Our Lady of the Lake Regional Medical Center
Pharmacokinetic Training Program
Module I: Vancomycin Dosing Guidelines (Adults)

Last revision date: July 2023

Section I: Objectives

After completing the training, participants will be able to demonstrate the following competencies:

1. Have a basic understanding of vancomycin pharmacodynamics in terms of antimicrobial action/spectrum, efficacy and toxicity
2. Understand basic principles of vancomycin dosing in adults
3. Understand the appropriate time for checking serum drug levels
4. Initiate the appropriate vancomycin dosing regimen and adjust the dose based on serum drug level for adult patients of various ages
5. Be able to write clear orders and progress notes in the patient's medical record

CAUTION: THIS PROTOCOL DOES NOT REPLACE SOUND CLINICAL JUDGEMENT NOR IS IT INTENDED TO STRICTLY APPLY TO ALL PATIENTS

Section II: Vancomycin Overview

Spectrum of Activity

Vancomycin is indicated as a penicillin alternative for the treatment of severe infections caused by *Staphylococcus*, *Streptococcus*, *Enterococcus*, and *Corynebacterium* species.

- Methicillin-sensitive isolates of *Staphylococcus* and *Enterococcus* should be treated with beta-lactams. Studies have shown that vancomycin is not as rapidly bactericidal and **should only be utilized for treatment of beta-lactam susceptible pathogens in the case of a confirmed penicillin and cephalosporin allergy**.

Mechanism of Action

Vancomycin is a tricyclic glycopeptide antibiotic that exhibits bactericidal activity by blockage of the glycopeptides polymerization in the bacterial cell wall.

Pharmacokinetic Parameters

- Absorption – Systemic absorption is negligible after oral administration.
- 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 – Renal elimination. Elimination half-life = 5-11 hrs in normal renal function (prolonged with renal impairment)
- Therapeutic Plasma Concentrations – peak = 30-40 mcg/mL, trough = 10-20 mcg/mL

Efficacy

Vancomycin exhibits concentration-independent killing against Gram-positive pathogens with the AUC/MIC as the primary predictive pharmacodynamic parameter for efficacy. Therefore, increasing antibiotic concentrations beyond the therapeutic threshold will not result in faster killing or eliminate a larger portion of the bacterial population.

Therapeutic range

Trough concentrations are used as a surrogate marker for monitoring vancomycin therapy. Normal therapeutic serum vancomycin trough range is 10-20 mg/dL, and should always be maintained above 10 mg/dL to prevent the development of resistance. Trough concentrations in that range should achieve an AUC/MIC of $\geq$ 400 in most patients if the MIC is $\leq$1 mg/dL.

Trough concentrations should be obtained within 30 minutes prior to the dose at steady-state (usually prior to 4th or 5th dose) in patients with normal renal function.

Adverse Effects & Toxicity

The most common adverse effects associated with vancomycin use are unrelated to serum drug concentration and include fever, chills, and phlebitis. Vancomycin infusion-related reaction (previously referred to as red man syndrome) may be associated with histamine release and manifest as tingling and flushing of the face, neck, and upper torso. **Vancomycin infusion-related reaction is NOT an allergy**, and is not a reason to discontinue use. In the case of vancomycin infusion reaction, length of infusion can be extended to minimize this adverse effect.

Vancomycin has the potential to cause 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 (piperacillin-tazobactam, aminoglycosides, amphotericin B, ACEIs, contrast dye, NSAIDS, etc). Many of the early reported cases of nephrotoxicity occurred with impure preparations of vancomycin. Modern formulations have excellent safety profiles; however, reports of vancomycin-related nephrotoxicity still surface, particularly recently with the recommendations to increase vancomycin trough concentrations from the typical range of 5-15 mg/L to 10-20 mg/L. Studies have found a greater risk of nephrotoxicity at trough levels >15 mcg/mL as compared to trough levels less than 15 mcg/mL. Another study has identified the total daily dose of 4 grams or more significantly associated with an increased risk of nephrotoxicity, even after controlling for potential confounding factors in a multivariate analysis. No correlation has been found between nephrotoxicity and peak vancomycin levels. Ototoxicity has in very rare cases been associated with vancomycin.

