Vancomycin Dosing and Monitoring Clinical Practice Guideline

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Purpose: This document is intended to assist the clinical pharmacist in the safe and effective use of intravenous (IV) vancomycin at Children's Wisconsin in pediatric patients (age < 18 years old).

Introduction: Vancomycin inhibits bacterial cell wall synthesis by blocking glycopeptide polymerization through binding tightly to D-alanyl-D-alanine portion of cell wall precursor. Vancomycin has poor oral absorption and is widely distributed in most bodily tissues and fluid, with the exception of the CSF (increases in the setting of inflammation). There is no apparent metabolism of vancomycin and excretion is primarily via glomerular filtration.

Vancomycin requires therapeutic drug monitoring due to its narrow therapeutic index. The pharmacokinetic/pharmacodynamic parameter best correlated with efficacy is an area under the curve (AUC) to mean inhibitory concentration (MIC) ratio ≥ 400 mg*hr/L for *Staphylococcus aureus*. Additional data, although less studied, suggests an optimal AUC/MIC ratio > 390 mg*hr/L for *Enterococcus spp* and AUC > 300 mg*hr/L in the first 24 hours of therapy and AUC >420 mg*hr/L in the second 24 hours for *coagulase-negative staphylococci* in neonates. When using AUC-based dosing, AUC values < 600-800 mg*hr/L are associated with decreased rates of acute kidney injury (AKI). Therefore, consensus guidelines recommend AUC-dosing and monitoring of vancomycin as the preferred approach to achieve clinical efficacy and improve safety, with a target AUC/MIC of 400 mg*hr/L, with allowance up to 600 mg*hr/L.

For patients ≥ 18 years old at Children's Wisconsin started on vancomycin, please reference the adult dosing and monitoring within the IDSA 2020 vancomycin guideline or other adult dosing guide.

AKI with Vancomycin

Literature-based evidence suggests the risk of AKI with vancomycin increases as exposure increases (trough concentrations > 15-20 mcg/mL and AUC > 600-800 mg*hr/L). Additional risk factors in pediatrics include concurrent nephrotoxic medications, ICU duration, and age < 1 year.

Scope: *Reference the "Pharmacy Policy" for pharmacist scope of practice with vancomycin therapeutic drug monitoring*

*****For situations that may require TDM and fall outside of the guidance listed in this document, please collaborate with ID/AMS/pharmacy for TDM monitoring*****

Empiric Dosing

For patients with recent TDM of vancomycin, it is recommended to order the same dose and frequency assuming no significant changes have occurred in renal function, clinical status, or body weight
Additional considerations in Section 3

Neonates and Infants < 2 kg

Weight and postnatal age	**< 1.2kg & 0-28 days**	**< 2kg & 0-28 days**	**< 2kg & >28 days**	**> 2kg & 0-28 days**	**>2 kg & 29-90 days**
Recommended dose/frequency	20 mg/kg q24H	15 mg/kg q18	15 mg/kg q12H	15 mg/kg q12H	15 mg/kg q8H

Use actual body weight
Suspected renal insufficiency may require more conservative dosing

Infants, Children, Adolescents

<table>
<tr><th>Age</th><th>Recommended Dose/Frequency</th><th>Low muscle mass or CICU*</th><th>ECMO</th><th>CrCl 30-50</th><th>CrCl 10-29</th><th>CrCl < 10</th></tr>
<tr><td rowspan="2">3 month – 12 years old</td><td>15 mg/kg/dose q6H</td><td>15 mg/kg/dose q8H</td><td>15 mg/kg/dose q12H</td><td rowspan="3">15 mg/kg q12H</td><td rowspan="3">15 mg/kg q24H</td><td rowspan="3">15 mg/kg ONCE then frequency based on TDM order “Vancomycin Placeholder”</td></tr>
<tr><td colspan="3">Max 1000 mg/dose (4000 mg/day)</td></tr>
<tr><td rowspan="2">13-18 years old</td><td>15 mg/kg/dose q8h</td><td>15 mg/kg/dose q12H</td><td>15 mg/kg/dose q18H</td></tr>
<tr><td colspan="6">Max 1250 mg/dose (4000 mg/day)</td></tr>
</table>

