Intravenous Vancomycin Use – Adult – Inpatient/Ambulatory Clinical Practice Guideline

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Introduction

Vancomycin has been in clinical use for over 50 years to treat Gram-positive bacterial infections. It was initially used as a penicillin alternative to treat penicillinase-producing strains of *Staphylococcus aureus*, and is now commonly employed against other Gram-positive infections such as those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) species and drug-resistant *Streptococcus* and *Enterococcus* species.[1] Optimal use of vancomycin is of great importance among hospitalized patients due to the high morbidity and mortality associated with infections caused by these organisms.[2] The dosing and monitoring of vancomycin need to be optimized to maximize efficacy and minimize toxicity.[1] Evaluation of the clinical necessity for vancomycin use is paramount as inappropriate utilization of vancomycin has the potential to promote the development of resistance to vancomycin.[2] Despite the recent development of antibiotics for Gram-positive infections, vancomycin remains the primary agent in the treatment of drug-resistant Gram-positive infections.

Scope

Intended Users: Physicians, Advanced Practice Providers, Pharmacists, and Nurses.

Objective:

The objective of this guideline is to improve the use of vancomycin by optimizing the evaluation of the clinical necessity for vancomycin therapy, dosing of vancomycin dosing based on pharmacodynamic and pharmacokinetic principles and parameters, and the monitoring of vancomycin, including therapeutic drug monitoring.

Target Population:

All adult patients requiring antimicrobial therapy with intravenous vancomycin with the following exclusions:

a. Patients under the age of 18 years are excluded from this guideline. These patients may receive care in accordance with these guidelines at the discretion of the pediatric primary team.
b. Intravenous vancomycin use for surgical prophylaxis is excluded from this guideline and can be found in the Surgical and Interventional Radiology Antimicrobial Prophylaxis – Adult and Pediatric – Inpatient – Clinical Practice Guideline.
c. Oral vancomycin use for the Treatment of *Clostridium difficile* infection is excluded from this guideline and may be found in the Prevention, Diagnosis, and Treatment of *Clostridium difficile* Infection – Adult/Pediatric – Inpatient/Ambulatory.

Definitions and Abbreviations

1. **Total body weight (TBW)** is defined as the actual total mass of the patient in kilograms.
2. **Body mass index (BMI)** is defined by the following equation[3]:
   a. $BMI = {TBW\ (kg)}/{[height(m)]^2}$
3. **Ideal body weight (IBW)** is defined by the following equations[4]:
   a. $Male\ IBW = 50\ kg + 2.3\ kg\ for\ each\ inch\ over\ 5\ ft.in\ height$
   b. $Female\ IBW = 45.5\ kg + 2.3\ kg\ for\ each\ inch\ over\ 5\ ft.in\ height$
4. **Adjusted body weight (AdjBW)** is defined by the following equation[5]:
   a. $AdjBW = IBW + [0.4 \times (TBW - IBW)]$
5. **Lean body weight (LBW)** is defined by the following equations[5]:
   a. $Male\ LBW = {(9270 \times TBW)}/{[6680 + (216 \times BMI)]}$
   b. $Female\ LBW = {(9270 \times TBW)}/{[8780 + (244 \times BMI)]}$
6. **Class I obesity** is defined as a BMI (kg/m^2) in the range of 30.00-34.99.[6]
7. **Class II obesity** is defined as a BMI (kg/m^2) in the range of 35.00-39.99.[6]
8. **Class III obesity** is defined as a BMI (kg/m^2) greater than or equal to 40.[6]
9. **ABW**: Actual Body Weight
10. **AUC**: Area under the curve

11. **HCAP**: Healthcare-associated pneumonia
12. **CAP**: Community-acquired pneumonia
13. **ABSSSI**: Acute bacterial skin and skin structure infection
14. **MIC**: Minimum inhibitory concentration
15. **HD**: Hemodialysis
16. **CRRT**: Continuous renal replacement therapy
17. **CVVHD**: Continuous veno-venous hemodialysis
18. **Dry weight**[7]: The weight of a patient when he/she clinically euvolemic
19. **SCr**: Serum creatinine
20. **Empiric therapy**[8]: Selection of antimicrobials based on clinical presentation prior to culture results
21. **Definitive therapy**[8]: Deescalation of antimicrobial selection to narrower spectrum based on specific pathogen-directed treatment with culture results or with no culture results after 72 hours
22. **Sepsis**[9-11]: suspected source of clinical infection and two or more systemic inflammatory response syndrome (SIRS) criteria

SIRS Criteria
Core temperature <36°C (98.8°F) or >38°C (100.4°F)
Heart rate >90 bpm
Respiratory rate >20 breaths/min or $paCO_2$ <32 mmHg or the requirement of invasive mechanical ventilation for an acute process
White blood cell count (WBC) >12 x 10^9 mm^3 or <4 x 10^9 mm^3 or >10% immature band forms

23. **Severe Sepsis**[9-12]**:** suspected source of clinical infection, two or more systemic inflammatory response syndrome (SIRS) criteria and the presence of sepsis-induced organ dysfunction not attributed to a baseline medical condition or medication (e.g. chronic kidney disease or warfarin use).

SIRS Criteria	Sepsis-induced organ dysfunction
Core temperature < 36°C (98.8°F) or > 38°C (100.4°F)	SBP <90 mm Hg
	MAP <65 mm Hg
Heart rate > 90 bpm	Creatinine >2.0 mg/dL or increase of >0.5 mg/dL from previous value
	Urine output <0.5 mL/kg/hr for >2 hours
Respiratory rate > 20 breaths/min or paCo2 < 32 mmHg or the requirement of invasive mechanical ventilation for an acute process	Bilirubin >2.0 mg/dL
	Platelets <100,000/µL
	INR >1.5 or PTT >60 secs
	Lactate above upper limits laboratory normal (e.g., >2.0 mmol/L)
WBC >12 x 10^9 mm^3or <4 x 10^9 mm^3 or >10% immature band forms	Acute respiratory failure with invasive or non-invasive ventilation

24. **Septic Shock**[13]**:** Patients meeting criteria for severe sepsis with sepsis-induced hypoperfusion, using markers of either systolic blood pressure (SBP) <90 mmHg or mean arterial pressure (MAP) <65 mmHg persisting despite adequate fluid resuscitation OR lactate $\geq$4 mmol/L (regardless of timing of fluid administration).