Table 1. Risk factors for development of nephrotoxicity		
Patient factors	**Vancomycin regimen**	**Concomitant drugs**
Renal dysfunction (baseline CrCl<60)	Duration of therapy	**Iodine contrast media**
Older age (>65 y/o)#	Trough levels remaining >15 mcg/mL	**Piperacillin-tazobactam**
Obesity*	High doses >4 grams/day	Aminoglycosides
Diabetes		Amphotericin B
Paraplegia/Muscle atrophy disorders#		Acyclovir
Advanced HIV/AIDS		ACE-I/ARBs (possibly)
High APACHE II score/ICU stay		Diuretics (especially loops)
Lupus		NSAIDs
Advanced liver disease/ESLD		Cisplatin
Shock, vasopressor requirement, dehydration		
Recent surgery		

Bolded risk factors are found in high rates (≥50%) of OLOL patients with supratherapeutic trough levels
*Initial high doses required, but **accumulation occurs after first few days**. Monitor closely and **decrease dose as indicated.** Many obese patients will eventually require maintenance doses of 10-12.5mg/kg (some sources recommend maintenance dosing with adjusted weight)
#Risk of overestimating renal function. Identify baseline SCr and prior vancomycin dosing if possible to estimate true clearance

Section III: Dosing & monitoring

Vancomycin Dosing

- Use clinical judgment when evaluating empiric dosing regimens. Consider indication for therapy, hemodynamics (i.e. hypotension, vasopressor, hydration status), renal function, risk factors for nephrotoxicity, previous dosing regimens
- Dosing will be based on the patient's actual body weight (ABW)
- **Maximum loading dose is 2.5gm. Maximum maintenance dose is 2gm.**

Step 1: Loading dose

- **ALL patients will receive a LD:** 25mg/kg (bacteremia, endocarditis, severe sepsis/septic shock, meningitis) or 20mg/kg (all other indications)

Step 2: Selecting an initial maintenance dose

- Dose: 15-20 mg/kg (Round to the nearest 250 mg; Maximum 2gm per dose)
- **Dosing interval: typically 1-1.5 times calculated T1/2**
- Initial total daily doses >4 g/day should be avoided unless indicated by measured levels or discussed with physician

CrCl	Suggested Regimen	Monitoring Levels
≥120	**Age ≤ 40:** 15 mg/kg q8h* *(Max empiric dose 1250mg)* Age ≥41: 15 mg/kg q12h*	q8h: Draw a trough level prior to 5th dose
>70	15 mg/kg q12h*	q12h: Draw a trough level prior to 4th dose - *utilize clinical judgement and obtain a pre-steady state level if indicated*
30-69	18 mg/kg q24h	Draw a pre-SS trough level prior to 3rd dose
< 30	25-20 mg/kg x 1 "Vancomycin pulse dosing by pharmacy" order	Draw random level 8-24 hours later - *Preferably draw with AM labs to decrease lab draws*
CVVHDF	15-20 mg/kg q24h	Draw a trough level prior to the third dose
SLED	1. 20mg/kg loading dose NOW - *And 500mg post-SLED if LD given prior to SLED* 2. 500-1250mg (~10mg/kg) after each SLED	Draw random level prior to next SLED session - *Many patients have irregular sessions, so consider daily AM random until schedule is known*
PD	15 mg/kg x 1 *(IV)*	Draw random level 24 hours later
IHD	1. 20mg/kg loading dose NOW - *Dot phrase in admin instructions to say give now* - *Additional 500mg post-HD if LD given prior to HD* 2. 500-1250mg (~10mg/kg) after each HD session	Draw a random level prior to next HD session - *Obese patients and serious infections: consider obtaining random level the following AM to ensure patient is not subtherapeutic*

*In quadriplegia w/ no vanc history, use SCr history to estimate current renal function. Recommend pre-SS trough

Vancomycin Monitoring:

