 L/kg (CHF, volume overload, ICU patients)
- Kel = .00293*(CrCl) + 0.014
- $T_{1/2}$ = 0.693/Kel
- Interval = $T_{1/2}$ x 3
- Dose = Vd(L/kg) x Cpk desired x Wt
  OR
- Dose/Vd (L) = Cpk desired
- Est. Ctr = Cpk desired ($e^{-Kel\ (interval\ –\ infusion\ time\ in\ hours)}$)

Calculated Dose post levels: Sawchuk-Zaske Method:

Assumptions: Concentrations represent steady state conditions; 1-compartment model; principle of superposition; linear elimination.

1. Verify administration and sampling times
2. $Kel = \frac{\ln(peak/trough)}{[interval - (trough+infusion+peak)]}$
3. $T_{1/2} = 0.693/Kel$
4. New Interval = $T_{1/2}$ X 3 OR $\frac{\ln[Pdesired] - [Tdesired]}{Kel}$
5. If peak drawn late: calculate if drawn at correct time
   a. True Peak = $\frac{peak}{e^{-Kel \times T \text{ (end of infusion to peak draw)}}}$
6. If trough drawn early, calculate as if drawn on time:
   a. True trough = $Ctr * e^{-Kel \times T \text{ (time drawn to time supposed to drawn)}}$
7. $Vd = \frac{dose/infusion\ time\ (1 - e^{-Kel \times infusion\ time})}{True\ Peak * Kel}$
8. New dosing interval :
   a. $Interval = \frac{\ln(Cpk/Ctr)}{Kel} + t + T$
9. New dose = $\frac{Peak\ desired * Vd\ (L) \times Kel(1 - e^{-Kel \times interval})}{(1-e^{-Kel \times infusion\ time})\ e^{-Kel \times T}}$

**Note that new dose = mg/hr and the dose must be adjusted to account for ½ hour infusion (e.g. if New dose = 200mg/hr, then the dose would be 100mg/30minutes)

10. Round dose to nearest 10mg then recalculate actual Cpk
    a. Desired Cpk * (actual rounded dose/calculated dose) = actual Cpk
11. $Peak = \frac{dose/infusion\ time\ (1 - e^{-Kel \times infusion\ time})}{Vd\ (L) \times Kel}$
12. $Trough = Peak\ (e^{-Kel\ (Interval - infusion\ time)})$

Factors affecting Vd (may or may not affect Vancomycin)

Increase Vd	Decrease Vd
↓ albumin	Lasix
edema	O>I (3+days >1000cc)
ventilator	N/V
steroids	Dehydrated
I>O (3+days >1000cc)	High sodium
CHF	
Low sodium	

Risk factors for toxicity: other renal toxic drugs (ampho B, gent/tobra, lasix), inc age, dehydrated, diabetic, high troughs, increase length of tx >10 days

Guidelines for Dosing in End Stage Renal Disease (ESRD)

Defined as CrCl < 15 ml/min or on renal replacement therapy (RRT)

Gentamicin and Tobramycin Dosing/Monitoring – Conventional HD

Guidelines for Monitoring

1. Initial dosing
   a. Assume Vd 0.3-0.35 L/kg
   b. Synergy dosing
      i. Loading dose 1.5-2mg/kg (DBW)
      ii. Maintenance dose 1mg/kg (DBW) after each HD
   c. Moderate to severe infections (aggressive management)
      i. Loading dose 2-2.5 mg/kg (DBW)

Effect of hemodialysis

1. Removes approximately 50% (4 hour high-flux session)
2. Levels taken post dialysis are true troughs; levels taken prior to dialysis can be used with the assumption of 50% removal.

Levels

1. Single drug level approach (synergy dosing)
    a. Most commonly used approach
    b. Pre-dialysis (random) concentration
    c. Extrapolate post-dialysis concentration (trough) by assuming 50% drug removal during a 4-hour session
    d. Target trough <2 mcg/mL (<8mcg/mL for amikacin) to conserve remaining kidney function and minimize risk for ototoxicity
2. Multiple drug level approach (aggressive management)
    a. Peak concentration drawn 2 hours after dose
    b. Pre-dialysis (random) concentration

Maintenance dosing (multiple drug levels)

1. Calculate Keoff IHD
    a. Keoff IHD = (Ln Cp1/Cp2)/t (Cp1=peak; Cp2=pre-dialysis; t=time between Cp1 and Cp2
2. Calculate half-life off IHD
    a. $T_{1/2}$ = 0.693/keoff IHD
    b. Extrapolate actual peak concentration
    c. Extrapolate post-dialysis concentration (trough) by assuming 50% drug removal
3. Determine Vd
4. Calculate maintenance dose using desired peak concentration
    a. Ko = (Cpk(desired) – Ctr(desired) x Vd
    b. Typical dosing is 1-1.8mg/kg after each dialysis session