Key Practice Recommendations

Vancomycin is used for empiric and definitive therapy of suspected and documented Gram-positive infections such as those involving methicillin-resistant *Staphylococcus aureus* (MRSA) and beta-lactam-resistant *Streptococcus* and *Enterococcus* species. Optimal use of vancomycin is of great importance among hospitalized patients due to the high morbidity and mortality associated with infections caused by these organisms. Optimization of vancomycin dosing and monitoring is paramount to maximize efficacy

and minimize toxicity. Evaluating the clinical necessity for vancomycin use is equally as important in order to curtail inappropriate utilization which is associated with increased adverse effects, the development of vancomycin-resistant bacteria, and increased costs and use of healthcare resources.[1,2]

1. Clinical investigation to evaluate the necessity for vancomycin use in acute bacterial skin and skin structure infections, diabetic foot infections, intraabdominal infections, and pneumonia should be pursued in accordance with the tools and recommendations in *Section 1*.[14-17]
2. The dosing of vancomycin for included patient populations should be based upon recommendations outlined in Table 1. In general, weight-based loading doses are utilized followed by maintenance dosing based on weight, renal function, and indication.
3. Monitoring of vancomycin therapy should include:[1]
   - Continual assessment of the need for vancomycin and the ability to discontinue therapy based on the results of diagnostic testing and clinical assessment of the patient
   - Therapeutic drug monitoring in certain scenarios as described in *Section 3.3*.
   - Monitoring renal function and performing dose adjustments for renal dysfunction
   - Minimizing the use of concomitant nephrotoxins as feasible
   - Assessing for other rare adverse effects such as serious systemic and dermatological reactions, ototoxicity, and hematological toxicity
4. When therapeutic drug monitoring is indicated it may occur via two different strategies: trough-based monitoring and AUC_{24}/MIC-based monitoring.[1,18-31]
   a. Refer to *Section 4.0* for guidance on which method is most appropriate.
   b. Pharmacodynamic targets are based on indication and outlined in Table 2.
   c. When not at target concentrations, vancomycin doses and/or dosing interval should be adjusted in a proportional fashion due to the linear pharmacokinetics of vancomycin.
5. Vancomycin may be administered to patients receiving renal replacement therapy. Dosing and therapeutic drug monitoring require special considerations in this population as outlined in *Section 5* for both intermittent hemodialysis and continuous renal replacement therapy.
6. Vancomycin administration can beneficial via continuous infusion in documented or highly suspected Gram-positive organism ventriculoperitoneal shunt or meningeal infections**.** Dosing for this is outlined in Table 3, and dose adjustments based on drug concentrations are outlined in Table 4.

Recommendations

1. **Evaluation of the clinical necessity for vancomycin use in acute bacterial skin and skin structure infections, diabetic foot infections, intraabdominal infections, and pneumonia.**
   1.1. Vancomycin is appropriate for the empiric coverage of infections suspected to be caused by most beta-lactam-resistant Gram-positive bacteria. Appropriate definitive vancomycin therapy depends upon identification of the infecting organism(s). *(UW Health Strong Recommendation, High Quality of Evidence)*
   1.2. Patients being treated for potential MRSA infection should have diagnostic testing performed to screen for the presence of MRSA. (*UW Health Strong Recommendation, Low Quality of Evidence*)
      1.2.1. Culture results from the suspected site(s) of infection should be used to determine the need for definitive vancomycin therapy. *(UW Health Strong Recommendation, Low Quality of Evidence)*
      1.2.2. For skin and soft tissue infections, MRSA polymerase chain reaction (PCR) swabs can be beneficial when performed on the nares and pooled groin and axilla. *(UW Health Strong Recommendation, Low Quality of Evidence)* If both are negative, there is a greater than 90% negative predictive value for MRSA infection and vancomycin discontinuation is reasonable.[14,15] (*UW Health Strong Recommendation, Low Quality of Evidence*).
      1.2.3. For pneumonia, a bronchoalveolar lavage, sputum culture, or MRSA PCR swab of the nares and throat can be beneficial to screen for the presence of MRSA.[16] (*UW Health Strong Recommendation, Very Low Quality of Evidence*).
         1.2.3.1. It is reasonable to discontinue empiric vancomycin in patients without adequate respiratory cultures who are receiving vancomycin for suspected MRSA pneumonia but have both nose and throat surveillance cultures negative for

MRSA. (*UW Health Strong Recommendation, Low Quality of Evidence*)

1.2.3.2. The combination of a nasal plus a throat culture negative for MRSA has a negative predictive value of 92 to 100% for MRSA colonization.[16,32]

1.2.4. For diabetic foot infections, a tissue culture or MRSA PCR swabs performed on the nares and pooled groin and axilla can be beneficial. The presence of a negative nares swab has a negative predictive value of 80% for MRSA colonization.[17] *(UW Health Strong Recommendation, Low Quality of Evidence).* The presence of a negative nares and pooled groin and axilla swab likely has a negative predictive value of greater than 80% for MRSA colonization. *(UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence)*

1.3. Patients being treated for potential drug-resistant *Enterococcus* species should have diagnostic testing performed to screen for the presence of drug-resistant *Enterococcus* species. *(UW Health Strong Recommendation, Low Quality of Evidence).*

1.3.1. Culture results from suspected site(s) of infection should be used to determine the need for definitive vancomycin therapy. *(UW Health Strong Recommendation, Low Quality of Evidence)*

1.3.2. In the absence of a positive culture, the benefits of ongoing empiric vancomycin coverage must be carefully weighed against the risks. *(UW Health Strong Recommendation, Low Quality of Evidence)*

1.4. Once an organism has been isolated that is not resistant to beta-lactams, de-escalation away from vancomycin and towards a beta-lactam is preferred. *(UW Health Strong Recommendation, Low Quality of Evidence)*

2. **Empiric Intermittent Vancomycin Dosing**

2.1. Intermittent dosing of vancomycin is reasonable for all indications. (*UW Health Strong Recommendation, Moderate Quality of Evidence*)

2.1.1. It may be reasonable to use continuous infusion vancomycin for confirmed bacterial meningitis (See *Section 6: Continuous Vancomycin Infusion* for additional information).[1] (*UW Health Weak/Conditional Recommendation, Low Quality of Evidence*)

2.1.2. It is reasonable to dose vancomycin based on total body weight, rounded to the nearest 250 mg increment for ease of preparation. (*UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence*)

2.1.3. It may be reasonable to cap vancomycin doses at 2000 mg per dose.[33,34] (*UW Health Strong Recommendation, Low Quality of Evidence*)

2.1.4. It is reasonable to limit total daily dose of vancomycin to 6000 mg in 24 hours (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

2.2. It may be reasonable for most patients to receive an initial dose of 25 mg/kg of total body weight, dose capped at 2000 mg to ensure adequate concentrations are reached sooner as early target attainment of the area-under-the-curve to minimum inhibitory concentration (AUC_{24}:MIC) ratio is important for clinical outcomes.[1,29,33] (*UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence*)

2.2.1. Peak vancomycin concentrations alone have never been shown to have a relationship with either efficacy or toxicity.[35]

2.2.2. A randomized trial comparing initial vancomycin loading doses versus no loading dose demonstrated that patients who received loading doses are more likely to have a trough greater than 15 mcg/mL at a time of 12 hours post-dose. There was no difference in nephrotoxicity.[36]

2.2.3. Patients with a *Staphylococcus aureus* infection exposed to vancomycin concentrations below 10 mcg/mL may be at risk for therapeutic failure and the potential for the emergency of vancomycin-intermediate or vancomycin-resistant *Staphylococcus aureus.* Therefore it may be reasonable to use vancomycin dosing strategies such as the use of a loading dose to minimize the time that *Staphylococcus aureus* is exposed to vancomycin concentrations below 10 mcg/mL.[1,37,38] (*UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence*)

2.2.4. In patients who are not critically ill and who are receiving vancomycin despite low likelihood of a drug-resistant Gram-positive infection, it may be reasonable to withhold

