ORLANDO HEALTH®
1414 Kuhl Ave.
Orlando, FL 32806

Title: **Vancomycin IV Dosing for Adult Patient**	Number: **PROT-(4710)-3105**

Issue date: 04/2009	Replaces Dept. Policy:
Revision dates: **06/2014, 05/2017, 06/2018, 1/2020**	Developed by: Pharmacy Services
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Department Numbers: **1422, 2422, 3422, 6422, 8422, 9422, 7070, 5422**	

I. PURPOSE:

A. This Collaborative Therapy Management Program outlines pharmacist-driven vancomycin dosing and monitoring for adult patients at Orlando Health.

II. DEFINITIONS

A. Obesity – BMI ≥30

III. DEPARTMENT PROCESS:

A. All intravenous (IV) vancomycin orders for adult patients will be an automatic pharmacy consult.
   1. WPH patients on vancomycin for group B streptococcus prophylaxis and/or premature rupture of membranes (PROM) are excluded from automatic consultation.

B. Upon receipt of a "Pharmacy Consult-Vancomycin Dosing" order or IV vancomycin order, the pharmacist will calculate and order the appropriate vancomycin regimen based on patient weight, renal function and indication. Pharmacists order drug levels and serum creatinine (SCr), as appropriate, for monitoring.

   1. If the Pharmacy Consult – Vancomycin order is not selected by the prescriber at order entry, the pharmacist will enter the consult order on behalf of the prescriber. One-time orders and surgical prophylaxis do not require a Pharmacy Consult order.
   2. Appendix I outlines vancomycin dosing and monitoring best practices based on published evidence and national guidelines (where applicable). This document is intended to guide the clinician in initiating, adjusting, and monitoring intravenous (IV) vancomycin therapy, but does not replace clinical judgement.
   3. As part of the initial consult, pharmacists should assess if appropriate cultures have been obtained for the indications listed in Appendix II. If appropriate cultures have not been ordered, the pharmacist may contact the prescriber to recommend appropriate cultures. If appropriate cultures have been ordered but not collected, the pharmacist may contact the nurse to ask nurse to obtain cultures.

C. Vancomycin orders and pharmacy consult orders require a duration of therapy to be entered upon order entry.

   1. Pharmacists should ensure that the initial ordered duration of therapy is appropriate for the selected indication. Appropriate durations based on indication are listed in the OH Antimicrobial Treatment

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Duration for Adult Non-neutropenic Patients. The pharmacist should contact the prescriber for clarification, as necessary.

2. If new information becomes available during therapy (e.g. new positive blood cultures) that changes the indication for therapy and the appropriate duration, pharmacists should contact prescriber for clarification.

D. Pharmacists may recommend that the prescriber discontinue therapy if patient does not meet criteria for continuation (see Appendix III).
E. The consult shall be considered "completed" when vancomycin is discontinued, the vancomycin consult is discontinued, or the patient is discharged.

IV. DOCUMENTATION:

A. Additional information about documentation of pharmacy consults is described in Pharmacy Policy and Procedure Pharmacy Consults 0320.
B. The pharmacist will document an initial progress note in the patient's electronic medical record. Progress notes are not required for one-time orders or orders for ≤ 48 hours.
C. Any accompanying orders will be entered into Sunrise XA as "MEC Approved RPh/RD Only". Additional progress notes will be recorded anytime a drug level results or a dose adjustment is made (based on drug levels, change in renal function, prescriber requested change, etc.).

V. REFERENCES: See Appendix V

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Appendix I: Vancomycin Dosing and Monitoring Best Practice

INITIAL VANCOMYCIN CONSULTATION

Table 1: Initial vancomycin dosing

All vancomycin doses are to be calculated based on actual body weight and should be rounded to the nearest 250 mg. Infusion time should not be faster than 1 gram/hour. The maximum concentration of the admixture should be 5 mg/mL (see "Administration" for details).