1. **Renal function panels (RFP)**
   - SCr (in RFP) should be monitored **daily for 72 hours at baseline** then q24-48h for most patients (see below):
     1. High target troughs (>15 mcg/mL)
     2. Concomitant nephrotoxic agent(s) and/or risk factors for nephrotoxicity (see Table 1)
     3. High doses to maintain therapeutic range (>20 mg/kg/dose or >4 g total daily dose)
     4. Frequency of dosing ≤ q8h (*Use q24hr monitoring up front and after dose changes)
     5. Impaired renal function (<60 mL/min)
     6. Rapidly changing renal function (See "Monitoring patients with AKI")
   - Patients not meeting the above criteria should have RFP monitored at baseline and at least q72h
   - Monitor daily RFP for 5 days post administration of IV iodinated contrast

2. **Vancomycin Serum Levels**
   1. Criteria for monitoring:
      i. Trough monitoring is recommended for most patients
         - Trough goal 10-20 mcg/mL
         - Patients at high risk of nephrotoxicity (e.g., patients receiving concurrent nephrotoxins)

      ii. Monitoring is NOT recommended in the following settings:
         - Patients treated for <3 days with target trough levels <15 mcg/mL
         - LOPA patients (diagnosed brain death awaiting procurement of organs)

      iii. Monitoring of peak levels is not necessary

Vancomycin Target Trough Guidelines	
Uncomplicated skin and soft tissue infections	10-15 mcg/mL
UTI	
MRSA bacteremia	15-20 mcg/mL
Pneumonia	
Endovascular (Endocarditis, line/graft infection)	
Meningitis	
Osteomyelitis, septic arthritis/PJI	
Severe sepsis/septic shock	
Intra-abdominal infection	

**The target trough for all other indications is 10-20 mcg/mL unless specified by physician

   2. When to obtain levels:

Dosing Interval	Q6hr, q8hr	Q12hr	Q24hr
Timing of trough level	Prior to 5th dose	Prior to 4th dose	Prior to 3rd dose (*Will be pre-steady state)*

      i. Timing of trough levels listed above should allow patient to reach steady-state
         - Patients who may need level prior to steady-state:
           - Acute change in renal function
           - At risk for high levels: CKD, advanced age, frail/muscle atrophy (ex. quadriplegia)
           - ≥ q24h dosing interval (Drawn pre-steady state to give earlier monitoring)
         - If troughs are drawn prior to steady state, use caution when interpreting the result: **serum concentration at steady state is expected to be higher than pre-steady state levels (~20%)**
           - **Use estimated steady-state trough level when determining dose adjustments**
           - If trough results close to goal, keep dosing the same and recheck in ~48hrs

      ii. Time of trough sampling is 30 minutes prior to the scheduled dose.
         - In patients with levels drawn consistently at incorrect times, consider adding a comment stating Ex: "Please draw vancomycin trough within 11 to 12 hours after previous administered dose."

      iii. **After each dosing adjustment**: repeat trough as indicated by dosing interval (listed in table above)

   3. Frequency of monitoring:
      i. **Once a therapeutic trough is obtained**, level should be repeated:
         - Within 2-3 days until two goal troughs are obtained (if therapy is to be continued for >7 days)

- After 2 therapeutic levels obtained, can recheck every 5-7 days IF: renal function is stable, AND patient does not meet one of the criteria for frequent monitoring of trough levels listed below.

ii. **Frequent monitoring of trough levels (every 24-48 hours)**
- High dose (>20 mg/kg/dose or >4 g total daily dose)
- Rapidly changing renal function (See "Monitoring in patient with AKI")
- Impaired renal function (<60 mL/min) (If stable, can consider less frequent monitoring)

4. Monitoring in patients with AKI:
   i. Situations which should be treated as an AKI:
   - SCr increases >0.3mcg/mL (or increases >50%) in 24-48 hrs
   - CrCl decreases by ≥50%
   - Urine Output decreases to <0.5 ml/kg/hr (assuming patient started with normal urine output)
   - Vancomycin trough > 22 mcg/mL

   ii. <u>For any of the 4 situations above:</u> Hold next dose of vancomycin & check a random level in 1.5-2 times the current interval
   - Ex: 1gm q12hr (0000/1200), next dose due at 1200. SCr jumped from 0.6 to 1.2 in 24 hours. Discontinue vancomycin dose due at 1200 & follow up with a random level at 1800 (18hrs post last dose given).
   - *Clinical judgment should be used when deciding the time of random levels*
5. Monitoring in patients with ESRD:
   i. After initial loading dose, order random level for 18-24 hours post-dose
   ii. See section IX for Dosing in ESRD/RRT