(i.e. not give) a loading dose and begin therapy with maintenance dosing (See Table 1). It is expected that the pharmacist make a reasonable effort to discourage vancomycin use when the risk of vancomycin use may outweigh the benefits.[1] (*UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence*)

2.3. Maintenance dosing of vancomycin should be based on weight, renal function, and desired drug concentrations. (*UW Health Strong Recommendation, Moderate Quality of Evidence*)

2.3.1. It is reasonable to estimate creatinine clearance in accordance with the UWHC Renal Function-Based Dose Adjustments Adult Inpatient Clinical Practice Guideline. (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

2.3.1.1. The Cockroft-Gault equation is preferred to calculate creatinine clearance in patients with a BMI between 18.5 and 30 kg/m^2.[39]

$$\left[\frac{(140 - age) \times ABW\ (kg)}{SCr\ \left(\frac{mg}{dL}\right) \times 72}\right] \times (0.85\ for\ females)$$

2.3.1.2. Obese patients (BMI equal to or 30 kg/m^2) have variable amounts of body fat versus muscle mass making creatinine clearance estimation even more challenging in this population. No one equation consistently demonstrates maximal precision or minimal bias.[40-43] Either the Salazar-Corcoran equation or using an adjusted body weight in the Cockcroft-Gault equation will overestimate creatinine clearance, whereas using ideal body weight will underestimate clearance. The Salazar-Corcoran equation is more complex and estimates fat free mass. If a precise estimate of creatinine clearance is required to improve efficacy or prevent toxicity, then a measured creatinine clearance is recommended. The equations are:

Salazar-Corcoran equation for men[44]	$\left[\frac{(137 - age) \times \left[(0.285 \text{ x TBW (kg)}) + (12.1 \times \text{Ht(m)}^2)\right]}{SCr\ \left(\frac{mg}{dL}\right) \times 51}\right]$
Salazar-Corcoran equation for men[44]	$\left[\frac{(146 - age) \times \left[(0.287 \text{ x TBW (kg)}) + (9.74 \times \text{Ht(m)}^2)\right]}{SCr\ \left(\frac{mg}{dL}\right) \times 60}\right]$
Cockroft-Gault with adjusted body weight equation[41]	$\left[\frac{(140 - age) \times AdjBW\ (kg)}{SCr\ \left(\frac{mg}{dL}\right) \times 72}\right] \times (0.85\ for\ females)$

2.3.2. Table 1 describes empiric intermittent vancomycin maintenance dosing for patients with stable renal function in the absence of any information on steady state trough concentrations from an ongoing course of therapy.[27,45]

2.3.2.1. Empiric maintenance dose/frequency adjustments are also reasonable if renal function changes until a new steady state vancomycin trough is reached.[23,46,47] *(UW Health Strong Recommendation, Very Low Quality of Evidence)*

2.3.2.2. It is reasonable for pharmacists to use clinical judgement to deviate from empiric dosing in Table 1.[23,24] (*UW Health Strong Recommendation, Low Quality of Evidence*)

2.3.2.3. Renal transplant recipients who are receiving concomitant nephrotoxins such as calcineurin inhibitors may be candidates for more conservative dosing. *(UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence)*

2.3.3. Adult cystic fibrosis patients exhibit vancomycin pharmacokinetics similar to that of healthy adults.[48]

2.3.3.1. Empiric dosing regimens (i.e. Table 1) is reasonable for the use of vancomycin in cystic fibrosis patients.[48] (*UW Health Strong Recommendation, Low Quality of Evidence*)

2.3.3.2. If available, historical drug monitoring data is probably recommended to guide

empirical dosing in cystic fibrosis patients.[49]

2.3.4. In patients with burn injuries, vancomycin pharmacokinetics is significantly altered and these patients may require higher total daily doses and increased frequency of administrations to achieve targeted vancomycin concentrations. However, due to insufficient clinical evidence, no standardized recommendations can be made on empiric dosing changes in this patient population.[50] (*UW Health Weak/Conditional Recommendation, Low Quality of Evidence*)

2.4. For patients transitioning from inpatient to ambulatory who will be receiving vancomycin in the ambulatory setting, it is reasonable to continue vancomycin dosing regimen the patient was receiving during hospital admission. For patients newly starting vancomycin in the ambulatory setting, it is reasonable to initiate therapy using "Non-sepsis Indication" dosing recommendations in Table 1. (*UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence*)

2.4.1. For patients requiring transition to a once-daily vancomycin regimen to facilitate discharge from the hospital to an ambulatory setting (including home with home infusion), the interdisciplinary care team (provider, pharmacists, case management, and/or social worker) should develop a vancomycin plan that meets the therapeutic needs and facilitates discharge as possible. (*UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence*)

Table 1. Empiric Intermittent Vancomycin Dosing Nomogram

Estimated Creatinine Clearance[A]	Loading Dose[B,C]	Maintenance Dose[C]	
		Severe Sepsis and Septic Shock	Non-sepsis Indication
>100 mL/min	25 mg/kg (maximum 2000 mg)	10-15 mg/kg Q8H	15 mg/kg Q12H or 10 mg/kg Q8H[D]
80- 99 mL/min		15 mg/kg Q12H	15 mg/kg Q12H
60 -79 mL/min		15 mg/kg Q12H	10 mg/kg Q12H
50-59 mL/min		10 mg/kg Q12H	15 mg/kg Q24H
40-49 mL/min		15 mg/kg Q24H	15 mg/kg Q24H
30-39 mL/min		15 mg/kg Q24H	10 mg/kg Q24H
20-29 mL/min		15 mg/kg Q48H, or monitor drug concentrations and re-dose when at target trough	15 mg/kg Q48H
<20 mL/min, not receiving HD		Monitor drug concentrations and re-dose when at target trough	
HD	20-25 mg/kg (maximum 2000 mg)	See *Section 5*	

[A] This nomogram has not been validated for use in patients with rapidly changing renal function.

[B] Information on the decision of whether or not to use a loading dose is contained in *Section 2.2*. In patients who are not critically ill and who are receiving vancomycin despite low likelihood of a drug-resistant Gram-positive infection, it may be reasonable to withhold (i.e. not give) a loading dose and begin therapy with maintenance dosing. It is expected that the pharmacist make a reasonable effort to discourage vancomycin use when the risk of vancomycin use may outweigh the benefits.

[C] All loading doses and maintenance doses for intermittent vancomycin is based on actual body weight and capped at a maximum of 2000 mg per infusion.

[D] Clinicians must use clinical judgement to select vancomycin doses in this situation. Initial dosing of 10 mg/kg every 8 hours should only be used in patients who are younger than 40 years of age, or who are critically ill, or who have severe infections (e.g. ophthalmologic emergencies, periorbital cellulitis, Fournier's gangrene, etc.). Renal transplant recipients who are receiving concomitant nephrotoxins such as calcineurin inhibitors may be candidates for more conservative dosing.

