Intravenous Vancomycin Use - Pediatric/Neonatal - Inpatient 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 needs 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] There have been many recent antibiotic developments for treating Gram-positive infections, resulting in more limited indications for vancomycin use, especially among patients with concerns of acute kidney injury or pre-existing renal disease. However, vancomycin is still judiciously used for treatment of drug-resistant gram-positive infections or for empiric therapy while awaiting further information.

As pediatric patients age from infancy to adolescence, there are developmental changes that affect the pharmacokinetic disposition of vancomycin. Total body water decreases with age (from up to 80% total body water as a premature neonate to 55% as an adult), which affects volume of distribution and influences the dose of vancomycin. Additionally, the ability to eliminate medications changes with age. For neonates, in-utero nephrogenesis and postnatal adaptation affects glomerular filtration rate (GFR). Premature neonates and those within the first week of life will often need lower frequency of vancomycin dosing. By 2 years of age, BSA-normalized GFR for both males and females will start to approximate that of adults. Absolute GFR continues to increase throughout childhood and adolescence, requiring higher daily doses of vancomycin.[3]

Scope

Intended Users: Any clinician treating a neonatal, pediatric or adolescent patient with intravenous vancomycin.

Objective: To optimize vancomycin use through standardizing the evaluation of the clinical necessity for vancomycin therapy, dosing of vancomycin based on pharmacodynamic and pharmacokinetic principles and parameters, and the monitoring of vancomycin, including therapeutic drug monitoring.

Target Population:

All neonates, infants, children, and adolescents requiring antimicrobial therapy with intravenous vancomycin with the following exclusions:

a. Patients aged 18 years and older at AFCH are excluded from this guideline. These patients may receive therapy in accordance with Intravenous Vancomycin Use – Adult – Inpatient Clinical Practice Guideline OR in accordance with this guideline at the discretion of the care 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/Pediatric – Inpatient – Clinical Practice Guideline.
c. Oral vancomycin for the treatment of Clostridium difficile infection is excluded from this guideline and may be found in the Prevention, Diagnosis and Treatment – Adult/Pediatric – Inpatient/Ambulatory/Emergency Department Clinical Practice Guideline

Definitions

1. **Actual body weight (ABW)** is defined as the actual total mass of the patient in kilograms.[4]
2. **Obesity** is defined as a patient's weight greater than the 95th percentile for age and gender.[5]
3. Modified Schwartz (eGFR/1.73 m^2) for estimated glomerular filtration rate (eGFR) calculation[4]:
    - $eGFR = {0.413 \times height\ (cm)} \Big/ {SCr\ \left(\frac{mg}{dL}\right)}$
4. **Gestational age (GA)** is defined as the period of time between conception and birth, measured in weeks and days.[6]
5. **Postnatal age (PNA)** is defined as the period of time between birth and current date, measured in weeks and days.[6]
6. **Postmenstrual age (PMA)** is defined as the GA plus the PNA, or the period of time between conception and current date, measured in weeks and days.[6]
7. **Neonate** is defined as a patient ≤ 28 days.[6]
    - **Preterm** is defined by GA < 37 weeks
    - **Very preterm** is defined by GA 28 to 32 weeks
    - **Extremely preterm** is defined by GA < 28 weeks
8. **Infant** is defined as PNA of 1 through 23 months.[6]
9. **Child** is defined as PNA of 2 to 12 years.[6]
10. **Adolescent** is defined as PNA 12 to 16-18 years.[6]
11. **AUC**: Area under the curve
12. **Empiric therapy:** Selection of antimicrobials based on clinical presentation prior to culture results.[7]
13. **Definitive therapy:** De-escalation of antimicrobial selection to narrower spectrum based on specific pathogen-directed treatment with culture results or with no culture results after 72 hours.[7]

Recommendations

1. Evaluation of the clinical necessity for vancomycin use

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).[1] (*UW Health Strong Recommendation, High Quality of Evidence*)