<u>Section IV: Dose adjustments based on vancomycin serum levels</u>

Guidelines for dosing adjustment to maintain a therapeutic trough level:

******Please note that these guidelines are NOT intended to and should NOT replace sound clinical judgment of the health care practitioner in the delivery of health care***

Doses can be adjusted by either by changing the dosing interval or changing the dose. In certain clinical situations, both the dose and the dosing interval may need to be changed to achieve therapeutic trough levels.

- **Verify administration and sampling times**
- **Dose adjustments should usually take place in increments of 250 mg**
- **Adjusting the dosing interval has a greater effect on trough level than changing the dose**
- **Lowest allowed dosing interval is every 6 hours**

Trough result	Suggested Dose Adjustment	
	Goal range 10-15 mcg/mL	Goal range 15-20 mcg/mL
<10 mcg/mL	Increase dose by 250mg	1. Decrease dosing interval - *Consider a decrease in dose by 250mg* 2. Increase dose by 500mg - *If dosing interval cannot be changed*
10-15 mcg/mL	Continue current dose	Increase dose by 250mg
15-20 mcg/mL	Decrease dose by 250mg	Continue current dose
20-22 mcg/mL	**HOLD dose** Resume at increased dosing interval - *Consider increasing dose by 250mg*	**Delay dose** by 0.5 times the dosing interval 1. Same dosing interval and decrease dose by 250-500mg 2. **OR** Increase dosing interval (Consider 250mg dose increase)
>22 mcg/mL	**HOLD dose** Resume at increased dosing interval	**HOLD dose** Resume at increased dosing interval - *Consider increasing dose by 250mg*

*After increasing a dose, (especially on ≤q8hr regimens), consider q24hr SCr monitoring until the next trough level

****For levels >22 with suspected harm from vancomycin, enter a safety event** (See Vancomycin Quantros SOP for instructions)

Delaying dose: Usually 0.5 times the dosing interval
- Ex: Dose due at 1000 on q12hr regimen. Adjust dose and schedule to restart at 1600

Holding dose: Usually 1 time the dosing interval
- Ex: Dose due at 1000 on q12hr regimen. Adjust dose and schedule to restart at 2200

- If suspicion that delaying by full interval would result subtherapeutic, can order an earlier random level prior to reinitiating dosing
- If obtaining a random level prior to restarting dose, order for 0.5-1x the previous dosing interval (ex. 4-8hrs later if on q8hr regimen)
- If random is scheduled overnight, pass off to overnight pharmacist, or place new order with hold parameters and discuss with RN

Individualized Vancomycin Dosing

Patients may require alternative dosing schedules (ex: q36hr or q48hr dosing) based on patient-specific clearance to remain therapeutic. Vancomycin exhibits linear pharmacokinetics. Increases or decreases in total daily dose have a proportional increase or decrease in trough values (assuming renal function is STABLE). Set up a proportional relationship to estimate the actual trough based on new dose.

Example (part 1): Pt. on 1000mg IV q12h, trough is 9 mcg/mL with 15-20 mcg/mL. Estimate the new trough if changed to 1500mg q12h.

Cmin(actual) = Current total daily dose → 9 mcg/mL = 2000 mg

x **New total daily dose** x 3000 mg Therefore, x = 13.5 mcg/mL

***Thus, the new dose of 1500mg IV q12h would be expected to produce of trough of ~13.5 mcg/mL.*

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 13.5 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.**

Example (part 2): For the same patient, you want to estimate the new trough if the patient is changed to 1000mg q8h.