Use actual body weight
*e.g. muscular dystrophy, cerebral palsy, spinal muscular atrophy, spastic quadriplegia
Suspected renal insufficiency may require more conservative dosing

Obesity Dosing

- Loading dose: 20 mg/kg ONCE based on total (actual) body weight (max load 2000 mg/dose)
- Scheduled dosing: Use adjusted body weight for scheduled dosing (see dosing chart above)

Dialysis Dosing

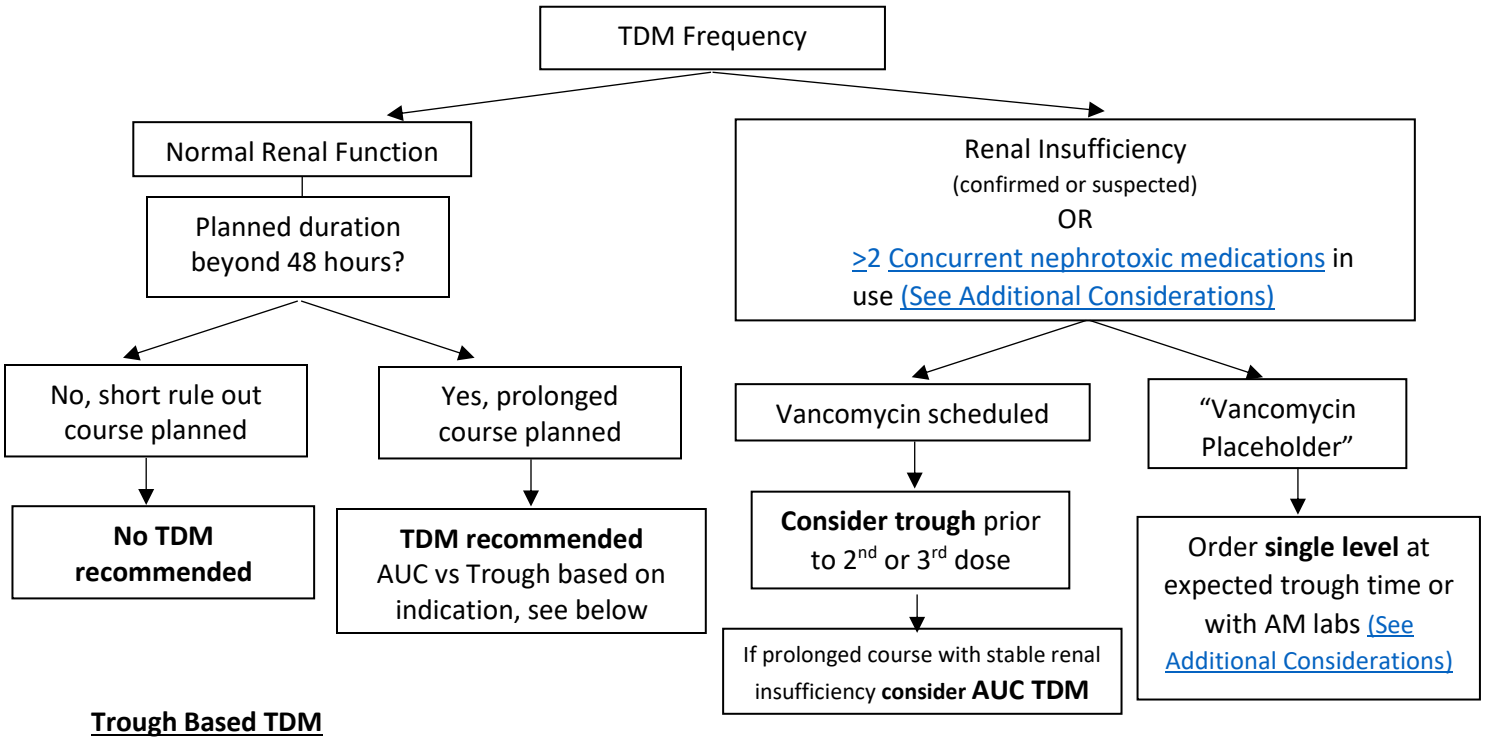
For all modes of dialysis (peritoneal dialysis, hemodialysis, and CRRT: CVVH, CVVHD, CVVHDF)