1.2. Patients being treated for potential MRSA infection should have screening or diagnostic testing performed to detect the presence of MRSA. (*UW Health Strong Recommendation, Very 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, Very Low Quality of Evidence*)

1.2.2. For purulent skin and soft tissue infections, direct MRSA polymerase chain reaction (PCR) swab of sample obtained during incision and drainage can be beneficial to guide antibiotic de-escalation. If negative, vancomycin discontinuation is reasonable (*UW Health Weak Recommendation, Very Low Quality of Evidence*). For non-purulent skin and soft tissue infections, MRSA PCR swabs for colonization can be beneficial when performed on the nares and pooled groin and axilla. If both are negative, there is a greater than 90% negative predictive value for MRSA infection and vancomycin discontinuation is reasonable.[8,9] (*UW Health Strong Recommendation, Very Low Quality of Evidence*).

1.2.3. For pneumonia, a bronchoalveolar lavage (BAL), sputum culture, or MRSA PCR swab of the nares and throat can be beneficial to screen for the presence of MRSA.[10] (*UW Health Strong Recommendation, 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.[10,11]

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

1.5. If the isolated organism is beta-lactam resistant but sensitive to another appropriate antibiotic, de-escalation from vancomycin may also be appropriate considering the specific indication, severity of illness, and characteristics of that antimicrobial agent. *(UW Health Strong Recommendation, Very Low Quality of Evidence)*

2. Empiric intermittent vancomycin dosing

2.1. Intermittent dosing of vancomycin is reasonable for all indications.[1] *(UW Health Strong Recommendation, Low Quality of Evidence)*

2.1.1. The Infectious Disease Society of America (IDSA) recommends intermittent infusion over continuous infusion due to the abundance of data validating its efficacy.

2.2. Due to changes in pharmacokinetic parameters throughout childhood, it is appropriate to base empiric dosing on patient age, ABW, and renal function.[12-16] *(UW Health Strong Recommendation, Moderate Quality of Evidence)*

2.3. Neonates

2.3.1. It is reasonable to use an initial dose of 15 mg/kg based on actual body weight in all neonates with normal or near normal renal function.[4,15] *(UW Health Strong Recommendation, Moderate Quality of Evidence)*

2.3.2. Dosing interval should be determined based on PMA and PNA as described in Table 1.[17] *(UW Health Strong Recommendation, Moderate Quality of Evidence)*

2.3.2.1. Studies evaluating this dosing regimen (based on PMA and PNA) have mixed conclusions on its ability to achieve higher trough concentrations of 10-20 mcg/mL.[18] However, this regimen was shown to be the best fit across all neonatal age ranges to meet trough goals that achieve AUC:MIC ratio greater than 400. Therefore, it is reasonable to continue using the PMA and PNA dosing algorithm.[19,20]

2.3.3. In neonates with renal dysfunction (defined as a serum creatinine rise greater than25% from baseline or urine output below 0.5 mL/kg/hr for 8 hours), it is reasonable to use an initial dose of 10 mg/kg.[21] *(UW Health Strong Recommendation, Moderate Quality of Evidence)*

Table 1. Empiric Intermittent Vancomycin Dosing Interval in Neonates[18,19]

Postmenstrual Age (PMA)[A]	Postnatal Age (PNA)[B]	Dosing Interval
≤ 29 weeks	0-14 days	18 hours
	>14 days	12 hours
30-36 weeks	0-14 days	12 hours
	>14 days	8 hours
37-44 weeks	0-7 days	12 hours
	>7 days	8 hours

[A] Postmenstrual age (PMA) is equal to gestational age (GA) plus postnatal age (PNA)
[B] Postnatal age is equal to the days after birth

2.4. Infants, Children and Adolescents

2.4.1. For most patients between the ages of 1 month and 18 years, dosing based on age and actual body weight is appropriate.[12,14-16] *(UW Health Strong Recommendation, Moderate Quality of Evidence)*