3. **Vancomycin Therapy Monitoring**
   3.1. Vancomycin therapeutic drug monitoring has been advocated to maintain drug concentrations within a narrow therapeutic index and to lessen the potential for drug-induced nephrotoxicity and ototoxicity. Although some debate still occurs about the conflicting evidence regarding the use of vancomycin concentrations to predict and prevent drug effectiveness or toxicity, vancomycin therapeutic drug monitoring has been widely adopted.[1]
   3.2. Assessing the potential for deescalation away from vancomycin when beta-lactam susceptible organisms are isolated should precede any consideration of vancomycin therapeutic drug monitoring. *(UW Health Strong Recommendation, Low Quality of Evidence)*
   3.3. Therapeutic drug monitoring of vancomycin is reasonable for patients in the following scenarios:[1] (*UW Health Strong Recommendation, Low Quality of Evidence*)
      - targeting vancomycin concentrations of 15 to 20 mcg/mL
      - obesity (BMI >30 kg/m^2)
      - high risk for nephrotoxicity (see *Section 3.3*)
      - changing urine output/ creatinine or dialysis patients
      - drug efficacy is questionable (patient not clinically improving)
      - non-compliance is suspected
      - concomitant disease states may be altering drug elimination
      - drug-drug interactions exist
      - therapy is expected to continue beyond 4 days
   3.4. Use of other potential nephrotoxins during vancomycin therapy should be avoided, as feasible, to prevent nephrotoxicity associated with vancomycin troughs greater than 15 mcg/mL and increased length of stay and poorer outcomes with vancomycin nephrotoxicity.[51] (*UW Health Strong Recommendation, Moderate Quality of Evidence*)
   3.5. Other risk factors for vancomycin-associated nephrotoxicity should be considered, including:[51-55]: (*UW Health Strong Recommendation, Low Quality of Evidence*)
      - targeting serum concentrations of 15 to 20 mcg/mL or greater[56]
      - vancomycin AUC_{24} > 700 mg*hr/L
      - vancomycin doses > 4000 mg/day
      - single vancomycin doses > 2000 mg
      - obesity (BMI >30 kg/m^2)
      - prolonged durations of vancomycin $\geq$ 2 weeks
      - history of acute kidney injury
      - preexisting renal insufficiency
      - critically ill status
      - sepsis
      - concurrent nephrotoxins
      - combination vancomycin and piperacillin/tazobactam therapy

      3.5.1. Combination therapy with vancomycin and piperacillin-tazobactam may increase the risk of acute kidney injury (AKI).[57,58] The risk for AKI is probably greatest after three days of combination therapy.[59]
         3.5.1.1. To reduce AKI risk with combination vancomycin and piperacillin-tazobactam, clinicians may select empiric antibiotics with lower AKI risk (e.g. cefepime) when clinically appropriate and/or may judiciously deescalate away from vancomycin, piperacillin-tazobactam, or both within 72 hours.[60] (*UW Health Strong Recommendation, Low Quality of Evidence*)

      3.5.2. Vancomycin treatment alone may be an independent risk factor for AKI based on results of a metaanalysis, demonstrating an AKI relative risk of 2.45 (95% confidence interval: 1.69-3.55). Notably, the studies included in the metaanalysis did not prespecify AKI as a primary outcome; therefore, a prospective, randomized clinical trial is needed to confirm findings of the metaanalysis.[61]

      3.5.3. Intermittent vancomycin therapy may be associated with higher risk of AKI compared to continuous vancomycin infusions.[62,63]

   3.6. Close monitoring and caution is recommended in cystic fibrosis patients receiving vancomycin who are at risk for nephrotoxicity, including patients with underlying kidney disease, patients with

a history of AKI, patients who previously received multiple courses of vancomycin, aminoglycosides and/or colistin, patients in whom vancomycin is used in conjunction with other nephrotoxic medications (e.g. aminoglycosides, colistin), and patients being treated for an extended duration (longer than 14 to 21 days).[49] (*UW Health Strong Recommendation, Low Quality of Evidence*)

3.7. Alternative treatment regimens and infectious disease advice should be considered and vancomycin toxicity risk should be weighed against the benefits of continued vancomycin therapy if a total daily dose of more than 4000 mg, but especially 6000 mg of vancomycin is required to achieve target trough concentrations. (*UW Health Strong Recommendation, Low Quality of Evidence*)

3.8. Vancomycin-induced histamine-release syndrome occurs in 3.7-47% of infected patients and is characterized by pruritus, an erythematous rash of the face, neck, and upper torso, dizziness, agitation, chills, fever, and paraesthesia around the mouth. Severe cases present with chest pain and dyspnea. Reactions can be immediate or delayed and may occur at any point during the treatment course with vancomycin. Vancomycin-induced histamine release syndrome is anaphylactoid, is a non-IgE- mediated reaction, and occurs due to mast call and basophil degranulation and histamine release.[64]

3.8.1. For the treatment of vancomycin-induced histamine release syndrome, it is reasonable to include: diphenhydramine 50 mg IV or PO (with or without H_2 receptor antagonist (e.g. ranitidine)) and the vancomycin infusion can reasonably be held.[64] (*UW Health Strong Recommendation, Very Low Quality of Evidence*).

3.8.1.1. True anaphylaxis, while very rare, is possible and must be ruled out. Hypotension requiring intravenous fluids and vasopressors is also rare.[64]

3.8.1.2. There is no established role for steroids in the treatment of vancomycin-induced histamine release syndrome.[64]

3.8.1.3. When the reaction dissipates, it is reasonable to resume vancomycin at a slower infusion rate.[64,65] (*UW Health Strong Recommendation, Very Low Quality of Evidence*).

3.8.1.3.1. Antihistamine pre-medication can be beneficial as a pretreatment to prevent future symptoms of vancomycin-induced histamine release syndrome.[66] *(UW Health Strong Recommendation, Low Quality of Evidence)*

3.8.1.3.2. Vancomycin-induced histamine release syndrome is not considered an allergy and should not preclude use of future vancomycin with premedication and slower infusion times.[64,65] *(UW Health Strong Recommendation, Very Low Quality of Evidence)*

3.8.2. Vancomycin should be administered at a rate less than or equal to the maximum infusion rate of 1000 mg per hour.[67] *(UW Health Strong Recommendation, High Quality of Evidence)*

3.9. Ototoxicity has occurred, rarely, in a few dozen case reports in patients receiving vancomycin.[67] It may be transient or permanent. It has been reported mostly in patients who have been given excessive doses, who have an underlying hearing loss, or who are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside. Vancomycin should be used with caution in patients with renal insufficiency because the risk of toxicity is appreciably increased by high, prolonged blood concentrations.[68] (*UW Health Strong Recommendation, High Quality of Evidence*)

3.10. Reversible neutropenia, usually starting 1 week or more after onset of therapy with vancomycin or after a total dosage of more than 25 grams, has been reported for several dozen patients. Neutropenia appears to be promptly reversible when vancomycin is discontinued. Thrombocytopenia has rarely been reported. Although a causal relationship has not been established, reversible agranulocytosis 3 (granulocytes < 500/mm^3).[67] *(UW Health Strong Recommendation, High Quality of Evidence)*

3.11. Infrequently, drug fever, eosinophilia, exfoliative dermatitis, linear IgA bullous dermatosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, vasculitis, and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in association with administration of vancomycin.[67] *(UW Health Strong Recommendation, High Quality of*

Evidence)