Cmin(actual) = Current total daily dose → 9 mcg/mL = 2000 mg

x **New total daily dose** x 3000 mg Therefore, x = 13.5 mcg/mL

***Although the TDD is 3000mg in both cases, 1000mg q8hr will provide a higher expected trough due to decreasing the interval*

***Pharmacokinetic calculations would estimate the new trough to be ~18 mcg/mL*

Section V: Dosing in patients with ESRD/RRT:

Intermittent hemodialysis

- This dosing strategy applies to adults with chronic kidney disease receiving intermittent HD
- Excluded patients: new hemodialysis initiation, chronic kidney disease patients receiving peritoneal dialysis, acute/chronic kidney injury receiving continuous renal replacement therapy (CRRT, CVVHD, etc)
- **Dosing based off an assumption of 3 times/week, complete IHD sessions**
  - Doses should be administered after each IHD session of additional sessions occur
- We assume that approximately 20-30% of vancomycin is removed by a standard IHD.
  - Ex: Pre-HD random = 18mcg/mL. Post-HD level estimated at 12.6-14.4 mcg/mL.

Management Steps	Recommended Management
Step 1: Loading Dose	20 mg/kg x1 (rounded to the nearest 250 mg, Maximum 2.5 gm)
Step 2: AM Random	For obese patients and those being treated for serious infections: • Obtain a random level the following morning with AM labs to ensure that patient is not subtherapeutic. If subtherapeutic, a small supplemental dose is recommended Other patients: • Obtain a random level with AM labs prior to the next HD session
Step 3: Maintenance Dose	500-1250mg (~10mg/kg) after each HD session (Max 1.5gm unless indicated by levels) • Adjust as needed. (See recommendations by level in table below)
Step 4: Follow-up Levels	Obtain a second random level prior to 2nd HD session • Patients on hemodialysis typically reach steady-state prior to their 3rd HD session (if same doses given after first 2 sessions) • After obtaining 2 levels in goal range, obtain follow-up levels once weekly • More frequent levels if: pre-HD levels rising, inconsistent timing of HD sessions

- Obtaining levels
  - **Obtain random levels prior to dialysis**
    - Redistribution post-dialysis takes ~6-8 hours. Levels immediately post-HD are falsely low
  - We assume that **approximately 20-30% of vancomycin is removed by a standard IHD**
    - Ex: Pre-HD random = 18mcg/mL. Post-HD level estimated at 12.6-14.4 mcg/mL.

- Following any dose adjustment (dose is different from previous dialysis dose), vancomycin level should be checked prior to the next two dialysis sessions to ensure level is stable, then weekly
- Goal for pre-HD random level will prevent subtherapeutic level between dialysis and next dose
  - **Pre-HD goal for non-serious infections**: 15-25mcg/mL (post-HD level 10.5-16mcg/mL)
  - **Pre-HD goal for serious infections**: 20-30mcg/mL (post-HD level 14-20mcg/mL)
  - In patients on temporary HD with expected renal recovery, try to target lower end of goal range to minimize additional nephrotoxicity

Random Level	Dose recommendation	
	Non-Serious Infections: Goal 15-25 pre-HD	Serious Infections: Goal 20-30 pre-HD
>25	**HOLD** post-HD dose Decrease future doses by 250mg	Consider decreasing post-HD dose by 250mg **Only hold dose if level >30**
20-25	Decrease post-HD dose by 250mg	Continue current dosing
15-20	Continue current dosing	Increase dose by 250mg
<15	Increase dose by 250mg	Increase dose by 250-500mg

Pulse dosing in ESRD or AKI

- **Strongly consider pulse dosing up front** in patients with a questionable history of dialysis requirements, even if they are not currently on scheduled HD (may indicate poor renal function but not full ESRD)
- Clinical judgment should be used to evaluate the degree of renal dysfunction and the direction it is trending to determine need for more conservative dosing.
- **When pulse dosing, utilize a vancomycin placeholder order on the MAR to show continued vanc therapy**
  - Vancomycin pulse dosing by pharmacy (scheduled to start in 1 month)
  - Contains admin instructions stating that the order is not intended for administration.