2.4.1.1. It is reasonable to cap vancomycin doses at 2000 mg per dose.[1,22] *(UW Health Conditional Recommendation, Low Quality of Evidence)*

2.4.2. For children and adolescents who are overweight and obese, may consider lengthening the dosing interval to avoid elevated trough concentrations.[23] *(UW Health Conditional Recommendation, Low Quality of Evidence)*

2.4.2.1. Multiple retrospective studies demonstrate significantly higher trough concentrations among overweight and obese patients when receiving the equivalent dose of their normal weight counterparts.[12,24-27]

2.4.2.2. Other studies suggest that an absolute weight threshold (ABW greater than 40 kg) is associated with increased risk of elevated trough concentrations.[12,28] However, this may be a function of patient age, as drug clearance declines during adolescence, and the weight effect in one study was eliminated when normalized by body surface area.[28]

2.4.3. Table 2 describes empiric intermittent maintenance and loading vancomycin dosing regimens based on patient age.[13,14,29-33]

2.4.3.1. A 2017 meta-analysis of 20 studies demonstrated that empiric dosing of greater than 60 mg/kg/day was associated with higher rates of target attainment (trough concentration of 10 to 20 mg/L or AUC:MIC greater than 400).[32]

2.4.3.2. Loading doses are recommended for treating serious confirmed or suspected MRSA infections to achieve more rapid AUC goal attainment.[15] (*UW Health Conditional Recommendation, Low Quality of Evidence*)

2.4.3.3. For children older than 2 years of age with serum creatinine below 0.45 mg/dL, consider empirically using a dose of 17.5 mg/kg/dose.[13] (*UW Health Conditional Recommendation, Low Quality of Evidence*)

2.4.3.4. Small studies in pediatric post-op cardiovascular surgery have shown that these patients may achieve higher trough concentrations compared to control counterparts, likely attributed to decreased renal function and prolonged cross-clamp time. Consider initially reducing frequency to every 8 hours in infants/children with aortic cross-clamp time longer than 1 hour.[34,35] (*UW Health Conditional Recommendation, Low Quality of Evidence*)

2.4.4. Table 3 describes empiric intermittent maintenance dosing regimens for patients with mild to moderate renal insufficiency based on creatinine clearance.[36,37]

2.4.4.1. In infants, children and adolescents, vancomycin drug clearance correlates to creatinine clearance.[29,36,37]

Table 2. Empiric Intermittent Vancomycin Dosing in Infants, Children, and Adolescents

Patient age	Loading Dose[A,B]	Dosing Interval	All Indications[A]
1 month to 2 years	20 mg/kg	6 hours	17.5 mg/kg/dose
≥2 years	20 mg/kg (Max 2 g/dose)	6 hours	15 mg/kg/dose[C] (Max 2 g/dose)

[A] Dose is based on actual body weight
[B] Consider using loading doses for treating serious infections per recommendations in 2.4.3.2
[C] Consider increasing dose to 17.5 mg/kg based on serum creatinine per 2.4.3.3
[D] Consider initially reducing the frequency to every 8 hours in infants/children with aortic cross-clamp time longer than 1 hour (see section 2.4.3.4)

Table 3. Empiric Intermittent Vancomycin Dosing in Infants, Children, and Adolescents with Renal Insufficiency

eGFR (mL/hr/1.73 m^2)	Dosing Interval	Total Daily Dose[B]
≥90	See Table 2	See Table 2
60-89	8 hours	45 mg/kg
30-59	12 hours	30 mg/kg
15-29	15 mg/kg x 1 dose, then check 12- or 24-hour random concentration, re-dose based on vancomycin concentration	
ESRD requiring renal replacement therapy	See Section 6.1 for dosing recommendations	

[A] Calculated using modified Schwartz equation using actual body weight
[B] Dose is based on actual body weight

3. Vancomycin Therapy Monitoring

3.1. As a narrow therapeutic index medication, it is important to monitor patients closely for adverse effects, primarily nephrotoxicity and histamine-related reactions. *(UW Health Strong Recommendation, Very Low Quality of Evidence)*