4. **Vancomycin Therapeutic Drug Concentration Monitoring**
   4.1. Vancomycin pharmacokinetic and pharmacodynamic activity is best described by the 24-hour area under the curve to minimum inhibitory concentration (AUC_{24}:MIC) ratio. Animal and human data indicate that the ratio of area under the curve AUC_{24}:MIC is predictive of clinical outcome when treating methicillin-resistant *Staphylococcus aureus* (MRSA).[46,65,69] The goal AUC_{24}:MIC ratio to optimize the chance of microbiological success in the treatment of *Staphylococcus aureus* is 400.[18,25,31,69] For serious infections, the optimal AUC_{24}:MIC goal may be 600. Although of poor quality, clinical evidence demonstrates that higher AUC_{24}:MIC targets (400 and greater) are associated with lower rates of treatment failure and lower mortality whereas trough targets of 15-20 mcg/mL do not demonstrate that same correlation.[70]
      4.1.1. The AUC_{24}:MIC goal to successfully treat non-*Staphylococcus aureus* infections with vancomycin is not known, but it is likely lower than 400.[71] (*UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence*)
      4.1.2. Although not well established, the optimal AUC_{24}:MIC ratio appears to 600 for serious MRSA infections.[19,21,31] (*UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence*)
      4.1.3. An AUC of 700 mg*hr/L represents the best conservative estimate of the upper threshold of safe vancomycin exposure with a minimal risk of nephrotoxicity. Above this threshold, the risk of vancomycin toxicity increases rapidly.[19]
   4.2. In patients who are not critically ill and without severe infection, a vancomycin trough concentration based approach is reasonable to use.[20] (*UW Health Strong Recommendation, Low Quality of Evidence*)
      4.2.1. Vancomycin trough concentration monitoring is subject to a high degree of inter-individual variability between the measured trough value and the actual AUC, and this therapeutic discordance may lead to suboptimal clinical outcomes such as treatment failure against less susceptible pathogens and nephrotoxicity with unnecessarily high doses. Trough monitoring alone is likely to underestimate the true AUC by up to 33%.[19]
      4.2.2. For severe infections such as meningitis, MRSA osteomyelitis, MRSA bacteremia, endocarditis, pneumonia due to MRSA, and septic shock the goal trough for intermittent dosing is 15-20 mcg/mL.
         4.2.2.1. Serum trough concentration targets must be integrated with the clinical response of the patient. If the target trough is 15-20 mcg/mL per Table 4 and the trough drawn is slightly below 15 mcg/mL and the patient is making an adequate clinical response, dose adjustment to achieve a higher trough may not be always necessary.[19,31] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)
      4.2.3. For other infections a reasonable goal vancomycin trough for intermittent dosing is 10-20 mcg/mL. To minimize toxicity, it is reasonable for vancomycin trough concentrations for intermittent dosing to not exceed 15 mcg/mL unless the target trough concentration is 15-20 mcg/mL.[72,73] (*UW Health Strong Recommendation, Low Quality of Evidence*)
         4.2.3.1. Review of existing clinical trial data demonstrates that there is no all-cause mortality difference between low (<15 mcg/mL) and high (>15 mcg/mL) vancomycin trough concentrations; notably, this result was not robust with the removal of one outlier study.[74] Additionally, a mortality difference was observed in the setting of MRSA pneumonia treatment with high vancomycin trough concentrations (>15 mcg/mL) and microbiological failure was more common with low vancomycin trough concentrations (<15 mcg/mL). A second meta-analysis found lower treatment failure in a bacteremia subgroup and high trough concentrations (>15 mcg/mL) but no difference among all infection types.[75]
      4.2.4. To avoid both vancomycin resistance development and treatment failure, troughs greater than 10 mcg/mL should be targeted.[76,77] (*UW Health Strong Recommendation, Low Quality of Evidence*)
      4.2.5. Vancomycin dosing to achieve troughs greater than 15 mcg/mL, although possibly

warranted to treat more serious infections, is associated with an increased risk of nephrotoxicity. Troughs greater than 20 mcg/mL have also been associated with nephrotoxicity.[1,25,56] (*UW Health Strong Recommendation, Moderate Quality of Evidence*)

4.2.5.1. As troughs are a surrogate marker for vancomycin efficacy, they are also a surrogate marker for vancomycin nephrotoxicity. The true marker for vancomycin nephrotoxicity risk is likely AUC greater than 700 mg·hr/L.[19,25]

Table 2. Vancomycin Target Pharmacodynamic Parameters

Treatment Population	Target Trough Concentrations	Target AUC_{24}:MIC
• Infection due to MRSA with a MIC = 1 mcg/mL • Hospital-acquired pneumonia (HAP) • Healthcare-associated pneumonia(HCAP) • Ventilator- associated pneumonia (VAP) • Meningitis treated with intermittent dosing • Endocarditis • MRSA osteomyelitis • Undifferentiated septic shock • Cystic fibrosis exacerbation	15-20 mcg/mL	400-700
Infections treated with continuous infusion vancomycin	20-28 mcg/mL	400-700
All other infections	10-15 mcg/mL	400-700

4.3. In critically ill patients with severe infections, an equation-based approach can be useful. For patients with definitive vancomycin therapy for at least 4 days with a target trough of 15-20 mcg/mL, it may be reasonable to consider AUC calculations.[20] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

4.3.1. AUC estimations are performed with two vancomycin concentrations. It is reasonable to draw the first concentration one to two hours after the end of the infusion and the second concentration near the end of the first dosing interval. AUC_{24}:MIC can be estimated in several different ways and may be calculated using equations in Appendix B.[23,28,65,69]. (*UW Health Strong Recommendation, Low Quality of Evidence*)

4.3.1.1. If the MIC is not known at the time of AUC_{24}:MIC calculation, it is reasonable to estimate the MIC based on current UWHC antibiogram surveillance data of *Staphylococcus aureus* vancomycin MIC distribution (See Appendix C). (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

4.3.1.2. If a patient has had previous MRSA isolates cultured with an MIC greater than 1 mcg/mL, it is reasonable to use the previous MIC in the AUC_{24}:MIC goal for empiric treatment. (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

4.4. In cystic fibrosis patients, target vancomycin concentrations of 15-20 mcg/mL are reasonable in order to target AUC_{24}:MIC of ≥400.[49] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

4.5. As pharmacokinetic parameters can fluctuate rapidly in a clinically unstable patient, clinicians should use clinical judgement to determine when vancomycin concentrations should be drawn.[1,20,69]

4.5.1. For calculation of an AUC_{24}:MIC, it is reasonable to draw vancomycin concentrations after any vancomycin dose. (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

4.5.2. For intermittent trough concentration monitoring, it is reasonable to consider drawing a vancomycin concentration prior to the fourth or fifth dose. For patients on infrequent dosing schedules (frequency of every 24 hours or longer) it may be reasonable to draw a

vancomycin concentration sooner than the fourth or fifth dose. (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

4.5.3. Patients with rapidly changing renal function in whom vancomycin kinetics are difficult to predict may be candidates for alternatives to vancomycin. (*UW Health Strong Recommendation, Low Quality of Evidence*)

4.6. In response to a supratherapeutic or subtherapeutic vancomycin trough concentration or AUC_{24}:MIC, it can be effective to adjust the total vancomycin daily dose in a proportional fashion due to the linear kinetics of vancomycin. Consideration may also be given to changing the dosing interval. (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

4.7. Therapeutic drug monitoring of vancomycin is probably indicated on a weekly basis in patients with stable hemodynamics and renal function. In unstable patients it is probably indicated to have drug concentrations checked more frequently. (*UW Health Strong Recommendation, Low Quality of Evidence*)

4.7.1. There is no evidence that obtaining daily vancomycin concentrations during therapy will be useful and this will likely result in unnecessarily increased cost.