- 15 mg/kg (max 1250 mg/dose) ONCE and “Vancomycin Placeholder”
- Order level to determine frequency
- Dose/frequency based on TDM as renal function or dialysis stabilize

Continuous Infusion Dosing

- Patients are started on scheduled intermittent vancomycin (see empiric dosing above)
- When converting patients from intermittent to continuous vancomycin therapy;
    - Subtherapeutic trough levels: start dose approximately 75-85 percent of the total daily dose received of intermittent dosing
    - Therapeutic trough levels (i.e. transitioning to continuous for home infusion): start dose approximately 60-75 percent of total daily dose received of intermittent dosing

Section 2: Therapeutic Drug Monitoring (TDM)



Trough Based TDM

- Recommended for NICU, Intermittent Dosing, and patients with:
  - Empiric therapy of unidentified organisms (including bacteremia, sepsis, and meningitis/CNS coverage)
  - Non-MRSA or low suspicion for MRSA (including CONS) infection that requires vancomycin based on susceptibilities
- Order **trough** (single level 30-60 min prior to 4th or 5th dose)
- Target Trough: 7-12 mcg/mL

Predicted Trough	Recommended Dose Adjustment	Ongoing Monitoring	Max dose and next step considerations
> 21 mcg/mL	Hold subsequent doses and enter placeholder order	Repeat level based on renal function	Enter placeholder until level is < 21 mcg/mL
17 - 20 mcg/mL	Decrease INTERVAL by one frequency step (i.e. decrease 15 mg/kg/dose q8h to 15 mg/kg/dose q12h)	Prior to the 4th dose of the new regimen (sooner if renal in insufficiency)	
13 – 16 mcg/mL	Decrease DOSE by 2.5 mg/kg/dose (i.e. decrease 15 mg/kg/dose q8h to 12.5 mg/kg/dose q8h)		
7 – 12 mcg/mL	No Change	Repeat in 3 – 5 days (sooner if renal insufficiency)	For therapy duration > 1 week, once stable, check weekly
3 – 6 mcg/mL	Increase DOSE by 2.5 mg/kg/dose (i.e. increase 15 mg/kg/dose q8h to 17.5 mg/kg/dose q8h)	Prior to the 4th dose of the new regimen (sooner if renal in insufficiency)	If dose is 20 mg/kg check peak level to calculate AUC, if still subtherapeutic convert to continuous infusion (see below)
< 3 mcg/mL	Increase INTERVAL by one frequency step If already at q6h, transition to continuous infusion vancomycin (see below)		

*this chart is based on expert opinion and should be considered as guidance for making pharmacokinetic changes

**For troughs drawn incorrectly (earlier/later than ordered, concurrently with drug infusing, etc) See Additional Considerations

AUC Based TDM

- Recommended for patients with:
    - Suspected or documented MRSA infections
        - Examples include pneumonia, myositis, endocarditis, meningitis, osteomyelitis, bacteremia, and necrotizing fasciitis
        - MIC > 1, vancomycin is not considered optimal treatment and should consider ID consult for an alternative agent
        - AUC based data should generally not be used for non-MRSA infections (ie CONS)
        - AUC monitoring may be unachievable while renal function or V_d is *acutely* changing, however should be recommended when stable (even if insufficient) for prolonged courses
- Order **2 levels**
    1. Peak (60-90 minutes after completion of infusion)
    2. Trough (30-60 min) prior to 4th or 5th dose
- Target: AUC/MIC ratio of 400 – 600 mg*hr/L
  There is limited data in children to support AUC/MIC targets >400 are associated with better outcomes. Utilizing a goal AUC of 400 may be more achievable than trough goals and decrease risk of nephrotoxicity[1]
- Recommend re-checking trough weekly if renal function and V_d is determined to be stable
- If renal function or V_d changes from initial AUC calculation- consider re-calculating AUC or transition to trough-based monitoring if renal function is significantly worse
- Input 2 levels into EPIC Vancomycin Pharmacokinetics form to calculate AUC and provide dosing recommendation