3.2. Nephrotoxicity

3.2.1. Overall incidence of nephrotoxicity with vancomycin in the pediatric population was 13.6% in a 2017 meta-analysis of almost 2500 patients.[38]

3.2.2. When vancomycin-induced acute kidney injury does occur, renal function returns to baseline after vancomycin discontinuation in most patients.[39,40]

3.2.3. Risk factors for nephrotoxicity include:
- Trough concentrations greater than 15 mg/L[38,41-44]
- AUC greater than or equal 800 mg·h/L[42]
- Length of therapy longer than seven days[40,42,45,46]
- Concomitant nephrotoxic medications, including piperacillin/tazobactam[39,42-44]
- Critical illness and ICU admission[42,43]
- Concomitant vasopressors[46]
- Hypovolemia[38]

3.2.4. To reduce the risk of nephrotoxicity in patients receiving intravenous vancomycin, practitioners should weigh the risks and benefits of administering concomitant nephrotoxic medications.[38,47] *(UW Health Strong Recommendation, Low Quality of Evidence)*

3.2.4.1. It is reasonable to use the Nephrotoxic Injury Negated by Just-in-time Action (NINJA) list to identify nephrotoxic medications.[48] *(UW Health Conditional Recommendation, Low Quality of Evidence)*

3.2.4.2. Furosemide was identified in multiple studies as an independent risk factor for vancomycin-induced nephrotoxicity.[43,44]

3.2.4.3. The combination of vancomycin and piperacillin-tazobactam has been shown to significantly increase risk of AKI when compared to the combination of vancomycin and other anti-pseudomonal β-lactam antibiotics (cefepime, ceftazidime, meropenem).[49]

3.2.5. Renal function should be monitored throughout vancomycin therapy.

3.2.5.1. Urine output should be monitored at least once daily based on clinical status, as it may reflect changes in renal function earlier than lab values.[50] (*UW Health Conditional Recommendation, Low Quality of Evidence)*

3.2.5.1.1. Serum creatinine should be obtained prior to initiating vancomycin, then every 72 to 96 hours during therapy or more frequently based on clinical status and the discretion of the care team.[51] *(UW Health Conditional Recommendation, Low Quality of Evidence)*

3.2.5.1.2. If the patient is on vancomycin for greater than or equal to three days, obtain serum creatinine every 24 hours per NINJA monitoring program.[48] *(UW Health Conditional Recommendation, Low Quality of Evidence)*

3.2.5.1.3. If the patient is on three or more concomitant nephrotoxic medications, obtain serum creatinine every 24 hours per the NINJA monitoring program.[48] *(UW Health Conditional Recommendation, Low Quality of Evidence)*

3.3. Vancomycin-induced histamine-release syndrome

3.3.1. Vancomycin-induced histamine-release syndrome occurs in 1 to 47% of infected patients and is characterized by pruritus, an erythematous rash, dizziness, agitation, chills, fever, and paresthesia 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.[52,53]

3.3.2. History of vancomycin-induced histamine-release syndrome is not a contraindication for future use and should not be the primary justification for use of an alternate antimicrobial agent.

3.3.3. Risk factors:
- History of histamine-release syndrome with past vancomycin exposure[54]
- Increasing vancomycin dose[54,55]
- Increasing vancomycin infusion concentration (lowest risk with vancomycin concentration 5 mg/mL or more dilute)[54]

3.3.4. Pre-medication with antihistamines may be reasonable in patients with history of histamine-release syndrome.[56] (*UW Health Conditional Recommendation, Low Quality of Evidence)*

3.3.4.1. Consider diphenhydramine 0.5 to 1 mg/kg intravenous or enteral (maximum of 50 mg) given 30 to 60 minutes prior to initiation of vancomycin infusion.