STEP 1:	Loading Dose¥	Loading doses are recommended for ALL patients (including patients on hemodialysis). A loading dose is optional in patients with heart failure or fluid restriction when on vancomycin for cellulitis. 20 mg/kg is preferred in most patients. ○ Patients weighing >150 kg (regardless of disease state) should receive 20 mg/kg. Confirm weight before entering loading dose. Can consider capping loading dose at 3000 mg. ○ NON-critically ill patients with sepsis or pneumonia should receive 20 mg/kg • 25 to 30 mg/kg: Confirmed or suspected *Staphylococcus aureus* bacteremia; confirmed or suspected endocarditis or meningitis; or critically ill patients with pneumonia or sepsis
	Booster Dose	Consider in patients who received an inadequate loading dose of vancomycin (i.e. received dose which was ≤ 50% of the calculated value). Booster doses can be given at any time between the initial vancomycin dose and the maintenance dose. Booster doses ≤ 500mg are likely not needed.
STEP 2:	Maintenance Dose	• 15 mg/kg dose at the appropriate interval listed below (maximum of 2 gram/dose) ○ Interval suggestions below are for patients with stable renal function. Patients with acutely changing renal function should be dosed by levels (i.e. pulse dosing). • 10 -12.5 mg/kg in obese patients* (see **obesity & volume of distribution** section in **BACKGROUND** for further detail) (consider maximum of 2 gram/dose initially). • Hemodialysis: consider 10 mg/kg per dialysis session, with subsequent doses adjusted based on levels◦

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STEP 3:	Determination of dosing interval	Estimated CrCl (mL/min)‡#	Dosing Interval
		≥90	Q8 to Q12 hours§ ○ **Q12 hours is preferred in patients ≥ 40 years of age** and indications of cellulitis ○ Q8 hours is preferred in pregnant patients ○ 10-12.5 mg/kg **Q12 hours** is **preferred in non-pregnant obese patients*** ▪ For obese patients ≥40 years of age and with less severe infections, start with lower end of the dosing range
		60-89	• Q12 hours • 10 mg/kg Q12 hours is recommended in obese patients*
		30-59	Q24 hours
		16-29	Q36-48 hours.+ For **confirmed** infections, consider checking a level 24 or 48 hours after the first dose to ensure adequate exposure. ^
		≤ 15	Pulse dosing. Check random level (i.e. timed vancomycin level) within 72 hours or sooner for patients with confirmed infection or who are critically ill (e.g. 24 hour level for patients with MRSA bacteremia). ^
		Hemodialysis	Check pre-dialysis (i.e. timed vancomycin level) level before second dialysis session or at 48 hours if no dialysis planned.^
		CRRT	Dose for an estimated CrCl of 30 mL/min. Pulse dosing may be considered as appropriate.
STEP 4:	When to start the maintenance dose	Schedule the first maintenance dose x hours after the START of the loading/booster dose, where x represents the determined dosing interval.	

¥ If a patient has missed ≥ 4 doses of their previous vancomycin regimen, re-loading the patient when starting the new regimen may be considered. Loading doses should rarely exceed 20 mg/kg in this circumstance. Random levels (i.e. timed level) prior to restarting vancomycin may also be considered.
◦For patients on chronic hemodialysis, doses should be tailored to be given with each dialysis session for ease of outpatient management. Some patients may only require 5-10 mg/kg after each dialysis. Once patients are on stable regimen, levels should be drawn once weekly.
§ For patients that are likely to be discharged on outpatient vancomycin therapy (e.g. osteomyelitis, prosthetic joint infection), Q12 hours is preferred for ease of outpatient transition.
*Obese is defined as BMI ≥30
‡Refer to the Aminoglycoside Dosing and Monitoring Collaborative Therapy Management Program for guidance on calculating an estimated CrCl
+ Intervals of Q36 hours are not ideal for administration after discharge and can lead to missed doses or levels. When possible, transition maintenance doses to every 24 hours for patients going home on vancomycin.
^ See **initial trough levels** section below.
# As renal function decreases ~1% per year after age 30, CrCl for patients 65 years or older is usually significantly less than 60 mL/min

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MONITORING VANCOMYCIN THERAPY

Monitoring AUC Exposure

- The area under the curve (AUC) in relation to the minimum inhibitory concentration (MIC) of the organism has been best correlated with efficacy for the treatment of invasive *S. aureus* infections. Additionally, AUC-guided dosing has been associated with reduced rates of nephrotoxicity as compared to trough-only monitoring for all patients on vancomycin regardless of infection type.
- AUC/MIC vs. AUC (independent of MIC): Since >90% of *S. aureus* isolates at our institutions have an MIC of 1 mcg/mL, toxicity is linked to AUC (independent of MIC), and there is a lack of efficacy data supporting lower AUC targets for an MIC ≤0.5 mcg/mL, **all AUC goals listed below are independent of the MIC.** Patients on vancomycin being treated for an invasive *S. aureus* infection with a vancomycin MIC of 2 mcg/mL should be discussed with an ID Pharmacist to assist in determining the best therapy.