- In patients with unstable renal function or risk for poor clearance, it is safer to target low peak concentrations
  - High peak concentrations could lead to further nephrotoxicity if the level clears very slowly
- Patients with AKI have unpredictable/non-linear clearance of vancomycin. When pulse dosing based on random levels it is important to take into consideration the resulting level (amount of drug that is already in the body) as well as the amount of drug that will be present after administering a dose.
- **To determine concentration provided immediately after a single dose:**
  $Cp = \frac{Dose}{Vd}$ **Cp= the amount the concentration will rise from a given dose, not the final concentration

  Example: Patient weighing 95 kg, with worsening AKI has a random level of 13.6 mcg/mL.

  1500 mg (15 mg/kg): $Cp = \frac{1500}{(95 \times 0.7)} = 22.5$ mcg/mL Final concentration = 22.5 + 13.6 = 37.1mcg/mL

  750 mg (8 mg/kg): $Cp = \frac{750}{(95 \times 0.7)} = 11.3$ mcg/mL Final concentration = 11.3 + 13.6 = 24.9mcg/mL

  A level of 37.1mcg/mL may hang around for a long period of time potentially causing more renal damage. Calculate a dose that will give you a predicted concentration in a safer range (~25 mcg/mL) to ensure adequate clearance.

Continuous renal replacement therapy (CRRT)

- Drug clearance is highly dependent on the method of renal replacement, filter type, and flow rate
  - Degree of drug removal: CVVHDF > CVVHD > CVVH
  - Most guidelines recommend to dose on an estimated CrCl of 30mL/min in CRRT
- **Loading Dose:** 20 mg/kg x 1 (rounded to the nearest 250 mg, Maximum 2.5g for loading dose)

- **Maintenance Dosing:**

CRRT Method	Recommended Management
Low flow rate: 1-2L/hr, ≤30mL/kg/hr, CVVH, or CVVHD	15-20 mg/kg q24h
High flow rate: >2L/hr, >30mL/kg/hr, or CVVHDF	10-15 mg/kg q12h

- **Monitoring:**
    - Trough levels rather than random levels are ordered, as vancomycin removal is continuous and mimics renal clearance. Drug redistribution occurs continuously rather than in a rapid phase as it does in IHD
        - Consider random levels instead if CRRT modality/settings are changing
    - Check trough prior to 3rd dose and adjust based on levels
- Follow up with renal replacement plans daily to monitor flow rates, interruptions in CRRT, etc.
    - Monitor nephrology notes and call nurse to confirm
- Additional considerations:
    - Patients may be on CRRT transiently due to AKI, but still have residual renal clearance of vancomycin
    - Dosing requirements may increase as renal function improves
- Add Smartphrase ".CRRTDOSING" to administration instructions for all scheduled regimens

Sustained low-efficiency dialysis (SLED)

- Drug clearance is highly dependent on SLED settings, duration of each session, and frequency of each session
    - Some patients receive SLED daily, while others receive intermittent sessions, similarly to IHD
    - An estimated 30-40% of vancomycin serum concentrations are removed with each SLED session
- **Loading Dose:** 20 mg/kg x 1 (rounded to the nearest 250 mg, Maximum 2.5g for loading dose)
- **Maintenance Dosing:** 15 mg/kg administered after SLED
    - Doses should only be administered if patients received SLED (unless otherwise indicated by levels)
    - In patients receiving daily SLED, can consider scheduling maintenance dose q24h
- **Monitoring:**
    - Check random level prior to SLED.
    - Goal pre-SLED random levels 20-25 (up to 30) are required to maintain post-SLED concentrations above 15mcg/mL
    - Refer to HD table above for assistance with dosage adjustments by level
    - After obtaining 2 levels in goal range, can obtain follow-up levels once weekly **if SLED schedule remains consistent**
- Follow up with renal replacement plans daily

Peritoneal Dialysis (PD)