3.3.4.2. One retrospective study demonstrated a decrease in the incidence and severity of flushing when antihistamine was given prior to vancomycin exposure in patients with a history of reaction, but no difference in pruritus or rash.[54]

3.3.5. If histamine-release syndrome occurs during infusion, it is reasonable to pause the infusion, treat with intravenous or enteral diphenhydramine 0.5 to 1 mg/kg (max dose 50 mg), then resume the infusion at a slower rate when symptoms have resolved.[53,56] *(UW Health Conditional Recommendation, Low Quality of Evidence)*

3.3.5.1. For subsequent doses, consider infusing over longer duration (max duration two hours) and premedicate with intravenous or enteral diphenhydramine 0.5 to 1 mg/kg (max dose 50 mg).[53,56] (*UW Health Conditional Recommendation, Low Quality of Evidence)*

3.3.6. Practitioners should avoid the use of the term “red man syndrome” to describe vancomycin-induced histamine-release syndrome, which may be culturally insensitive to patients, families, and/or healthcare providers of Native American heritage.[57] *(UW Health Strong Recommendation, Low Quality of Evidence)*

4. Vancomycin Therapeutic Drug Concentration Monitoring

4.1. It is appropriate to apply AUC: MIC goals derived from adult data to neonatal and pediatric populations. Vancomycin pharmacokinetic and pharmacodynamic activity is best described by the 24-hour area under the curve to minimum inhibitory concentration (AUC:MIC) ratio. Animal and human (adult) data indicate that the ratio of area under the curve AUC:MIC is predictive of clinical outcome when treating methicillin-resistant Staphylococcus aureus (MRSA).

4.1.1. The goal AUC:MIC ratio to optimize the chance of microbiological success in the treatment of Staphylococcus aureus is 400 mg/dL/hr.[1]

4.1.2. It is appropriate to use AUC:MIC monitoring for pediatric patients receiving vancomycin for treatment of active or serious infection.[33,58] (*UW Health Conditional Recommendation, Low Quality of Evidence*)

4.1.2.1. AUC calculation requires two laboratory values (near peak and near trough), preferably drawn after reaching steady-state (prior to the fourth or fifth dose).

4.1.2.2. 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.

4.1.2.2.1. For patients with undetectable troughs, consider re-drawing the second vancomycin concentration 4 hours after the first serum concentration drawn, during the next dosing interval.[30]

4.1.3. A set of concentration may also be drawn if patient has acute changes in their renal function defined by serum creatinine rise greater than 25% from baseline or urine output below 0.5 mL/kg/hr for 8 hours.[59] *(UW Health Strong Recommendation, High Quality of Evidence)*

4.1.4. If the MIC is not known at the time of AUC:MIC calculation, it is reasonable to estimate the MIC based on current UWHC antibiogram surveillance data of *Staphylococcus aureus* vancomycin MIC distribution. *(UW Health Conditional Recommendation, Very Low Quality of Evidence)*

4.2. In patients who are not critically ill without severe infection, and who have normal renal function, a vancomycin trough concentration-based approach is reasonable.[60]*(UW Health Conditional Recommendation, Low Quality of Evidence)*

4.2.1. The 2011 IDSA guideline on the treatment of MRSA recommends trough concentrations of 10 to 15 mg/L for most patients and 15 to 20 mg/L for patients with severe infections or for those with high suspicion for MRSA. This recommendation is extrapolated from adult data that has demonstrated that 15 to 20 mg/L correlates with AUC:MIC greater than 400 in adults. However, multiple pharmacokinetic modeling studies and prospective

validation studies have demonstrated that lower trough concentrations can achieve similar AUC:MIC values in children.[13,58]

4.2.1.1. Additionally, multiple observational and pharmacokinetic modeling studies have demonstrated the difficulty with obtaining trough concentrations between 15 to 20 mg/L in children.[13,58,61]

4.2.2. First trough concentration should be drawn 30 minutes prior to the fourth or fifth dose, when the drug concentration is at steady state. Subsequent concentrations should be collected as follows *(UW Health Conditional Recommendation, Low Quality of Evidence*)