4.8. In the ambulatory setting, vancomycin concentration monitoring and other laboratory monitoring is guided by the *UW Health Clinical Monitoring of OPAT and Selected Oral Antimicrobial Agents – Adult – Inpatient/Ambulatory Clinical Practice Guideline* or as otherwise directed by the prescribing provider.

5. **Vancomycin in renal replacement therapy**

5.1. **Inpatient intermittent hemodialysis (HD)**

5.1.1. It may be reasonable for inpatients on intermittent HD to receive a loading dose of 20 mg/kg (dose capped at 2000 mg) based on an estimated dry weight at the time of order initiation if it is anticipated for there to be 24 hours between the loading dose and the next HD session.[78-81] (*UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence*)

5.1.2. It may be reasonable to use a loading dose of 25 mg/kg (dose capped at 2000 mg) if it is anticipated for there to be 48 hours between the loading dose and next HD session.[78] (*UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence*)

5.1.3. Scheduled post-dialysis maintenance doses may be considered to prevent unintentional delays or omissions during vancomycin therapy.

5.1.4. Patients receiving dialysis are highly variable (ranging from chronic anuric HD patients to temporary intermittent HD patients to peritoneal dialysis) and these factors may be considered when evaluating vancomycin dosing. (*UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence*)

5.1.5. It may be reasonable to monitor vancomycin for HD patients to account for variables that can influence clearance, including residual renal function, complex elimination kinetics (intradialytic phase, post-rebound phase and interdialytic phase), dialyzer membrane type, dialyzer reprocessing and reuse, dialysis blood flow rate, dialysis solution flow rate and length of HD sessions.[82-84] (*UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence*)

5.1.6. For scheduled, chronic (three times weekly) HD patients, it may be reasonable to consider patient weight and residual renal function when empirically choosing a post-HD maintenance dose.[78] (*UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence*).

5.1.6.1. Maintenance doses for chronic HD patients typically range from 500 mg to 1000 mg.

5.1.6.2. A 500 mg initial maintenance dose may be considered for a small (50-70 kg), anuric adult patient.[81,85]

5.1.6.3. A 750 to 1000 mg maintenance dose may be considered for larger patients or patients with residual renal function.[82,86,87] (*UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence*)

5.1.7. After the initial loading dose is given, it may be reasonable to draw a post-HD vancomycin trough no sooner than two hours after the end of the next HD session, although it is preferable to draw three hours after the end of the session to allow maximal

redistribution and plasma rebound.[83] (*UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence*)

5.1.8. Maintenance dose adjustment may be considered for any post-HD trough that is less than the limit of the therapeutic goal range as shown in Table 2.[81]

5.1.8.1. It may be reasonable to hold the post-HD dose if the trough is greater than the upper limit of the therapeutic.

5.1.8.1.1. If the dose is held, it is reasonable to reduce the next scheduled post-HD maintenance dose.[78,88] (*UW Health Weak/Conditional Recommendation, Low Quality of Evidence*)

5.1.8.2. A vancomycin dose may be reasonable even if the post-HD concentration is within the target range, since vancomycin clearance still occurs outside of the HD session both by renal mechanisms (residual renal function) and minor non-renal mechanisms.

5.2. **Continuous renal replacement therapy (CRRT)**

5.2.1. Patients receiving CRRT should be managed following the CRRT-based Dose Adjustment – Adult – Inpatient Clinical Practice Guideline.

6. **Continuous infusion vancomycin**

6.1. Vancomycin administration can beneficial via continuous infusion in documented or highly suspected Gram-positive organism ventriculoperitoneal shunt or meningeal infections**.** (*UW Health Strong Recommendation, Low Quality of Evidence*)

6.2. Continuous infusion vancomycin is generally not recommended for the treatment of other infections due to lack of evidence. However, in critically ill patients with severe infections, sepsis, and ventilator-associated pneumonia, the use of continuous infusion vancomycin has been found to achieve target trough and the target AUC_{24}:MIC ratios more frequently than patients receiving intermittent infusion vancomycin. Providers may consider continuous infusion vancomycin for non-central nervous system infections at their discretion.[89-91] (*UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence*).

6.2.1. Continuous infusion vancomycin is less nephrotoxic than intermittent infusion vancomycin.[92-94] (*UW Health Strong Recommendation, Moderate Quality of Evidence*)

6.3. Continuous infusion vancomycin is not intended for empiric therapy of community-acquired pneumococcal meningitis in the absence of a positive Gram stain, CSF antigen or culture. Distribution into the cerebral spinal fluid is poor unless the meninges are inflamed.[95] Penetration of vancomycin in the CNS is limited by its hydrophilicity, relatively large molecular weight, and in part because it crosses the blood-brain barrier by paracellular pathways. Peak concentrations of vancomycin in the CNS are delayed compared to vancomycin concentrations, and the elimination half-life of vancomycin in the CNS is longer than in the serum.[96]

6.4. A 25 mg/kg (maximum 2000 mg) loading dose with of vancomycin may be considered prior to the initiation of continuous infusion vancomycin.[97] (*UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence*)

6.5. Total body weight is reasonable to use for dose calculations for patients with a BMI below 30 kg/m^2. For patients with a BMI greater than or equal to 30 kg/m^2, it is reasonable to use adjusted body weight for dose calculations. (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

6.6. It may be reasonable to use Initial dosing be based on the nomogram in Table 3.[92,98] (*UW Health Weak/Conditional Recommendation, Low Quality of Evidence*

Table 3. Continuous Infusion Vancomycin Dosing

Estimated Creatinine Clearance	Loading Dose	Continuous infusion
>90 mL/min	25 mg/kg (maximum 2000 mg)	45 mg/kg/24 hours
75-89 mL/min	25 mg/kg (maximum 2000 mg)	35 mg/kg/24 hours
60-74 mL/min	25 mg/kg (maximum 2000 mg)	30 mg/kg/24 hours
45-59 mL/min	25 mg/kg (maximum 2000 mg)	25 mg/kg/24 hours
<45 mL/min	Intermittent traditional dosing is preferred	

6.7. The continuous infusion may be started as soon as the loading dose is complete.[92,98] (*UW Health Weak/Conditional Recommendation, Low Quality of Evidence*)
  6.7.1. The continuous infusion should be prepared in normal saline (0.9% sodium chloride).
    6.7.1.1. The calculated 24-hour dose should be added to a 500 mL or 1000 mL bag of normal saline and the infusion rate calculated from the total volume of antibiotic plus diluent divided by 24 hours.
  6.7.2. For peripheral administration it is reasonable for the final concentration of the product to be less than or equal to 5 mg/mL.[67] (*UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence*)