- **AUC Goal Levels**
    a. Invasive Gram-positive infections: AUC goal 400-650 mg*h/L
        i. ASHP, IDSA, PIDS and SIDP Consensus Guideline recommend an AUC goal of 400-600 mg*h/L. The higher range was chosen here to allow for slight variations in AUC calculations. Nephrotoxicity has been associated with AUC >650 mg*h/L.
        ii. Cellulitis (unless concern for necrotizing fasciitis or osteomyelitis) and Gram-positive cystitis (bacteremia ruled out) are not considered invasive infections and monitoring for efficacy is not necessary. Consider trough-only monitoring for toxicity in these patients when necessary (see below) with goal trough levels 8-15 mcg/mL.
        iii. AUC goals have not been established for CNS infections (e.g. meningitis). Consider trough monitoring in these patients.
- **Determining AUC Exposure**
    a. Methods for determining AUC are not reliable for patients with acutely changing renal function (i.e., AKI) or those on renal replacement therapy; therefore, these patients should be monitored via trough monitoring until more data become available to support AUC monitoring
    b. Formula-based Approach
        i. Used as a quick estimate of AUC, however since relies on SCr-estimation of renal function may significantly over- or underestimate true exposure
            1. Less accurate in patients with low muscle mass, elderly patients, obese patients, and patients with augmented renal function
            2. Not recommended for pregnant patients. See section C below on two-level pharmacokinetics.

Table 2: Method to quickly estimate a vancomycin AUC

1. Estimate creatinine clearance	Refer to the Aminoglycoside Dosing and Monitoring Collaborative Therapy Management Program for guidance on calculating an estimated CrCl
2. Estimate vancomycin clearance, CL_{VANCO} using CrCl†	CL_{vanc} = [(CrCl x 0.79) + 15.4] * 0.06
3. Estimate 24-hour AUC (AUC_{0-24})‡	$AUC_{0-24} = \frac{Total\ vancomycin\ dose (in\ mg)\ over\ 24\ h}{CL_{VANCO}}$

† Vancomycin clearance and creatinine clearance are NOT equal (they generally are for aminoglycosides).
‡ For example, for a patient receiving vancomycin 1 g every 8 h, 3000 mg would be entered into the numerator.

c. Two-level Pharmacokinetics
   i. More accurate since uses patient-specific pharmacokinetic parameters to calculate AUC using a 2-level AUC calculator or using calculations listed in Appendix IV
   ii. Recommended for:
      1. Patients being treated for invasive *S. aureus* infections: bacteremia, endocarditis, or pneumonia
      2. Elderly or obese patients with an intended duration >7 days
   iii. Timing of levels
      1. Level 1 (i.e. peak): 1-2 hours after the end of the infusion
         a. Recommended to wait at least one hour after the end of the infusion to account for the alpha distribution phase
      2. Level 2 (i.e. trough): 30-60 minutes prior to the next scheduled dose
      3. Steady state vs non-steady state levels
         a. Near steady state levels may be preferred; however, levels drawn before steady state conditions are achieved may be used to optimize AUC exposure in the first 48 hours. If calculating levels before steady state, non-steady state equations must be used (see Appendix IV). If using a calculator, ensure non-steady state calculations are performed.
      4. Levels should be at least half the interval apart (e.g. 6 hours apart for q12h frequency) as the closer levels are together the more minor variations in documentation will affect the calculation. Pharmacists should confirm time of levels and most recent dose administration with nurse when possible.
   iv. After AUC goal met, weekly trough level can be used for ongoing toxicity monitoring with a goal trough <20 mcg/mL. If follow-up level <8, consider repeating 2 levels and calculate AUC. If level >20 mcg/mL, see section on "Dose adjustment".