4.2.2.1. If the initial trough concentration is within the goal range, consider rechecking concentration as described in section 4.5 or with any changes in renal function.[51]

4.2.2.2. If the trough concentration is out of target range, recheck concentration prior to the fourth or fifth dose of the adjusted dosing regimen.[51]

4.2.3. When dosing interval is greater 12 hours, it is reasonable to collect the first trough concentration earlier (before the second or third dose).[51] (*UW Health Strong Recommendation, Low Quality of Evidence*)

4.2.4. It is appropriate to target trough concentrations based on disease state as described in Table 4.

4.3. For patients receiving intermittent vancomycin infusions and receiving dialysis, vancomycin trough concentrations should be monitored as there is limited data on AUC:MIC monitoring in this population. (*UW Health Conditional Recommendation, Very Low Quality of Evidence*)

4.4. In response to a supratherapeutic or subtherapeutic vancomycin trough concentration or AUC: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 Conditional Recommendation, Very Low Quality of Evidence*)

4.5. 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 evaluated more frequently. Clinicians should use clinical judgement to determine when concentrations should be drawn. (*UW Health Conditional Recommendation, Low Quality of Evidence)*

4.6. If appropriate vancomycin pharmacokinetic parameters are unable to be achieved with daily doses of 100 mg/kg/day or greater on intermittent dosing, it may be reasonable to consider a switch to continuous infusion vancomycin, pursue alternative agents, or consider Pediatric Infectious Diseases consult. *(UW Health Strong Recommendation, Very Low Quality of Evidence)*

Table 4. Target vancomycin trough concentrations based on age and indication

Age	Osteomyelitis, Meningitis, Endocarditis, MRSA Pneumonia (mcg/mL)	All other indications (mcg/mL)
Neonates to 18 years	10-15	7-12

5. Continuous infusion vancomycin

5.1. Continuous infusion vancomycin dosing described in Table 5 and 6 may be reasonable for patients with subtherapeutic trough concentrations despite dose escalation.[15,62-65] (*UW Health Conditional Recommendation, Moderate Quality of Evidence*)

5.2. Vancomycin administration via continuous infusion may decrease the risk of nephrotoxicity compared to intermittent infusion.[66]

5.3. Dosing adjustments are based on therapeutic dose monitoring described in Table 7 for a goal of AUC:MIC greater than 400.

5.3.1. Administration via continuous infusion simplifies AUC calculations, requiring only a single steady-state concentration.

5.3.2. Vancomycin concentrations should be drawn at least 24 hours after initiation of continuous infusion or 24 hours after dose changes.[62,64,67] *(UW Health Conditional Recommendation, Low Quality of Evidence)*

5.3.3. Treatment of meningitis/ventriculitis should be done under the guidance of infectious diseases consultation (*UW Health Conditional Recommendation, Expert Opinion)*

5.4. In practice, it has been observed that 50% of the total daily dose received with intermittent dosing results in a similar random vancomycin concentration with 24-hour continuous infusion.

5.4.1. Example: patient receiving 1000 mg every six hours as intermittent infusion with a trough of 12 mcg/mL correlates to 2000 mg every 24 hours administered as a continuous infusion would provide roughly the same concentration (12mcg/ml) after 24 hours.

Table 5. Empiric vancomycin dosing for continuous infusion vancomycin in neonates

Postnatal Age	Birth Weight	Loading Dose	Initial 24-hour Dose
0-7 days	<1kg	10 mg/kg	25 mg/kg
	1-2 kg		30 mg/kg
	>2 kg		35 mg/kg
8-14 days	<1 kg		25 mg/kg
	1-2 kg		35 mg/kg
	>2 kg		45 mg/kg
15-28 days	<1 kg		30 mg/kg
	1-2 kg		45 mg/kg
	>2 kg		50 mg/kg

Table 6. Empiric vancomycin dosing for continuous infusion vancomycin in infants and children[A]