Dialysis factors that may lead to lower percentage of drug removed

1. Dialysis duration < 2 hours
2. Blood flow reduced to < 200ml/min
3. Ultrafiltration only (no hemodialysis)
4. Less permeable dialyzers (filters) used
5. Patient is volume overloaded

Aminoglycoside Dosing/Monitoring – Continuous Renal Replacement Therapy (CRRT)

Dosing recommendations for critically ill adults receiving CVVHD/CVVHDF*

	Gram positive bacteria	**Gram Negative Infections**	
Aminoglycoside	**Synergy dosing**	**Loading dose**	**Maintenance Dose**
Gentamicin	1mg/kg q24-36hours	3mg/kg	2mg/kg q 24-48h
Tobramycin	NA	3mg/kg	2mg/kg q 24-48h
Amikacin	NA	10mg/kg	7.5mg/kg q24-48h

Note: Use appropriate body weight based on presence or absence of obesity. Target peak and trough levels vary based on infection (see previous chart) *Trotman RL et al. CID 2005;41:1159-66.

Guidelines for monitoring

1. Typical dosing interval during CRRT is q24-48h
2. Higher target peaks required for longer dosing intervals

Levels

1. Obtain random level when next earliest re-dose may need to occur based on chart above
2. Determine appropriate maintenance dose based on calculated PK parameters (ensure CRRT uninterrupted between concentrations)
3. If CRRT parameters remain constant, a dosing interval may be scheduled based on initial monitoring results

Factors that may lead to changes in amount of drug removed

1. Changes in ultrafiltration rate
2. Dialysis interrupted (i.e. clotted filter, overnight issues)
3. Alterations in existing renal function (ARF vs CRF)

References:

1. Dager WE, King JH. Aminoglycosides in intermittent hemodialysis: pharmacokinetics with individual dosing. Ann Pharmacother 2006;40:9-14.

2. Trotman RL, Williamson JC, Shoemaker M Salzer WL,. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. CID 2005; 41:1159-66.

Vancomycin

- Exhibits time-dependent killing and is usually slowly bactericidal by inhibition of bacterial cell wall synthesis
- AUC/MIC is the PK/PD parameter thought best to correlate with bactericidal activity. There are limited data suggesting a relationship between serum drug concentration (i.e. troughs) and clinical outcomes and toxicity.
- A few studies have found better bacterial eradication with trough concentrations >10mcg/ml (Pharmacotherapy 1995; 15:85-91).
- PAE of 2-3 hours against gram-positive bacteria
- Vancomycin requires actively growing bacteria to exert its effect.

1. General Guidelines for Dosing
    a. Loading Dose:
        i. Loading doses are warranted for severely ill patients when achieving therapeutic drug concentrations more rapidly may be beneficial (e.g. severe sepsis or shock)
    b. Maintenance Dose:
        i. Use Dosing Advisor (Appendix #2)
        ii. Typically 15-20mg/kg Q8/12/24H based on renal function (may consider doses of 10-15mg/kg if empirically starting a Q8H dosing frequency)
    c. Dose Adjustments
        i. Adjust dosing interval/dose per clinical judgment to achieve desired trough levels
2. Monitoring
    a. Vancomycin serum drug concentrations may **NOT** be necessary in:
        i. Adult patients <60 years of age with normal body weight, stable renal function with CrCl >50 mL/min, and a likely short course of therapy (e.g. <72 hours)
    b. Trough concentration obtained within 30 to 60 minutes prior to infusion
    c. Concentrations should be obtained for:
        i. Patients on vancomycin ≥ 3 days
        ii. Dialysis
        iii. Changing renal function: increase in SCr by 0.3 mg/dL or 50% from baseline
        iv. Special patient populations with altered/changing volume of distribution
            1. Elderly (≥60 years old)
            2. Burn
            3. Cancer
            4. Obesity (>125% IBW)
        v. Patient with suspected inadequate drug levels/failing therapy
        vi. Presence of nephrotoxic drugs that may alter CrCl, including:
            a. Aminoglycosides
            b. Amphotericin B
            c. Loop diuretics
            d. Vasopressor agents
            e. IV contrast
            f. Acyclovir
            g. Ketorolac/NSAIDS
    d. Repeat Ctr once during the first week when duration of therapy >4 days. If a patient continues on vancomycin for >1 week and SCr remains stable, the pharmacist may change to weekly troughs with close daily monitoring.
3. Therapeutic Range:
        i. Trough **8-12 mcg/ml** for less acute infections (e.g. uncomplicated skin and soft tissue infections, UTI)
        ii. Trough **12-17 mcg/ml** for life threatening infections, organisms with high MICs (MRSA) or to target higher vancomycin concentrations at the site of infection.
            1. Use 12-17mcg/mL as the target therapeutic range for patients on vancomycin post-heart or post-lung transplant even if the order indication is prophylaxis
4. Dosing in Impaired Renal Function
    a. Mild-Moderate:
        i. Use appropriate dose per patient characteristics (height, weight, infection)
        ii. Use clinical judgment when selecting dosing interval based on SCr and CrCl (see Appendix B)
    b. Severe:
        i. Utilize spot dosing (Vancomycin dose x 1, then follow levels and re-dose as appropriate).
5. Dosing in Hemodialysis
    a. Initial dose of 20-25 mg/kg ABW
    b. If limited IV access:

i. May give vancomycin during last hour of dialysis (will not remove significant amount of drug)

c. Levels:
    i. It is preferred to obtain levels with AM labs on days prior to high-flux hemodialysis. However, levels may be drawn 4-6 hours after completion of high-flux hemodialysis if unable to draw with AM labs.
    ii. Re-dose when pre-HD level is 18-24 mcg/ml or when post-HD level is expected to be $\leq$ 18 mcg/ml
    iii. Approximately 30-35% of vancomycin is removed over a 3- to-4-hour hemodialysis session. Average half-life in ESRD patients is 4-5 days depending on residual kidney function
    iv. 10% of vancomycin is removed per day non-renally

6. Dosing in Continuous Renal Replacement Therapy
    a. Initial dose of 15-25mg/kg
    b. Levels:
        i. Initial level typically scheduled 24h after first dose
        ii. Schedule vancomycin dosing interval q24-48h depending on level and CRRT parameters
    c. Maintenance doses of 10-15mg/kg

Appendix A: Initial Aminoglycoside Dosing Nomogram

Important Considerations

- Use ABW if less than IBW or < 120% ofABW. Use AdjBW [IBW + 0.4 (actual body weight – IBW)] if ABW ≥ 120% of IBW
- **Aminoglycoside use is discouraged in patients with myasthenia gravis**
- Dose rounding: gentamicin/tobramycin: nearest 10 mg; amikacin: nearest 50 mg
- Do not use as monotherapy except for genitourinary infections
- Target peak:MIC at least 8-10

ONCE DAILY/EXTENDED INTERVAL DOSING

Exclusion criteria (use traditional dosing)

Extensive ascites	CrCl < 30 mL/min
Pre-partum pregnancy	Age > 65 years
On CRRT/iHD	Paraplegic/quadriplegic
Weight < 50 kg	Amputee

Infection	Peak Goal (mcg/ml)	Trough Goal (mcg/ml)	Dose
GENTAMICIN/TOBRAMYCIN			
Stretococcal IE	8-12*	< 0.5	3 mg/kg
Endometritis/ chorioamnionitis	10-15*	< 0.5	5 mg/kg
UTI	10-15*	< 0.5	
Surgical prophylaxis	N/A	N/A	
Sepsis	20-30*	< 0.5	7 mg/kg
Pneumonia	20-30*		
Osteomyelitis	20-30*		
Intra-abdominal infection	20-30*		
Cystic fibrosis	25-40*		10 mg/kg
AMIKACIN			
Cellulitis or UTIs	20-30*	< 2.3	20 mg/kg
Other infections	30-40*	< 2.3	20 mg/kg

CrCl (ml/min)	Empiric Interval
>60	q24h
40-60	q36h
30-40	q48h
< 30	use traditional dosing

Monitoring: trough level prior to 2nd dose, with a repeat trough if continued for >4 day. If continued for >7d may consider once weekly if stable while inpatient. SCr at least twice weekly.
*Peak levels not usually performed
Infusion time: 60 minutes