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Trough-only Monitoring

- The indication for and planned duration of therapy should be assessed prior to obtaining trough levels. Routine monitoring of serum concentrations can lead to unnecessary interventions if continued vancomycin therapy is not warranted (see Appendix II). In most cases, trough levels are not recommended during the first 72 hours if planned duration is ≤7 days (e.g. cellulitis, sepsis rule out), especially in non-critically ill patients with stable renal function.
    - Consider getting levels during planned short courses in patients with any of the following:
        - Acutely changing renal function (e.g. >30% in SCr in 24 hours and/or UOP decrease to <0.5 mL/kg/24 hour)
        - New culture data is available (e.g. methicillin-resistant *S. aureus*) from a culture site typically associated with longer durations of therapy with vancomycin (e.g. bone, blood)
    - Daily SCr monitoring recommended for the following patients with short courses of vancomycin. A trough should be considered if SCr indicates acute changes in renal function and vancomycin is planned to continue.
        - Patients >65 years old
        - Receiving other nephrotoxic agents (e.g. aminoglycosides, IV contrast)
        - Q8H regimens – especially in patients >30 years old or obese

- Goal serum vancomycin troughs are listed in Table 3.
    - **Initial trough**:
        - Obtain at steady state (see section on steady state) if planned to continue for >7 days or patient has documented invasive Gram-positive infection.
        - Consider obtaining a trough earlier in patients at high risk of accumulation to avoid supratherapeutic levels.
            - Obese patients (BMI ≥30)
            - Acutely changing renal function (e.g., >30% in SCr in 24 hours and/or UOP decrease to <0.5 mL/kg/24 hour)
            - Patients on every 48-72 hour or pulse dosing regimens
        - A trough before the 4th or 5th dose does not always ensure the patient is at steady state (see Table 5). The initial vancomycin trough level should be evaluated as to whether it may be artificially low because steady-state has not been reached, prior to recommending maintenance dose elevations. When levels are drawn before steady state is reached, clinical judgement may warrant deviation from the Collaborative Therapy Management Program and repeat levels may be needed.
            - In patients with stable renal function and less severe infections, waiting before the 5th or 6th dose is reasonable and will be closer to steady state

    - **Follow-up trough**
        - Stable renal function: every 5 – 7 days
        - Follow-up troughs to assess a recent regimen change (e.g. once at steady state of a new regimen) are not recommended in patients with stable renal function
            - Vancomycin follows linear kinetics and proportional change in serum level can be assumed based on the dosage change. A follow-up trough after 5-7 days in recommended in these cases.

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Exceptions may include aggressive dosage changes, when a patient's prior level may not have been at steady state (e.g. obese, elderly) or in patients with unexpected clearance of vancomycin as assessed by an unexpectedly low or high trough level.

- Hemodialysis: levels should be timed to be drawn on dialysis days before dialysis. Once patients are on stable regimen, levels should be drawn once weekly. In patients on HD with residual renal function (e.g. UOP >100 mL/day), levels in between dialysis sessions may be required due to intradialytic clearance; however, daily levels in this population are usually not necessary.

Patients Receiving Intermittent Hemodialysis

- Removal of vancomycin during hemodialysis is highly variable and can be affected by the length of the treatment, type of filter used (high or low-flux) and receipt of dialysis versus ultrafiltration.
    - Filter
        - High-flux filters (typical at Orlando Health): remove about 25-30% of vancomycin
        - Low-flux filters (not typically used at Orlando Health): less efficient, remove about <15% of vancomycin
    - Dialysis or ultrafiltration
        - Dialysis: removal of fluid WITH removal of drugs/electrolytes
        - Ultrafiltration (sometimes referred to as "slow continuous ultrafiltration," or "SCUF"): removal of fluid WITHOUT significant removal of drugs/electrolytes
- Clarification of any of the above parameters can be achieved by contacting the dialysis nurse
- Pre-dialysis levels are preferred for dialysis patients due to potential delays in therapy and redistribution issues with post-dialysis levels. If a post-dialysis level is necessary, it should be drawn at least 2 hours after the dialysis session to allow for redistribution.
    - When assessing pre-dialysis levels, must confirm that patient received the entire dialysis session.
    - It is usually possible to order an "Add-on" vancomycin level to the morning labs drawn prior to dialysis in the event of a pre-dialysis level not being ordered or drawn.
- Goal serum vancomycin pre-dialysis timed/random levels are listed in Table 3.