Patient age	Loading dose	Initial 24-hour dose
1 month - 8 years	15 mg/kg	50 mg/kg
8-18 years		45 mg/kg

[A] Consider using 50% of total daily dose of intermittent infusion as a starting point for continuous infusion

Table 7. Target vancomycin steady-state concentrations for continuous infusions

Age	Continuous Infusion Concentration Goal (mcg/mL)
Neonates to 18 years	15-25

6. Renal replacement therapy

6.1. In patients requiring intermittent or continuous renal replacement therapy, it is reasonable to consider an alternate antimicrobial with MRSA activity. *(UW Health Conditional Recommendation, Very Low Quality of Evidence)*

6.1.1. Vancomycin is poorly dialyzable, and the amount of drug removed is highly variable based on dialysis type, settings and duration, making dosing of this narrow therapeutic index drug challenging. However, due to the established efficacy reference range, it may be preferable to other anti-MRSA agents without validated therapeutic drug monitoring parameters. Therefore, use of vancomycin in this population must be based on a careful risk/benefit analysis.

6.1.2. Additionally, there is a high degree of inter-individual variability in non-dialysis drug clearance for patients on renal replacement therapy due to residual renal function and non-renal clearance pathways.

6.2. Intermittent hemodialysis and peritoneal dialysis

6.2.1. In patients established on intermittent hemodialysis or peritoneal dialysis, it is reasonable to give a 15 mg/kg loading dose.[21] *(UW Health Conditional Recommendation, Low Quality of Evidence)*

6.2.2. It is reasonable to base individualized dosing regimens on post-dialysis vancomycin drug concentrations.[68] *(UW Health Strong Recommendation, Moderate Quality of Evidence)*

6.2.2.1. The first vancomycin concentration should be drawn no sooner than two hours after the completion of the next hemodialysis or peritoneal dialysis session to account for drug redistribution phase.[68]

6.2.2.2. Subsequent post-dialysis doses should be based on the results of drug concentrations.

6.2.2.3. If the first post-dialysis concentration is in the goal range, it is reasonable to give a 10 mg/kg dose. If the next post-dialysis concentration is also within range, then it is reasonable to continue with that regimen with only once weekly post-dialysis concentrations if the hemodialysis or peritoneal dialysis parameters are consistent.[21] It is reasonable to obtain additional trough concentrations after changes to hemodialysis or peritoneal dialysis parameters based on clinical judgement by the care team. *(UW Health Conditional Recommendation, Low Quality of Evidence)*

6.2.2.4. If the post-dialysis dose is above goal range at any point, it is reasonable to hold the next dose until after the next session, then give a reduced dose. Decision to obtain a vancomycin concentration prior to administering that dose should be based on the degree of elevation.[21] *(UW Health Conditional Recommendation, Low Quality of Evidence)*

Table 8. Target vancomycin trough concentrations for patients receiving renal replacement therapy

Age	Osteomyelitis, Meningitis, Endocarditis, MRSA Pneumonia (mcg/mL)	All other indications (mcg/mL)
Neonates to 18 years	10-15	7-12

6.3. Continuous renal replacement therapy (CRRT)

6.3.1. It is reasonable to initiate therapy at 15 mg/kg (based on ABW) every 12 hours.[21] *(UW Health Conditional Recommendation, Low Quality of Evidence)*

6.3.2. It is reasonable to obtain the first trough concentration before the third or fourth dose.[21] *(UW Health Conditional Recommendation, Low Quality of Evidence)*

6.3.3. If the first trough concentration is within goal range, it is reasonable to obtain a second concentration after an additional 48 hours to ensure steady state, then every five to seven days if CRRT parameters remain unchanged.[21] *(UW Health Conditional Recommendation, Low Quality of Evidence)*

6.3.4. It is reasonable to obtain additional trough concentrations after changes to CRRT parameters based on clinical judgement by the care team.[21] *(UW Health Conditional Recommendation, Very Low Quality of Evidence)*

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

Development Process

Each guideline is reviewed and updated a minimum of every 3 years. All guidelines are developed using the guiding principles, standard processes, and styling outlined in the UW Health Clinical Practice Guideline Resource Guide. This includes expectations for workgroup composition and recruitment strategies, disclosure and management of conflict of interest for participating workgroup members, literature review techniques, evidence grading resources, required approval bodies, and suggestions for communication and implementation.