Continuous Infusion TDM

- After initiation of continuous infusion draw **single level** 20-24 hours after start of infusion
- Note: utilize lumen that vancomycin is NOT infusing through; if single lumen, ensure catheter is flushed with normal saline prior to measurement

Actual Serum Concentration	Recommended Dose Adjustment	Ongoing Monitoring
> 31 mcg/mL	Hold dose, recheck level in 6-8 hours, once level is 26-30 restart at 30 – 40% reduction of total daily dose	Order level 20-24 hours after the new regimen has started
26-30 mcg/mL	Hold dose, recheck level in 4-6 hours, once level is 16-25 restart at 10 – 20% reduction of total daily dose	
16-25 mcg/mL	No Change	Repeat in 3 – 5 days (sooner if renal insufficiency)
10-15 mcg/mL	Increase total daily dose by up to 10%	Order level 20-24 hours after the new regimen has started
< 10 mcg/mL	Increase total daily dose by up to 20%	

Renal Monitoring

- Urine output should be monitored daily
- Order SCr every 3 days if planned duration > 48h

Additional Considerations

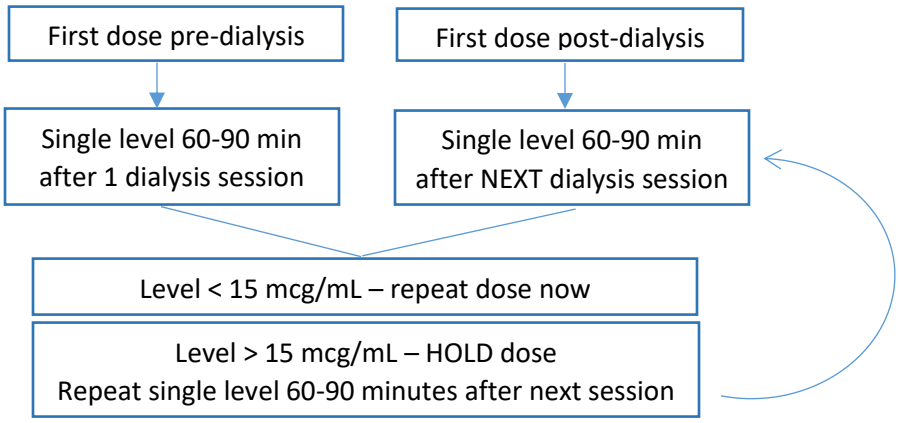
Obesity Bolus Considerations:

- Loading dose "boluses" are preferred in obese patients
- Obese patients with serious infections
    - Boluses are strongly recommended
    - If bolus not given as first dose, consider a bolus dose for the second dose on the floor

Dialysis Considerations

Vancomycin removal by dialysis varies by dialyzer permeability, duration of dialysis sessions, and frequency of sessions. Changes in dialysis mode, duration, and frequency will ultimately affect vancomycin clearance.

- Hemodialysis: There is approximately 30-50% extraction rate of vancomycin



    - If patient has confirmed infection requiring extended duration of therapy: order pre- and post-dialysis (60-90 minutes after end of session) levels to calculate clearance in order to provide optimized dose/frequency

- Peritoneal dialysis: Vancomycin is not removed to a significant extent during PD
    - Consider intraperitoneal vancomycin administration for peritonitis
    - Consider alternative agent cleared by PD if systemic therapy is necessary (consult ID)
    - Order first level 48 hours after first vanco dose and vancomycin is confirmed to continue
    - Most patients do not require re-dose of vancomycin until 48-120 hours after initial dose
- Continuous Renal Replacement Therapy (CVVH, CVVHD, CVVHDF):
    - Order first level 12-18 hours after first vanco dose or changes to CRRT flow, fluid removal, or dialyzer type occur
    - In one small study of pediatric patients receiving CVVHD and CVVHDF, doses required to reach therapeutic goals were typically achieved with q12H frequency