- Drug clearance is highly dependent on the frequency of peritoneal dialysis
- Studies have shown that vancomycin t1/2 in peritoneal dialysis is ≥72 hours
- **Loading Dose:** 15-20 mg/kg x 1 (rounded to the nearest 250 mg, Maximum 2.5g for loading dose)
- **Monitoring (goal level 15-20mcg/mL):**
    - Check initial random level 24 hours after initial dose to ensure serum level is not subtherapeutic
    - Check subsequent random level 48-72 hours after each dose
    - Random level should be checked at least 6 hours after PD session completed to allow for drug redistribution
- **Maintenance Dosing:** 5-10 mg/kg (500-1000mg) administered after PD
    - Frequency of dosing required will vary based upon frequency of PD sessions
- Follow up with renal replacement plans daily
- Contact nephrologist to discuss all dose adjustments and monitoring plans

Appendix A: Pharmacy vancomycin consult service

a. **Certification**

1. OLOL pharmacists must be certified as per current department and hospital policy prior to independent utilization of this protocol. Pharmacists not certified must gain approval from a certified pharmacist prior to making any

recommendations. Deviations from this protocol must be well substantiated, documented in the patient progress section of the electronic medical record and discussed with the patient's physician.

2. An ongoing peer review process will occur with vancomycin consults, and direct feedback will be provided in the case of unsubstantiated protocol deviations/dosing errors in order to improve education and prevent future errors.

b. **Consultation Process**

1. The pharmacist is automatically consulted to evaluate, adjust, and monitor all vancomycin therapy in adult patients upon initiation of vancomycin by the prescriber. Once consulted, pharmacists will follow the patient's progress and adjust doses until the vancomycin and/or the consult is discontinued.
2. The pharmacist will assess the patient and evaluate the appropriateness of the current drug regimen, potential for toxicity, current dose, dosing interval, dosing times, serum sampling times, previous serum levels or the need for future serum levels, and patient's fluid status.
3. The pharmacist is responsible for ordering vancomycin levels and other monitoring parameters as indicated
   - Communicate with nursing and/or the laboratory to assure proper sample collection
   - Document the day and time for the pending drug level in the patient's electronic profile to ensure follow up
4. The pharmacist adjusts initial and subsequent dosage regimens based on dosing guidelines for vancomycin and/or interpretation of serum levels as indicated in this protocol**.**
   - Estimate a creatinine clearance and patient-specific pharmacokinetic parameters
   - Analyze the validity of plasma concentrations and collection times

c. **Documentation**

1. The certified pharmacist receiving the TDM order will enter an initial consult note in the EMR within 24 hours using the "Vancomycin Initial Consult Note" template to notify healthcare providers of pharmacist monitoring and to communicate plans for dosing, evaluation of levels and any other changes made to the existing plan.
   - Additional notes will be entered within 24 hours evaluation of a serum level or dosage change.
2. Notes should contain all relevant patient information and pharmacokinetic parameters necessary to produce the dosing and monitoring recommendations. Verbal communication with the physician is also encouraged.
3. The pharmacist initiates a daily monitoring form for pharmacy records. The patient's information will be kept in the daily monitoring form while the consult is active. The information should be maintained in an organized manner so that continuity of care is facilitated in the event the patient is transferred to another area of the hospital.
4. An abbreviated vancomycin note will be utilized for progress notes afterhours and on weekends due to collapsed staffing model

d. **Monitoring parameters**

1. The pharmacist will assess the following patient parameters <u>DAILY</u> to assess clinical appropriateness of therapy. Applicable information will also be recorded on the daily therapeutic drug monitoring form
   i. Indication and goals of therapy (target trough goals)
   ii. Cultures and sensitivities
   iii. Duration of vancomycin therapy and justification for continuation
   iv. WBC, serum creatinine/estimated calculated creatinine clearance, Tmax, Ins/UOP
   v. Patient's clinical status (i.e response to therapy, changes in renal function)
   vi. Pertinent past medical history (i.e. CKD/renal dysfunction, previous vancomycin dosing, etc.)
   vii. Risk factors for nephrotoxicity (see Table 1)
   viii. Concomitant antibiotics
   ix. Dose, frequency, and vancomycin administration times
   x. Serum levels and times they were obtained

<u>Appendix B: Pharmacokinetic Definitions and Principles</u>

Creatinine Clearance – CrCl

- Calculating the creatinine clearance (CrCl) using the Cockcroft-Gault (CG) equation is the most common and practical approach for estimating renal function for medication dose adjustments.
    - If patient weighs < IBW use Actual Body Weight (ABW) for calculating CrCl
    - If patient weighs >20% IBW then use Adjusted Body Weight (DW) for calculating CrCl