TRADITIONAL DOSING

Infection	Peak Goal (mcg/ml)	Trough Goal (mcg/ml)	Dose
GENTAMICIN/TOBRAMYCIN			
Synergy (non-streptococcal IE)	3 - 5	< 1	1 mg/kg
UTI	4 - 5		1.5 mg/kg
Pyelonephritis	6 -8	< 2	1.7 mg/kg
GYN	6 - 8		1.7 mg/kg
Intra-abdominal	6 – 8		1.7 mg/kg
SSTI	6 – 8		1.7 mg/kg
Bacteremia	7 - 8		2 mg/kg
Pneumonia	~ 8		2 mg/kg
Osteomyelitis	~ 8		2 mg/kg
AMIKACIN			
Mild	15	< 5	5 mg/kg
Moderate	20-30	<8	6 mg/kg
Severe	25-35	<8	7.5 mg/kg

CrCl ml/min	Empiric Interval
>60	q8h
40-60	q12h
30-40	q24h
< 30	Spot dose based on levels

Monitoring: trough/peak level prior to/after 3rd dose, then repeat trough if continued for >4 day. If continued for >7d may consider once weekly if stable while inpatient.. Peak levels only need to be rechecked if dose/interval changes, V_d significantly changes, or suspect therapeutic failure

Appendix B: Initial Vancomycin Dosing Nomogram

Infection Severity	**Standard**	**Moderately Severe**	**Severe**
Loading Dose	20 mg/kg (optional)	20 mg/kg (optional)	25 mg/kg
Trough Goal	8-12 mcg/ml	12-17 mcg/ml	
Maintenance Dose* (based on creatinine clearance)			
< 30 ml/min	Spot dose and PK consult**		
30-44 ml/min	15 mg/kg q24h	15 mg/kg q24h	
45-59 ml/min	20 mg/kg q24h	10 mg/kg q12h	
60-89 ml/min	10 mg/kg q12h	15 mg/kg q12h	
≥ 90 ml/min AND Age < 50 years	12.5 mg/kg q8h	15 mg/kg q8h	
≥ 90 ml/min AND Age ≥ 50 years	10 mg/kg q12h	15 mg/kg q12h	

Standard Infection: SSTI/SSI, surgical/procedural prophylaxis,
Moderately Severe Infection: Bone/joint, prosthesis/foreign body, clinically stable febrile neutropenia
Severe Infection: Pneumonia, endocarditis, meningitis/CNS, bloodstream/sepsis, clinically unstable febrile neutropenia

*All doses will be rounded to nearest 250 mg with a maximum dose of 2000 mg.
**Automatic consults will be placed for the following patient groups: quadriplegic/paraplegic, chronically bedridden (> 30 days) or amputee (BKA/AKA), weight < 40 kg, cirrhosis, CRRT or Hemodialysis or CrCl < 30 mL/min

Clinical Pearls

- Monitor trough levels for patients expected to receive therapy for > 3 days
- Initial trough level should be obtained prior to 4th or 5th total dose (including loading dose); may obtain earlier if renal function necessitates
- After a therapeutic trough level, repeat Ctr once during the first week when duration of therapy >4 days. If a patient continues on vancomycin for >1 week and SCr remains stable, the pharmacist may change to weekly monitoring. May need to obtain earlier if significant change in Vd or SCr/UOP occurs, suspect therapeutic failure, or suspect toxicity
- Typically infused for 15 minutes for every 250 mg, may need to pre-medicate with diphenhydramine and double infusion time for patients who experience or have history of vancomycin infusion reaction

Appendix C: Assigned Cross-Coverage of Therapeutic Drug Monitoring

Primary Pharmacokinetics (PK) Pharmacist:
Ben Ereshefsky, PharmD, BCIDP
Phone: 615-343-3784
Pager: 615-835-9108
Email: ben.ereshefsky@vumc.org

Back-up PK Pharmacist:
Austin Ing, PharmD or Laura Bobbitt, PharmD
Email: austin.r.ing@vumc.org or laura.bobbitt@vumc.org

Coverage:

1. Team pharmacists self-assign consults based on patient list as of 0700
    a. PK pharmacist can assist with coverage if a team is uncovered and if there is uncertainty about covering pharmacist
    b. PK pharmacist reviews list to determine if any uncovered consults
2. Clinical pharmacist to manage and write consult notes for their consulted patients daily.
    a. Consults should be completed by 1530 each day.
    b. May assign pharmacy resident on their rotation to complete consult for patients they are covering
    c. Resident to complete all consults for their service in the event the preceptor is not present.
    d. Clinical pharmacist to clearly mark consults that must be followed up with each night.
        i. Evening PK pharmacist follows up on consults needing immediate monitoring and changes to the regimen.
3. Cross Coverage when Primary PK pharmacist is not available:
    a. Back-up PK pharmacist takes over complete responsibilities
    b. May ask for assistance from other clinical pharmacists to assist in completing consults based on workload