Nephrotoxic medications

- Refer to APPENDIX A for a list of nephrotoxic medications
    - Risk increases as number of concurrent nephrotoxic medications increases
    - Consider checking "safety level" (according to TDM flowsheet) for:
        - ≥2 nephrotoxic medications (if at least 1 is **BOLD** on chart) OR
        - ≥3 nephrotoxic medications

Levels Drawn Incorrectly

- Level drawn early
    - Trough- If drawn early, likely falsely elevated, can consider linear calculations to estimate trough during correct timing
    - Peak
        - If drawn < 30 min after completion of infusion (i.e. immediately after infusion)- likely falsely elevated due to time needed for appropriate distribution
        - If drawn > 60 minutes after completion of infusion- ok to use in 2-point kinetics (AUC calculator) as long as second level was appropriately drawn
- Level drawn during infusion: likely falsely elevated
    - Confirm timing of lab collection with RN who performed documentation if able
    - Determine timeline of obtaining repeat level based on patient renal function and clinical indication

ECMO max dose considerations

- Use of vancomycin while on ECMO results in increased volume of distribution as well as opportunity for drug sequestration, therefore larger doses may be appropriate to accomplish TDM goals (may be acceptable to escalate to 22.5 mg/kg/dose based on previous subtherapeutic levels)
- Patients on ECMO often have increased risk factors for renal dysfunction, therefore less frequent doses are empirically recommended. Risk factors include:
    - Concurrent nephrotoxic medications (inotropes/vasopressors and loop diuretics)
    - Decreased renal perfusion (post-op cardiac surgery, post-cardiac code event, or baseline cardiac dysfunction)

Stewardship considerations

- Evaluate if vancomycin can be de-escalated based on culture susceptibility data
- Consider de-escalation to a less nephrotoxic and more effective antibiotic (e.g., beta lactam) if the organism is methicillin-susceptible *Staphylococcus aureus*

APPENDIX A- Nephrotoxic medications

*__BOLDED__ medications have specific increased risk when used concurrently with vancomycin

Drug Class	Nephrotoxic Medications	
ACEIs/ARBs	captopril enalapril lisinopril	losartan valsartan
Antivirals/Antiretrovirals	**acyclovir** cidofovir foscarnet ganciclovir	tenofovir valacyclovir valganciclovir
Aminoglycosides	amikacin gentamicin tobramycin	
Antibiotics	ceftriaxone (increased with concurrent calcium) [4] colistimethate mitomycin	nafcillin **Piperacillin-tazobactam** polymixin B (systemic)
Antifungals	**Amphotericin liposomal** **Amphotericin B (traditional)**	
Antiseizure/neurologic	lithium topiramate	zonisamide
Bisphosphonate	pamidronate zoledronic acid	
Chemotherapy	cisplatin cyclophosphamide cytarabine ifosfamide	methotrexate mitomycin vincristine
Contrast dye	diatrizoate meglumine diatrizoate sodium iodixanol iohexol iopamidol	ilpromide ioversol ioxaglate meglumine-ioxaglate sodium
Diuretics	**Loop diuretics**	
Inotropes/Vasopressors	**++none specified (all considered)**	
Iron Chelator	deferasirox	
Immunosuppressants	**cyclosporine** methotrexate mycophenolate mofetil	sirolimus tacrolimus
Antiinflammatory (NSAID/COX-inhibitors/ salicylate)	aspirin celecoxib **ibuprofen** **indomethacin**	**ketorolac** mesalamine naproxen sulfasalazine

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Original: 01/2024
Last revised: 10/2024
Process owner: Pharmacy and Antimicrobial Stewardship Program