Patients Receiving Peritoneal Dialysis (PD)

- Peritoneal dialysis is generally performed daily, rather than a few times a week as with hemodialysis.
- Intravenous vancomycin (preferred for systemic infections)
    - Patients should be dosed by levels, initially, as clearance varies by patient and type of peritoneal dialysis. Consider getting a level 24-48 hours after the first dose to determine subsequent dosing.
    - Patients should be re-dosed when the vancomycin level is less than 20 mcg/mL for serious infections and <15 mcg/mL for mild to moderate infections, as outlined in table 3. **Do not use pre-dialysis goal levels in these patients unless they have been transitioned to hemodialysis.**
- Intraperitoneal vancomycin (preferred for PD-associated peritoneal infections).
    - Dosing of intraperitoneal vancomycin is outlined in the Orlando Health Intraperitoneal Antibiotic Dosing Guidelines for Peritoneal Dialysis.
    - Vancomycin should be given either intravenously or intraperitoneally, not by both routes simultaneously

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Table 3: Recommended Vancomycin Serum Concentrations For Patients Without AUC Calculated By Two Levels**

Trough Levels	
12-20 mcg/mL	Severe infection: bacteremia, endocarditis, osteomyelitis, meningitis, pneumonia, or severe skin and soft tissue infection (e.g. necrotizing fasciitis), line-related bloodstream infections caused by *S. aureus* or *S. lugdunensis*. AUC monitoring recommended for most patients with severe infections (see AUC monitoring section above)
8-15 mcg/mL	Mild-moderate infection: skin & soft tissue infection (including skin abscesses), intraabdominal infections (including abscesses), line-related bloodstream infection (except if caused by *S. aureus* or *S. lugdunensis*), pyelonephritis, or cystitis
Pre-hemodialysis Timed/Random Levels	
18-25 mcg/mL	Severe infection: bacteremia, endocarditis, osteomyelitis, meningitis, pneumonia, or severe skin and soft tissue infection (e.g. necrotizing fasciitis), line-related infections caused by *S. aureus* or *S. lugdunensis*. Corresponds with target trough of 15-20 mcg/mL
11-20 mcg/mL	Mild-moderate infection: skin & soft tissue infection (including skin abscesses), intraabdominal infections (including abscesses), line-related bloodstream infection (except if caused by *S. aureus* or *S. lugdunensis*), pyelonephritis, or cystitis. Corresponds with a target trough of 10-15 mcg/mL.

** AUC has been best correlated with efficacy and safety. Patients may have troughs less than goal with AUC levels >400 mg*h/L. If AUC has been calculated by two levels to be ≥400, goal trough level is <20 mcg/mL.

Dose adjustments:

- Vancomycin doses should be adjusted to maintain serum trough concentrations within the desired therapeutic range based on measured serum concentrations if using trough-only monitoring.

  - **Goal trough of 12–20 mcg/mL**: dose should be adjusted if trough >20 mcg/mL
    - Troughs should not be maintained >20 mcg/mL in non-dialysis patients as these levels are associated with nephrotoxicity.
    - An initial trough (drawn at steady state) in the upper end of the range should prompt closer monitoring and possible dose adjustment as this may be an early sign of accumulation.

  Goal trough of 8-15 mcg/mL: if patient has an initial trough <8 mcg/mL with an adequate AUC level the dose may not need to be adjusted.

  - For levels close to the recommended range, remember to interpret a trough in the context of the previous dose(s), which may have been given early or late, as well as whether or not the patient has reached steady state. In these instances, the true trough would be lower or higher than the measured level. Dose adjustments outside of those described above or repeat levels may be needed depending on clinical judgement.

Serum Creatinine Monitoring: Serum creatinine should be measured at least every 2 to 4 days in most patients, unless the patient is receiving dialysis. Daily SCr monitoring may be necessary in patients with fluctuating renal function. Patients on vancomycin for >14 days on a stable regimen with stable renal function may have once weekly SCr measured.