6.8. Vancomycin concentration monitoring is not recommended until at least 24 hours after the continuous infusion has begun or 24 hours after dose adjustments.[1,46,65] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)
  6.8.1. Reasonable target steady-state concentrations for continuous infusion vancomycin for meningitis are 20-28 mcg/mL (See Table 2).[92] (*UW Health Strong Recommendation, Low Quality of Evidence*)
  6.8.2. Dose adjustments should be made in 250 mg/day intervals.
  6.8.3. Once steady-state is attained, further vancomycin concentration monitoring likely is not indicated unless there are significant changes in renal function or body weight.
    6.8.3.1. In patients with normal renal function the vancomycin half-life ranges from 6 to 12 hours; as a result it can take up to 60 hours to reach steady state in patients with normal renal function and even longer in patients with renal compromise.[46]

6.9. If the vancomycin plateau concentration is above 30 mcg/mL, it is reasonable to pause the continuous infusion adjust as described in Table 4.[92,98] (*UW Health Weak/Conditional Recommendation, Low Quality of Evidence*)

Table 4. Adjustments for Continuous Vancomycin Infusions with Vancomycin Plateaus above 30 mcg/mL

Creatinine Clearance	Vancomycin plateau 30-32 mcg/mL	Vancomycin plateau 33-36 mcg/mL	Vancomycin plateau 37-40 mcg/mL
>90 mL/min	Hold infusion for 2 hours; decrease daily dose by 20%	Hold infusion for 3 hours; decrease daily dose by 25%	Hold infusion for 4 hours, decrease daily dose by 35%
75-89 mL/min	Hold infusion for 4 hours: decrease daily dose by 20%	Hold infusion for 5 hours; decrease daily dose by 25%	Hold infusion for 6 hours; decrease daily dose by 35%
60-74 mL/min	Hold infusion for 6 hours; decrease dose by 20%	Hold infusion for 8 hours; decrease daily dose by 25%	Hold infusion 10 hours; decrease daily dose by 35%
45-59 mL/min	Hold infusion for 8 hours; decrease dose by 20%	Hold infusion for 10 hours; decrease daily dose by 25%	Hold infusion for 12 hours; decrease dose by 35%

Disclaimer

Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

Methodology

Methods Used to Collect/Select the Evidence:

For the first version of the guideline and subsequent 2017 revision, a review of PubMed database and Google Scholar was conducted with combinations of the keywords: vancomycin and treatment, Gram positive infection, de-escalation, resistance, adverse effects, monitoring, therapeutic drug monitoring, dosing, pharmacokinetics, pharmacodynamics, administration, hemodialysis, continuous renal replacement therapy, or special populations. References from the articles were also searched. Finally, the personal libraries of the authors were queried. The 2017 revision evaluated new clinical evidence published between 2015 and 2017.

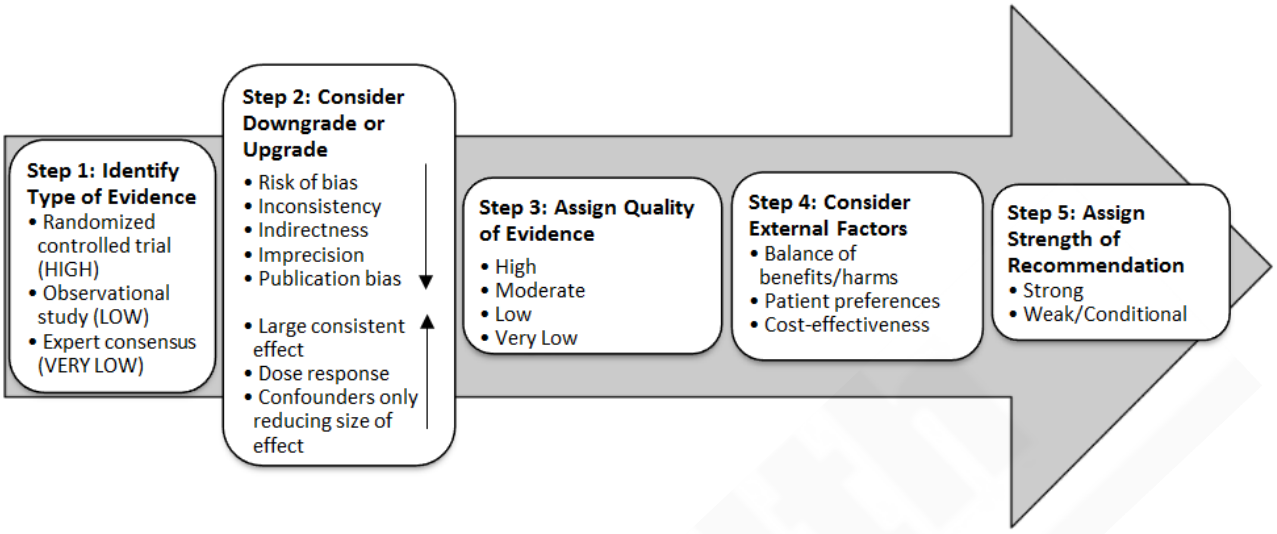
Methods Used to Formulate the Recommendations:

The workgroup members agreed to adopt recommendations developed by consensus through discussion of the literature and expert experience. All recommendations endorsed or developed by the guideline workgroup were reviewed and approved by other stakeholders or committees.

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendation:

Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see Figure 1).

Figure 1. GRADE Methodology adapted by UW Health



GRADE Ranking of Evidence

High	We are confident that the effect in the study reflects the actual effect.
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.
Low	The true effect may differ significantly from the estimate.
Very Low	The true effect is likely to be substantially different from the estimated effect.

GRADE Ratings for Recommendations For or Against Practice

Strong	The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.
Weak/conditional	Recommendation may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.

Recognition of Potential Health Care Disparities: No potential health care disparities were identified.

Collateral Tools and Resources

Metrics

Successful management of patients treated with vancomycin including: clinical cure rate, microbiological cure rate, achievement of target pharmacokinetic and pharmacodynamic parameters, incidence of acute kidney injury, and mitigation of the development of vancomycin-resistant bacteria.