Methods Used to Collect the Evidence:

The following criteria were used by the guideline author and workgroup members to conduct electronic database searches in the collection of evidence for review.

Literature Sources:

- PubMed
- Google Scholar
- Cochrane Library
- Textbooks
- Hand-searching journals, external guidelines, and conference publications

Time Period: 1995 to 2018

Search Terms:

- Pediatric vancomycin AUC:MIC monitoring
- Vancomycin dosing in children
- Continuous vancomycin infusion
- Neonatal vancomycin dosing

Methods to Select the Evidence:

Selection of the literature for this guideline only included studies that were written in English. Both adult and pediatric studies were included in this guideline. Adult literature was only used if an extensive search for pediatric literature did not result in providing a recommendation. All study designs were considered in the selection of the evidence.

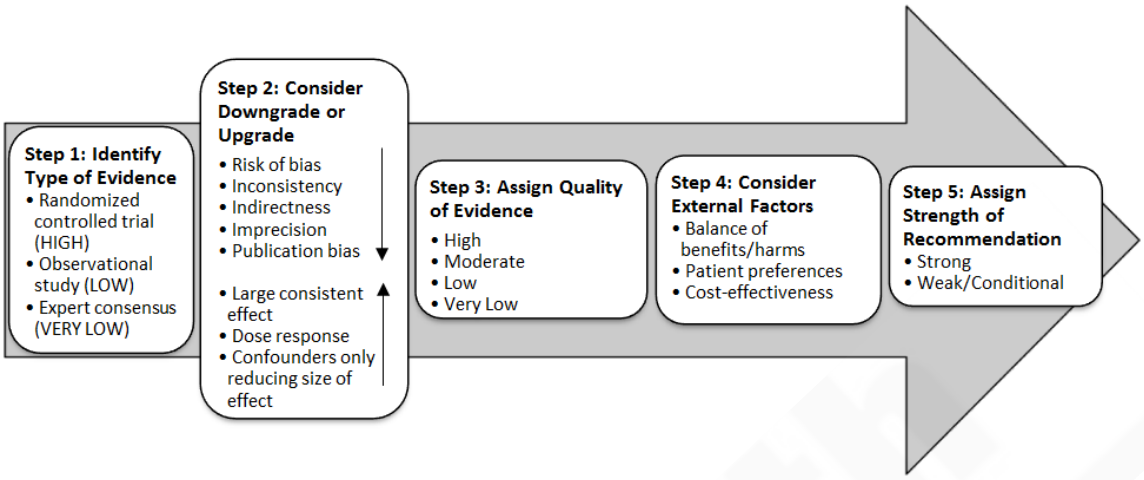
Methods Used to Formulate the Recommendations:

The workgroup members created recommendations internally via a consensus process using discussion of the literature and expert experience/opinion. If issues or controversies arose where consensus could not be reached, the topic was escalated appropriately per the guiding principles outlined in the UW Health Clinical Practice Guideline Resource Guide.

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

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



Rating Scheme for the Strength of the Evidence/Recommendations:

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 (S)	The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.
Conditional (C)	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: None identified

Collateral Tools & 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.

Clinical Practice Guidelines

- Surgical and Interventional Radiology Antimicrobial Prophylaxis – Adult/Pediatric – Inpatient/Ambulatory
- Clinical Monitoring of Outpatient Parenteral Antimicrobial Therapy (OPAT) – Adult – Inpatient/Ambulatory
- Management of Fever and Neutropenia – Pediatric – Inpatient/Ambulatory/Emergency Department

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