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PRE-, PERI- and POST-OPERATIVE SURGICAL PROPHYLAXIS

- Vancomycin pre-operative doses should be adjusted to 15 mg/kg, rounded to the nearest 250 mg, with a maximum dose of 2.5 grams
    - Vancomycin should be started between 60 minutes and 120 minutes prior to incision
    - Surgical delay
        - If surgery is delayed more than 120 minutes from the start of the infusion and incision and the delay is *less* than 8 hours, an additional 500 mg of vancomycin should be dispensed
        - If surgery is delayed more than 120 minutes from the start of the infusion and incision and the delay is *more* than 8 hours, SCr should be assessed
            - SCr ≤ 1.5 mg/dL, an additional 1 gram of vancomycin should be dispensed
            - SCr > 1.5 mg/dL, an additional 500 mg of vancomycin should be dispensed
- Vancomycin peri-operative dosing is not recommended as pre-operative doses are weight-based and should maintain adequate concentrations in the tissue for the duration of surgery
- Vancomycin post-operative doses for surgical prophylaxis should not last longer than 48 hours for cardiac procedures or more than 24 hours for all other procedures in accordance with core measures (please refer to the Adult Automatic Stop for Postoperative Prophylactic Antimicrobials Collaborative Therapy Management Program [4710]).
    - Patients receiving therapy for 24 hours after surgery should receive no more than one dose*
    - Patients receiving therapy for 48 hours after surgery should receive no more than 3 doses*
    - Post-operative doses should be 15 mg/kg with a maximum dose of 2 grams

  * In patients with normal renal function, assuming Q12 hour dosing. Maximum frequency should be Q12 hours in patients with adequate renal function for post-operative prophylaxis. If creatinine clearance is < 40 mL/min, no post-operative vancomycin is needed for most procedures. For cardiac procedures, no more than one post –operative dose is needed.
- No notes are required for surgical prophylaxis regimens lasting <48 hours

"OUR LEGACY" (ORGAN DONATION) PATIENTS

- If providers wish to start vancomycin for prophylaxis without a documented Gram-positive infection, a one-time pre-operative dose of vancomycin 15 mg/kg (max 2.5 grams) starting 60-120 minutes before the incision for organ harvest is recommended
    - A Pharmacy Consult and/or progress note is not required for single doses
- Longer durations are not indicated unless patient has evidence of a Gram-positive organism on a surveillance culture (MRSA nares screens are not surveillance cultures)
    - For durations longer than 1 day, enter a Pharmacy Consult with indication "Our Legacy"
    - Ensure dosing is appropriate for age, weight and renal function
    - Monitor for toxicity with daily SCr - vancomycin levels are not recommended

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ADMINISTRATION

Vancomycin Bag Preparation:

The concentration of any vancomycin admixture should be ≤ 5 mg/mL (Table 4). Most commonly, this will be prepared in normal saline.

Table 4: Recommended admixture volumes based on Vancomycin dose*

500 mg in 100 mL	2 gram in 500 mL
750 mg in 250 mL	2.25 gram in 500 mL
1 gram in 250 mL	2.5 gram in 500 mL
1250 mg in 250 mL	3 gram in 600 mL
1500 mg in 500 mL	4 gram in 1000 mL
1750 mg in 500 mL	5 gram in 1000 mL

* For fluid restricted patients, the maximum concentration is 5 mg/mL (e.g. 1500 mg in 300 mL)

Loading doses, in general, should be prepared in one IV bag.

Infusion rate: The rate of vancomycin infusion should not be faster than 1 gram/hour. For example, 2 grams of vancomycin should be administered over at least 2 hours. Longer infusion times and central line administration may be considered in patients experiencing infusion-related reactions. To have the lowest risk of Redman's syndrome, doses should be administered at a maximum of 10 mg/min (i.e. 600 mg/h).

BACKGROUND SUPPORT FOR COLLABORATIVE THERAPY MANAGEMENT PROGRAM

INITIAL VANCOMYCIN CONSULTATION

LOADING DOSE:

- The rationale for a loading dose is to achieve therapeutic concentrations on day 1 of therapy.
- The patient's RENAL CLEARANCE OF VANCOMYCIN (e.g. CREATININE CLEARANCE) HAS NO BEARING ON THE LOADING DOSE. The accuracy of the loading dose is based solely on the volume of distribution (i.e. C_p = Dose/V_d)

BOOSTER DOSE:

Administer a "booster dose" upon a pharmacy consult when the patient is "inadequately loaded" (i.e. the dose given was ≤ 50% of the calculated loading dose). For example, if the calculated loading dose is 3 gram, but the patient received 1 gram prior to a pharmacy consult, order a "booster dose" of 2 grams x 1 to be given immediately, followed by the maintenance dosage regimen. Booster doses can be given at any time between the initial vancomycin dose and the maintenance dose. Booster doses ≤ 500 mg are likely not needed.