Protocols

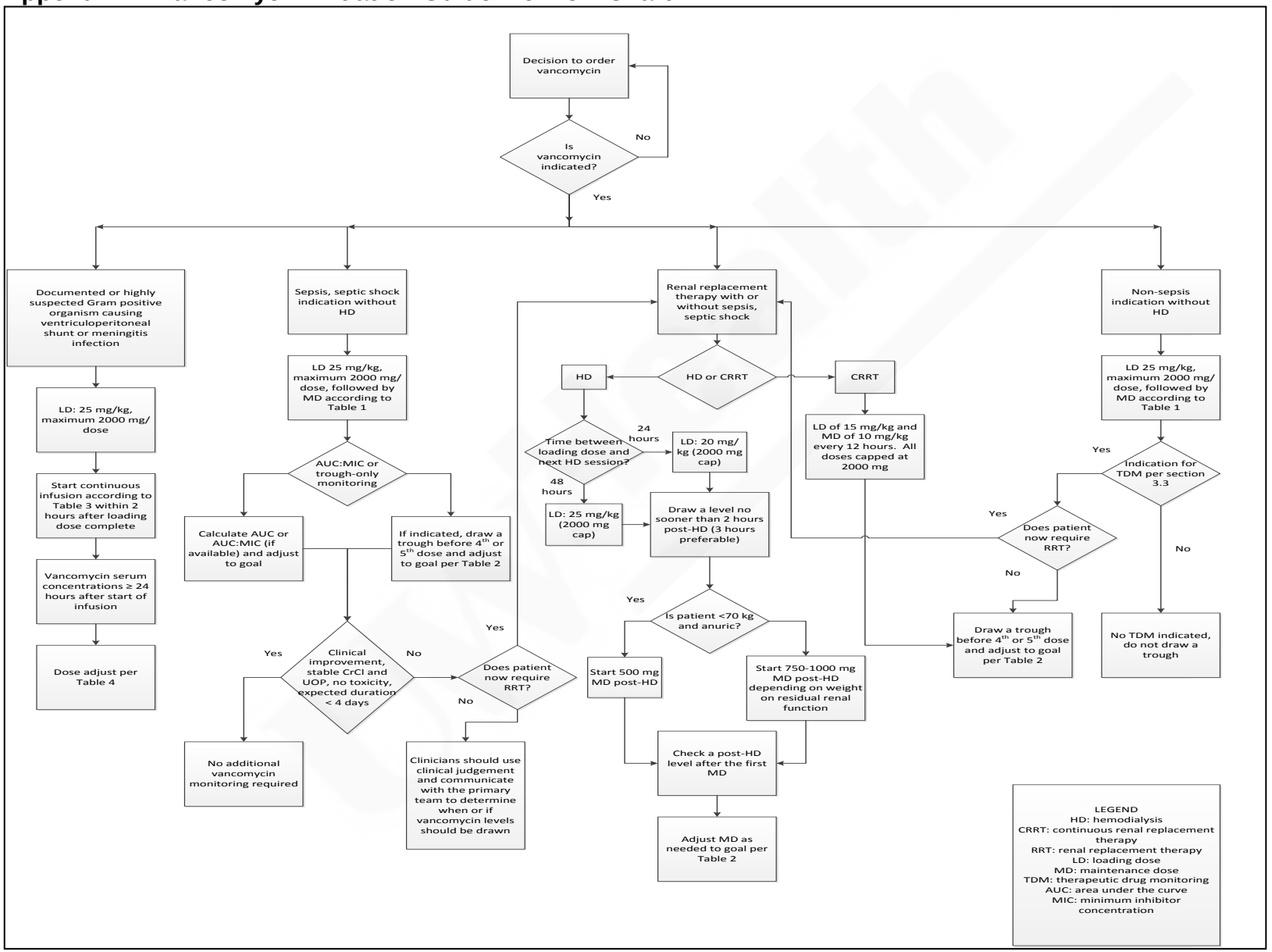
Vancomycin Dosing and Monitoring – Adult – Inpatient [129]

Clinical Practice Guidelines

- Skin, Skin Structure, and Soft Tissue Infection Diagnosis and Treatment – Adult-Inpatient/Ambulatory
- Urinary Tract Infections Diagnosis and Treatment – Adult – Inpatient/Ambulatory
- Renal Function-Based Dose Adjustments – Adult – Inpatient

- UWHC Guideline for Continuous Renal Replacement Therapy Based Dose Adjustments – Adult – Inpatient
- Surgical and Interventional Radiology Antimicrobial Prophylaxis – Adult/Pediatric – Inpatient/Ambulatory
- Clinical Monitoring of Outpatient Parenteral Antimicrobial Therapy (OPAT) – Adult – Inpatient/Ambulatory
- Prevention, Diagnosis, and Treatment of *Clostridium difficile* Infection – Adult/Pediatric – Inpatient/Ambulatory

Appendix A. Vancomycin Initiation Guideline Flow Chart [1,20,46,72,81,88,97,99-101]



Appendix B. Vancomycin Pharmacokinetic Equations[102]

$$AUC_{24} = \frac{D}{[(CL_{CR} \times 0.79) + 15.4] \times 0.06}$$

where AUC_{24} is expressed as mg • h/L, CL_{CR} is expressed as mL/min and D is vancomycin dosage in mg/24 hours.

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$$k_{el} = \frac{Ln\left(\frac{C_p}{C_t}\right)}{t} \quad (1)$$

where C_p is the peak concentration, C_t is the trough concentration, and t is the difference in time between these two concentrations. The AUC_{24} can be expressed as the summation of the area of a triangle (after the first dose) or a trapezoid (multiple doses) plus the integral of the concentration-time curve (Fig. 1). The equations for these computations are provided as follows: for single-dose AUC_{24} (first dose as an example),

$$AUC_{0\text{-}24} = 0.5 \cdot t' \cdot C_{max} + \int_{t'}^{infinity} C_{max} \cdot e^{-k_{el} \cdot (t)}\, dt - \int_{24}^{infinity} C_{min} \cdot e^{-k_{el} \cdot (t)}\, dt \quad (2)$$

Equation 2 can be simplified to

$$AUC_{24} = \frac{t' \cdot C_{max}}{2} + \frac{C_{max} - C_{min}}{k_{el}} \quad (3)$$

For multiple-dose AUC_{24} (fifth dose as an example),

$$AUC_{96\text{-}120} = 0.5 \cdot t' \cdot (C_{max} + C_{min}) + \int_{t'}^{infinity} C_{max} \cdot e^{-k_{el} \cdot (t)}\, dt - \int_{120}^{infinity} C_{min} \cdot e^{-k_{el} \cdot (t)}\, dt \quad (4)$$

□

Equation 4 can be simplified to

$$AUC_{24} = \frac{t \cdot (C_{max} + C_{min})}{2} + \frac{C_{max} - C_{min}}{k_{el}} \quad (5)$$

where t' is the time of infusion (h), C_{max} is the peak concentration at the end of infusion, and C_{min} is the trough concentration at the end of the dosing interval.

Appendix C. Evaluating Vancomycin Concentrations

- $Population\ K_e = 0.00083 \times (CrCL) + 0.0044$
- $Population\ V_d = 0.7\ \times (Actual\ Body\ Weight)$
- $Change\ in\ concentation = \Delta C = \frac{Dose}{V_d}$
- $C_2 = C_1 e^{(-k_e t)}$; t = time between concentrations

Example assessment

- Use ΔC equation to assess anticipated peak concentration from 1500 mg vancomycin dose in a 100 kg patient
    - $\Delta C = {}^{1500\ mg}/_{70\ L} = 21.4\ mg/L$

Appendix D. Characterization of Vancomycin MICs against *Staphylococcus Aureus*

MICs of vancomycin against *Staphylococcus aureus* isolates from blood, catheter tip, sputum, bronchioalveolar lavage, bone, and cerebrospinal fluids from 1/1/2013 to 4/12/2015 at UWHC are characterized below:

	Total Adult Inpatient Isolates		Adult Intensive Care Units		All Adult Non-Intensive Care Units		B4/6		B6/6	
MIC=0.5	1%	(8/1026)	0%	(2/422)	1%	(6/604)	30%	(3/10)	0%	(0/35)
MIC=1	87%	(888/1026)	89%	(377/422)	85%	(511/604)	70%	(7/10)	91%	(32/35)
MIC=1.5	2%	(17/1026)	1%	(3/422)	2%	(14/604)	0%	(0/10)	0%	(0/35)
MIC =2	11%	(113/1026)	9%	(40/422)	12%	(73/604)	0%	(0/10)	9%	(3/35)

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