IBW_{male} = 50kg + (2.3 x Inches over 60) IBW_{female} = 45.5kg + (2.3 x Inches over 60)

- Serum creatinine values <1 mg/dl can falsely elevate the calculated creatinine clearance in patients with reduced muscle mass as a fraction of total body weight. This includes patients with the following conditions: malnutrition, liver disease, muscle wasting (i.e. paraplegic patients), amputation, advanced age.
    - Refer to prior SCr values to establish a baseline for that patient
    - Utilize percent change in SCr to monitor for AKI in patients with low SCr values

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

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.
- Estimated with 2 drug levels taken between doses (the slope of the line).

$$K_e = (0.00083 \times \text{CrCl}) + 0.0044$$

$$\text{Patient-specific Ke} = \frac{\ln(\text{level 1} \div \text{level 2})}{\text{time between levels}}$$

$t_{1/2}$ or Half-life

- The time required for the TOTAL amount of remaining drug in the body to decline by 50%.
- Vancomycin half-life is utilized to select an appropriate dosing interval for each patient

$$T_{1/2} = 0.693/k_e$$

$$\text{Patient-specific Ke} = \frac{\ln(\text{level 1} \div \text{level 2})}{\text{time between levels}}$$

Patient-specific T1/2 = 0.693 ÷ Patient-specific Ke

Peak, C max

- The peak is the measured drug concentration AFTER distribution.
- C max is the maximum measurable drug concentration at the end of an infusion BEFORE significant distribution occurs.

$$\text{estimated Cmax} = \frac{\text{Dose} \times (1-e^{-ke \times t})}{K_e \times Vd \times t \times (1-e^{-ke \times T})}$$

** t=infusion time in hours, T = dosing interval in hours

Vd or Volume of Distribution

- The volume of distribution is the theoretical size of the compartment necessary to account for the total drug amount in the body if it were present throughout the body in the same concentration found in the plasma.
- Factors that may affect the volume of distribution include; protein binding, hydration, lean body mass, third spacing, burns, nutrition, fever, sepsis, disease states, drug-drug interactions, etc.
- Expressed in liters (L) or liters/kg (L/kg)

Normal Vd = 0.7 L/kg

Appendix C: Monitoring Checklist/Progress Notes

Monitoring Checklist

When monitoring a patient on vancomycin, the pharmacokinetic monitoring form should be used. This checklist maybe used to ensure that all vital information is recorded and examined.

- ☐ Indication/Therapeutic goals
  - Was the H&P, progress notes, operative reports reviewed to determine indication?
  - Is vancomycin therapy appropriate for the infectious indication?
  - What is goal trough?

- ☐ Patient Demographics and pertinent past medical history
  - What is patient's height and weight (actual/ideal)?
  - Does patient have any co-morbidities that would pre-dispose/increase risk of nephrotoxicity or affect vancomycin tolerance?

- ☐ Severity of illness
  - Were WBC and Tmax trends evaluated?
  - Is patient critically ill/septic?

- ☐ Renal function
  - Was SCr and I/UOP trends evaluated?
  - Does patient have any risk factors for developing nephrotoxicity? (IV contrast, concomitant nephrotoxic medications)
  - Have pharmacokinetic parameters been calculated? (creatinine clearance, T1/2, ke, estimated Cmin/Cmax)

- ☐ Cultures
  - Has anything grown?
  - Are there new cultures?
  - Does therapy or goal trough need to be adjusted based on culture results?

- ☐ Medication Administration Times
  - Has first dose or previous vancomycin therapy been administered?

- ☐ Therapeutic Monitoring Plan
  - When should levels be ordered?
  - If following up, were levels drawn appropriately?
  - Are levels within therapeutic range?
  - Has indication for vancomycin changed or been further defined requiring alternate therapeutic goals?
  - What other factors may have contributed to these levels (fluid status, administration times, etc)?
  - How does therapy need to be adjusted based on these levels and any calculated parameters?

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