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MAINTENANCE DOSE:

- **Obesity & Volume of Distribution**: In the majority of obese patients (BMI ≥ 30) maintenance doses of ≥ 15 mg/kg will lead to significantly elevated steady-state vancomycin trough levels. This is due to a markedly elevated vancomycin volume of distribution in these patients and is independent of the patient's renal clearance of vancomycin. (Notice, the vancomycin volume of distribution is not considered in Table 1 as a method to determine the dosing interval.)

Recommendations:

- **Maintenance dosing regimen**: 15 mg/kg [based on actual body weight (ABW); (initial maximum of 2 gram/dose)] dosed at the appropriate dosing interval (Table 1) is recommended in most patients.

- **Obese patients:** A lower maintenance dose (i.e. 10 mg/kg) is recommended once an adequate vancomycin loading dose has been administered.

MONITORING VANCOMYCIN THERAPY

RECOMMENDATIONS FOR DOSE ADJUSTMENTS:

Evaluation of whether vancomycin has reached steady-state for trough-only monitoring: A common error involving vancomycin dosing and monitoring by pharmacists is failure to recognize that a low trough may be due to drawing a level before the patient has reached steady-state, and many of these patients may have adequate AUC or clinical response without further dose adjustment. The "normal" half-life of vancomycin in patients without renal impairment is between 6 to 12 hours. Steady-state is generally achieved after five half-lives; therefore a steady-state trough concentration in "normal" patients will not be obtained until 30 – 60 hours after the first dose. Time to steady-state is unaffected by the amount of drug given (15 vs. 25 mg/kg) or the frequency (e.g. Q8 vs Q12 vs Q24). The common practice is to obtain a vancomycin trough immediately preceding the 4th dose; however, this may or may not represent steady-state. A pharmacist may increase the daily dose of vancomycin (either by increasing the dose or decreasing the frequency) without considering whether a vancomycin serum trough level is low because steady-state has not been reached. Subsequently, in a few days, the increased dose and achievement of steady-state leads to markedly elevated levels. This most often occurs in older patients (e.g., >65 yo), patients receiving Q6 or Q8 hour dosing of vancomycin and patients who have elevated vancomycin volume of distributions (i.e. obese patients). A simple way to estimate the vancomycin half-life and subsequent time to steady-state is described in table 5.

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Table 5: Method to quickly estimate when steady-state is reached at the bedside

1. Estimate creatinine clearance, CrCl	Refer to the Aminoglycoside Dosing and Monitoring Collaborative Therapy Management Program for guidance on calculating an estimated CrCl
2. Estimate vancomycin clearance, CL_{VANCO} using CrCl†	• CL_{vanc} = [(CrCl x 0.79) + 15.4] * 0.06
3. Estimate vancomycin volume of distribution (V_d)	Approximately 0.57 to 0.83 L/kg (average 0.7 L/kg) based on actual body weight
4. Estimate the elimination rate constant (k):	$k = \frac{CL_{vanco}}{V_d}$
5. Half-life ($t_{1/2}$)	$t_{1/2} = \frac{0.693}{k}$
6. Estimate time to reach steady-state	Achieved after approximately 5 half-lives.

† Vancomycin clearance and creatinine clearance are NOT equal (they generally are for aminoglycosides).

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Appendix II: Appropriate Cultures by Indication

- Upon initial evaluation of a vancomycin consult, the pharmacist should review the chart to see if appropriate cultures have been obtained based on the indication in the order for the indications listed below. If cultures have not been ordered, the pharmacist may contact prescriber to recommend ordering (see table below).
- If cultures have been ordered but not collected, pharmacist may contact the nurse to recommend collecting cultures as soon as possible if applicable (e.g. call for pending blood, sputum, or MRSA PCR collection which are easily obtainable by the nurse. Do not call for pending CNS or operative culture collection which cannot be obtained by the bedside nurse).
- Recommended cultures should be collected prior to antibiotic administration to improve culture yield whenever possible. Patients with sepsis should have blood cultures drawn before antibiotics however antibiotic administration should not be delayed more than 1 hour from ordering. Invasive cultures (e.g. operative, CNS) are sometimes delayed due to difficulty obtaining and it is typically not appropriate to hold antibiotics to obtain these cultures. Pharmacists should not delay antibiotic verification to wait for appropriate culture ordering or collecting but recommending these cultures be ordered and/or collected may help facilitate timely collection.

Vancomycin Indication	**Recommended Culture(s)/Lab Data**
Bacteremia	Two sets of blood cultures
Febrile neutropenia	Two sets of blood cultures (one peripheral line and one central line if applicable), clarify suspected source with prescriber for further recommendations.
Infection	Clarify site of infection with prescriber and obtain appropriate cultures
Pneumonia	Sputum culture MRSA PCR Flu A/B PCR*
Sepsis^	Two sets of blood cultures^
UTI	Urinalysis r/o UTI (preferred recommendation if nothing ordered) OR Urinalysis AND Urine culture

*Only recommended during flu season (October-May). ^Cultures should be obtained from presumed source of sepsis (e.g., pneumonia, urine, etc.). #Unless listed as recommended, blood cultures are optional except in patients that have signs of systemic infection (e.g., fever, hypotension).

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Appendix III: Criteria For Appropriate Continuation Beyond 72 Hours

1. Confirmed MRSA infection
   - MRSA pneumonia
     i. Sputum culture collected before or within 12 hours of vancomycin initiation should be used to determine the need for vancomycin. If sputum culture is negative for MRSA, it should be recommended to discontinue vancomycin (regardless of the MRSA surveillance culture/PCR result).
     ii. If sputum cultures are not drawn before or within 12 hours of vancomycin initiation a **negative** MRSA surveillance culture/PCR can be used to recommend stopping vancomycin given its high negative predictive value
     iii. A positive MRSA surveillance culture/PCR has a poor positive predictive value for MRSA pneumonia, as most patients colonized with MRSA do not have MRSA pneumonia, therefore a positive result cannot be used to determine the need for vancomycin for treating pneumonia.
2. Confirmed Gram-positive infection with organism with known resistance to Beta-lactam antibiotics (e.g. methicillin resistant *S. epidermidis*) or pending susceptibilities
3. Confirmed Gram-positive infection in patient with severe allergy or intolerance to Beta-lactam antibiotics
   - Patients should have their allergy information confirmed
   - For confirmed allergies, alternative beta-lactams may be preferred and discussed with prescribers on a case-by-case basis (e.g. use of cephalosporins in patients with methicillin sensitive *Staphylococcus aureus* infections with a penicillin allergy)
4. Febrile neutropenia* patients with fever (38.0° C) in the past 24 hours or with cellulitis, port infection, confirmed Gram-positive infection from another source, radiologic evidence of pneumonia, hemodynamically unstable, or on aztreonam for Gram-negative coverage
5. Purulent cellulitis and unable to transition to PO
6. Infectious Disease Consult

*Febrile neutropenia is defined as fever of ≥38.0 in the setting of severe neutropenia (absolute neutrophil count [ANC] ≤500 cells). If ANC is not reported in the labs, ANC can be calculated by multiplying white blood cells (WBC) x total neutrophils (segmented neutrophils% + bands%) x 10 OR WBC x % total neutrophils x 10

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Appendix IV: AUC Equations

Non-Steady State Levels

1. Calculate patient's true k_e

$$k_e = \frac{\ln\ (C_1/C_2)}{(t_2 - t_1)}$$

2. Calculate true $t_{1/2}$

$$t_{1/2} = \frac{0.693}{k_e}$$

3. Calculate true C_{max}

$$C_{max} = \frac{C_1}{1 - \left(e^{-k*\Delta T}\right)}$$

ΔT=time between end of infusion and time level drawn

4. Calculate patient's V_d

$$Vd = \frac{Dose}{t} * \frac{(1 - e^{-kt})}{(k_e * C_{max})}$$

5. Calculate true vancomycin clearance

$$Cl_{van} = Vd * k_e$$

6. AUC_{24} based on current regimen

$$AUC = \frac{TDD}{k * Vd}$$

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Steady State Levels

1. Follow steps 1-3 above

2. Calculate true C_{min}

$$C_{min} = C_{max} * \left(e^{-k_e*(Tau-t)}\right)$$

3. Calculate patient's V_d

$$Vd = \frac{Dose}{t} * \frac{(1 - e^{-kt})}{k_e * (C_{max} - [C_{min} * e^{-kt}])}$$

4. Calculate true vancomycin clearance

$$Cl_{van} = Vd * k_e$$

5. AUC_{24} based on current regimen

$$AUC = \frac{TDD}{k * Vd}$$

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Appendix V: References

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